Copper(I)-Catalyzed Azide–Alkyne Cycloadditions in Ionic Liquids under Amine-Free Conditions

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Abstract: Copper(I) iodide catalyzed cycloadditions of various combinations of structurally diverse organic azides and terminal alkynes were carried out in a commercially available, polyoxygenated ionic liquid (AMMOENG 100™) without addition of free amine. Unlike the previously tested ionic liquids, this solvent led exclusively to the 1,4-disubstituted triazole regioisomer.

Key words: alkynes, azides, carbohydrates, copper, cycloadditions

The copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC),[1] discovered independently in the Meldal and Sharpless laboratories,[2] constitutes a substantial improvement of the classical Huisgen-type thermal 1,3-dipolar cycloaddition. While the latter takes place by a one-step concerted mechanism and requires high temperature and long reaction time to give mixtures of 1,4- and 1,5-disubstituted triazoles,[3] catalytic copper(I) affects the kinetics and mechanism[4] of the reaction that, in fact, is a multistep process that goes to completion in short time at room temperature to give exclusively 1,4-disubstituted triazole derivatives. For its remarkable efficiency and specificity, as well as the stability of the triazole ring under a variety of conditions, this reaction has become one of the most used ligation tools in material, organic, and bioorganic sciences over the last years.[5] CuAAC can be carried out in a variety of molecular solvents ranging from the apolar, aprotic dichloromethane and toluene to the polar, aprotic acetonitrile and *N*,*N*-dimethylformamide. Quite interestingly for bioorganic applications, the reaction can be performed equally well in water as the solvent.[6]

In two recent papers from this laboratory,[7] we have extended the scope of the CuAAC by using ionic liquids (ILs) as solvents. ILs, with their vanishing low vapor pressure, are safe and environmentally benign solvents.[8] They are convenient as media for metal-catalyzed reactions because of their capability to dissolve metal salts and stabilize the formation of metal nanoparticles and nanorods.[9] Moreover, ILs have proven to be good microwave absorbers[10] and therefore are well suited in reactions using microwave dielectric heating[11] by reducing substantially the reaction time that is needed with thermal heating.[7b] Finally, the recovery of unaltered ILs from reaction mixtures and recycling compensate for their cost that, however, is in general quite reasonable. Thus, we have reported on a study of a model copper(I) iodide catalyzed cycloaddition of a sugar azide to a sugar acetylene in a wide variety of ILs.[7a] Aiming at simplifying the reaction conditions, we performed the reaction without addition of free amine with the expectation that suitable ILs bearing basic nitrogen atoms could play the role of a base that is traditionally used in copper(I) iodide catalyzed azide–alkyne cycloadditions.[2b] The most commonly used bases are amines[1] such as *N*,*N*-diisopropylethylamine, that are thought to serve both as a base for the deprotonation of the alkyne and as a ligand for the stabilization of copper(I) ion.[4,12] In contrast to our expectations, the model reaction carried out in a range of basic ILs turned out to afford mixtures of 1,4- and 1,5-disubstituted triazoles in low overall yield.[7a] We considered that the lack of regioselectivity was due to the occurrence of the thermally induced, concerted Huisgen 1,3-dipolar cycloaddition instead of the desired multistep copper(I)-catalyzed process.

We now report on the copper(I) iodide catalyzed reactions of structurally different azides and terminal alkynes in a commercially available ionic liquid (IL), i.e. the densely oxygenated nonbasic IL **8** (AMMOENG 100™), in the absence of any added amine. All the CuAACs gave exclusively the 1,4-disubstituted triazole derivatives[13] in high isolated yields.

We set out to investigate the copper(I) iodide catalyzed cycloadditions of azides **1**–**4** to alkynes **5**–**7** in AMMOENG 100™ (**8**) under basic ligand-free conditions (Table 1). Each reaction was carried out at 80 °C for 2 hours by microwave dielectric heating[14] using a single-mode cavity dedicated reactor (Biotage Initiator); the temperature was measured externally on the outside vessel wall with an IR sensor. Initial experiments were conducted in the IL **8** using benzyl azide (**1**) and phenylacetylene (**5**) on a 0.5 mmol scale in the presence of 0.50 equivalents of copper(I) iodide as described in our earlier report.[7a] The cycloaddition afforded the triazole **9** in 95% yield as pure 1,4-regioisomer. Then, the same cycloaddition was repeated using gradually reduced amounts of the copper catalyst. We found that the very efficient reaction took place even in the presence of 0.025 equivalents of copper(I) iodide, affording pure **9** in 92% isolated yield. This ap-

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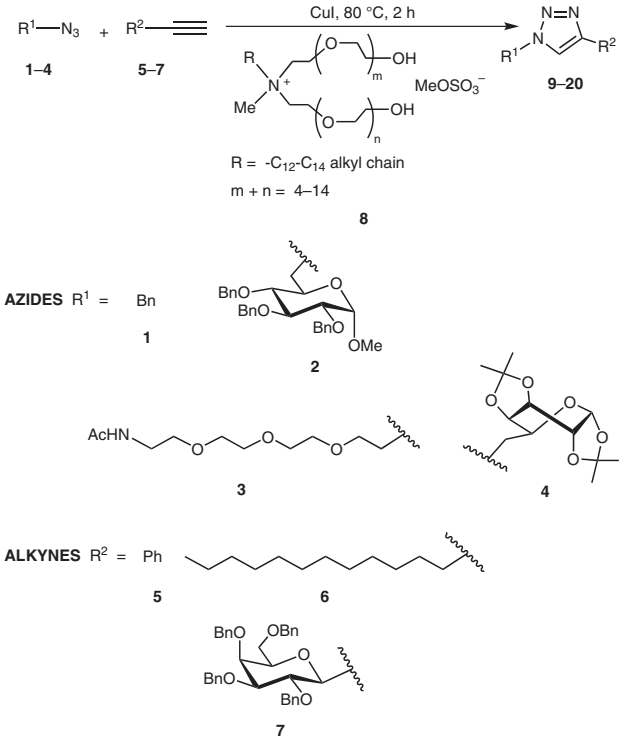
Table 1 Copper(I) Iodide Catalyzed Reactions of Azides **1–4** with Alkynes **5–7** in the Absence of Amine Additive

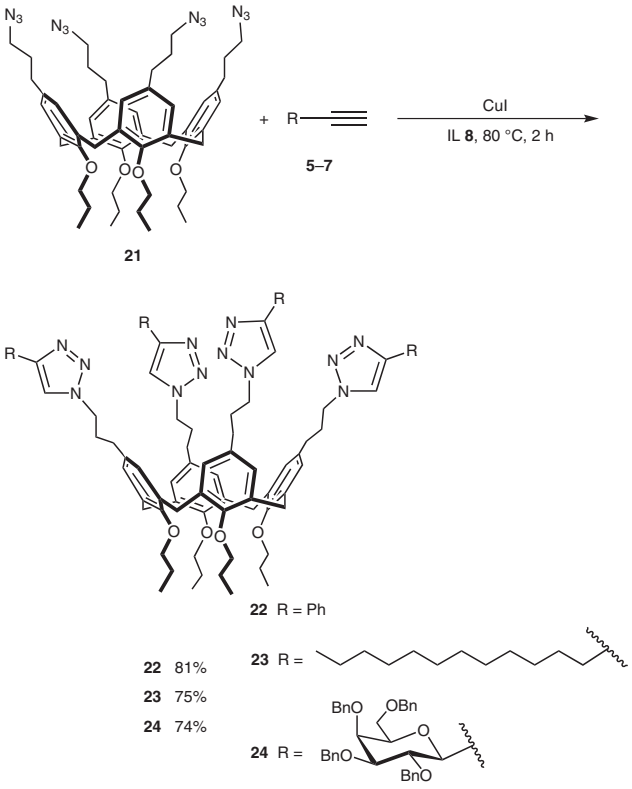


Entry	Azide	Alkyne	Triazole	Yield[a] (%)
1	**1**	**5**	**9**	92
2	**1**	**6**	**10**	71
3	**1**	**7**	**11**	80
4	**2**	**5**	**12**	56
5	**2**	**6**	**13**	58
6	**2**	**7**	**14**	68
7	**3**	**5**	**15**	72
8	**3**	**6**	**16**	87
9	**3**	**7**	**17**	82
10	**4**	**5**	**18**	95
11	**4**	**6**	**19**	90
12	**4**	**7**	**20**	89

[a] Yield of product isolated by column chromatography.

peared to be close to the lower limit of catalyst as compound **9** was obtained in only 46% yield with 0.01 equivalents of copper(I) iodide. Therefore, all the other azides and alkynes were allowed to react in AMMOENG 100™ (**8**) in the presence of a catalytic amount of copper(I) iodide, such as 0.025 equivalents.

Even multiple reactions of three different terminal alkynes on the same substrate, such as with the tetraazidocalixarene **21**,[13] appeared to occur with high efficiency and total selectivity without addition of free amine (Scheme 1).



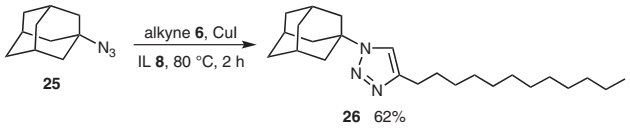
Scheme 1

All the cycloadducts, with the exception of **26**, were recovered from the reaction mixtures by direct extraction with diethyl ether or diethyl ether–ethyl acetate (1:1), i.e. without dilution of the IL with water, and then purified by column chromatography on silica gel. The latter operation removed all the copper salts and the small amounts of IL (5–8%) that were extracted by the molecular solvents.

The economical aspect was also examined by recycling five times the IL **8** used in the reaction between benzyl azide (**1**) and phenylacetylene (**5**) (Table 1, entry 1). The observed yields of the isolated 1,4-disubstituted triazole **9** were 92% (first run) and 92%, 90%, 91%, 88%, and 84% (subsequent runs). Hence, the IL appeared not to be deteriorated throughout six consecutive runs and very likely could be reused as an effective solvent in further experiments. Unfortunately, in the workup of the reaction mixture in each cycle, the copper(I) iodide was extracted from the IL together with the product and was lost in the chromatographic purification of the latter. Therefore, fresh copper(I) iodide (0.025 equiv) was added before each recycle. It is worth noting, however, that reuse of the IL was simplified by the fact that the workup of the reaction mixture usually did not require dilution with water and therefore the drying of IL **8** was easily performed at room temperature under reduced pressure (0.1 mbar, 2 h).

It is important to notice that although the standard conditions under which the CuAAC is currently carried out in-

volve the use of a ligand (an amine or a densely nitrogenated molecule) for the stabilization of copper(I) ion and copper(I) complexes, all reactions reported in Table 1 and Scheme 1 were performed without addition of free amine. Therefore, we speculate that the densely oxygenated IL **8** and/or the reagents/products bearing oxygen atoms or phenyl rings served as ligands. In agreement with this hypothesis, the reaction between two aliphatic partners such as 1-adamantyl azide[15] (**25**) and 1-tetradecyne (**6**) in toluene did not produce any cycloadduct whereas in the presence of *N*,*N*-diisopropylethylamine afforded the expected triazole derivative **26** in 57% yield. By contrast, the same reaction carried out in the IL **8** under amine-free conditions gave the product **26** in 62% yield (Scheme 2).



Scheme 2

From the above results it may be concluded that the click CuAAC can be conveniently carried out in ILs, AMMOENG 100™ being the solvent of choice. In this solvent the reaction is a fast and high-yielding process. Moreover, the process is operationally simplified because the reaction occurs without the addition of free amine and it requires 2.5 mol% of copper(I) iodide as the catalyst. The same reaction efficiency and regioselectivity, i.e. exclusive formation of the 1,4-disubstituted triazole in high yield, can be reached by microwave dielectric heating or simply by using an oil bath. It is noteworthy that the IL can be easily recovered from the reaction mixture and reused several times in subsequent runs. This compensates for the cost of the solvent, which, however, is quite reasonable. Therefore, given the advantages provided by the use of ILs as green solvents, the valuable click CuAAC appears to be endowed with the additional value of being a process that can be efficiently performed under the principles of green chemistry.

Anhydrous solvents were dried over standard drying agents[16] and freshly distilled prior to use. Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with sulfuric acid. Flash column chromatography[17] was performed on silica gel 60 (40–63 μm) using distilled solvents. Melting points were determined with a capillary apparatus. Optical rotations were measured at 20 ± 2 °C in the stated solvent; $[\alpha]_D$ values are given in deg·mL·g^{-1}·dm^{-1}. ^{1}H NMR (300 and 400 MHz) and ^{13}C NMR (75 MHz) spectra were recorded for $CDCl_3$ solutions at r.t. unless otherwise specified. Peak assignments were aided by ^{1}H–^{1}H COSY and gradient-HMQC experiments. In the ^{1}H NMR spectra, the *n* and *m* values quoted in geminal or vicinal proton–proton coupling constants $J_{n,m}$ refer to the numbers of the corresponding sugar protons. For accurate mass measurements, the compounds were analyzed in positive ion mode using an electrospray hybrid quadrupole orthogonal acceleration time-of-flight mass spectrometer (Q-TOF) fitted with a Z-spray electrospray ion source (Waters, Manchester, UK). The capillary source voltage and the cone voltage were set at 3500 V and 35 V, respectively; the source temperature was kept at 80 °C; N_2 was used as a drying gas at a flow rate of ca. 50 L/h. The time-of-flight analyzer was externally calibrated with NaI from *m*/*z* 300 to 2000 to yield an accuracy near to 5 ppm. When necessary, an internal lock mass was used to further increase the mass accuracy. Accurate mass data were collected by directly infusing samples [10 pmol/μL in MeCN–H_2O (1:1) containing 10 mM ammonium formate] into the system at a flow rate of 5 μL/min. The acquisition and data processing were performed with MassLynx 4.1 software (Waters, Manchester, UK). AMMOENG 100™ (**8**) was supplied by Solvent Innovation. Commercial phenylacetylene (**5**) was distilled prior to use. Commercially available 1-tetradecyne (**6**) and CuI (light grey powder, Aldrich 215554) were used without further purification. Benzyl azide (**1**) was prepared from benzyl bromide and NaN_3 in MeOH (r.t., 18 h); then, the reaction mixture was partially concentrated, diluted with H_2O, and extracted with Et_2O; the organic phase was dried (Na_2SO_4) and concentrated under a stream of N_2 at r.t. Azide **3** was prepared by acetylation of commercial 1-amino-11-azido-3,6,9-trioxaundecane.

Cycloadditions in the Ionic Liquid; General Procedure

A mixture of an azide **1** (1.5 equiv) or **2**–**4**, **21**, **25** (1 equiv), an alkyne **5**–**7** (1.0–1.1 equiv), CuI (0.025 equiv), and AMMOENG 100™ (**8**; 0.50 g) was sonicated or magnetically stirred at r.t. for a few min, then heated to 80 °C (external vessel wall temperature) for 2 h in a single-mode cavity dedicated Biotage Initiator microwave reactor. The crude reaction mixture was extracted with Et_2O (4 × 6 mL) or EtOAc–Et_2O (1:1, in the case of products **17** and **22**), or (only in the case of product **26**) first diluted with H_2O (1 mL) and then extracted with CH_2Cl_2 (4 × 6 mL). The combined organic phases were concentrated to give the crude products containing 5–8% of IL and most of the copper salts. The residue was eluted from a column of silica gel to give the triazole derivatives in analytically pure form.

Recycling of the Ionic Liquid

A mixture of phenylacetylene (**5**; 51 mg, 0.50 mmol), crude benzyl azide (**1**; 100 mg, ca. 0.75 mmol), CuI (2.4 mg, 12.5 μmol), and AMMOENG 100™ (**8**; 0.50 g) was sonicated at r.t. for 3 min, then heated to 80 °C (external vessel wall temperature) in a microwave reactor for 2 h. The crude reaction mixture was extracted with Et_2O (4 × 6 mL) to recover crude **9** that was isolated in a pure form by flash chromatography (see below). The IL was dried under reduced pressure (0.1 mbar) at r.t. for 2 h, then alkyne **5** (51 mg, 0.50 mmol), azide **1** (100 mg, ca. 0.75 mmol), and CuI (2.4 mg, 12.5 μmol) were added. The mixture was treated as described above in five subsequent runs.

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (9)

The reaction between phenylacetylene (**5**; 51 mg, 0.50 mmol) and crude benzyl azide (**1**; 100 mg, ca. 0.75 mmol) gave, after column chromatography on silica gel (CH_2Cl_2–acetone, 1:0 → 1:1), known[18] **9** as a solid; yield: 108 mg (92%).

1-Benzyl-4-dodecyl-1*H*-1,2,3-triazole (10)

The reaction between 1-tetradecyne (**6**; 68 mg, 0.35 mmol) and benzyl azide (**1**; 69.2 mg, 0.52 mmol) gave, after column chromatography on silica gel (CH_2Cl_2–acetone, 1:0 → 1:1), **10** as a solid; yield: 81 mg (71%).

Mp 78–79 °C (Et_2O).

^{1}H NMR (300 MHz): δ = 7.43–7.35 (m, 3 H, Ar), 7.30–7.25 (m, 2 H, Ar), 7.19 (s, 1 H, H-5 Tr.), 5.52 (s, 2 H, PhC*H*$_2$), 2.70 (t, *J* = 7.8 Hz, 2 H, CH_2), 1.65 (tt, *J* = 7.7, 7.8 Hz, 2 H, CH_2), 1.40–1.20 (m, 18 H), 0.90 (t, *J* = 6.5 Hz, 3 H, CH_3).

^{13}C NMR: δ = 149.1 (C-4 Tr.), 134.8 (C), 129.2 (CH), 128.6 (CH), 128.0 (CH), 120.6 (C-5 Tr.), 54.1 (CH_2), 31.9 (CH_2), 29.6 (CH_2),

29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 25.8 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

HRMS (ESI/Q-TOF): *m/z* [M + H]$^+$ calcd for $C_{21}H_{34}N_3$: 328.2753; found: 328.2733.

1-Benzyl-4-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)-1*H*-1,2,3-triazole (11)

The reaction between ethynyl *C*-galactoside **7** (99 mg, 0.18 mmol) and benzyl azide (**1**; 36 mg, 0.27 mmol) gave, after column chromatography on silica gel (cyclohexane–EtOAc, 4:1 then 3:1), **11** as a solid; yield: 98 mg (80%).

Mp 109–111 °C (MeOH); $[\alpha]_D$ –14.0 (*c* 0.6, $CHCl_3$).

^{1}H NMR (400 MHz): δ = 7.38–7.15 (s, 24 H, Ar, H-5 Tr.), 6.99–6.96 (m, 2 H, Ar), 5.49 and 5.43 (2 d, *J* = 14.8 Hz, 2 H, PhCH_2Tr.), 4.96 and 4.64 (2 d, *J* = 11.7 Hz, 2 H, PhCH_2), 4.77 and 4.72 (2 d, *J* = 11.8 Hz, 2 H, PhCH_2), 4.68 and 4.30 (2 d, *J* = 10.7 Hz, 2 H, PhCH_2), 4.49 (d, $J_{1,2}$ = 9.7 Hz, 1 H, H-1), 4.44 and 4.38 (2 d, *J* = 11.8 Hz, 2 H, PhCH_2), 4.20 (dd, $J_{2,3}$ = 9.6 Hz, 1 H, H-2), 4.03 (dd, $J_{3,4}$ = 2.7 Hz, $J_{4,5}$ = 0.5 Hz, 1 H, H-4), 3.70 (dd, 1 H, H-3), 3.69 (dt, $J_{5,6}$ = 6.5 Hz, 1 H, H-5), 3.56 (d, 2 H, 2 H-6).

^{13}C NMR: δ = 146.5 (C-4 Tr.), 138.8, 138.4, 138.2, 137.9, and 134.6 (C Ar), 129.0, 128.7, 128.4, 128.1, 127.9, 127.8, 127.6, and 127.5 (CH Ar), 122.4 (C-5 Tr.), 84.4 (C-3), 78.3 (C-2), 77.4 (C-5), 74.9 (Ph*C*H_2), 74.6 (Ph*C*H_2, C-1), 73.9 (C-4), 73.5 (Ph*C*H_2), 72.4 (Ph*C*H_2), 68.7 (C-6), 54.1 (Ph*C*H_2Tr.).

HRMS (ESI/Q-TOF): *m/z* [M + H]$^+$ calcd for $C_{43}H_{44}N_3O_5$: 682.3281; found: 682.3254.

Methyl 2,3,4-Tri-*O*-benzyl-6-deoxy-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-α-D-glucopyranoside (12)

The reaction between phenylacetylene (**5**; 28.6 mg, 0.28 mmol) and methyl 6-azidoglucopyranoside **2** (122.3 mg, 0.25 mmol) gave, after column chromatography on silica gel (cyclohexane–EtOAc, 4:1 → 2:1), **12** as a solid; yield: 83 mg (56%).

Mp 126–127 °C (MeOH); $[\alpha]_D$ +59.7 (*c* 0.6, $CHCl_3$).

^{1}H NMR (400 MHz): δ = 7.84–7.81 (m, 2 H, Ar), 7.80 (s, 1 H, H-5 Tr.), 7.45–7.28 (m, 18 H, Ar), 4.98 and 4.82 (2 d, *J* = 10.8 Hz, 2 H, PhCH_2), 4.92 and 4.78 (2 d, *J* = 10.9 Hz, 2 H, PhCH_2), 4.76 and 4.62 (2 d, *J* = 12.1 Hz, 2 H, PhCH_2), 4.61 (dd, $J_{5,6a}$ = 5.7 Hz, $J_{6a,6b}$ = 14.0 Hz, 1 H, H-6a), 4.56 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1), 4.55 (dd, $J_{5,6b}$ = 3.1 Hz, 1 H, H-6b), 4.02 (dd, $J_{2,3}$ = 9.7 Hz, $J_{3,4}$ = 9.0 Hz, 1 H, H-3), 4.00 (ddd, $J_{4,5}$ = 10.0 Hz, 1 H, H-5), 3.42 (dd, 1 H, H-2), 3.23 (s, 3 H, CH_3), 3.19 (dd, 1 H, H-4).

^{13}C NMR: δ = 147.6 (C-4 Tr.), 138.4, 137.95, 137.92, and 130.6 (C Ar), 128.8, 128.5, 128.45, 128.42, 128.2, 128.05, 128.00, 127.94, 127.87, 127.68, and 125.64 (CH Ar), 121.1 (C-5 Tr.), 98.1 (C-1), 81.8 (C-3), 79.9 (C-2), 77.9 (C-4), 75.7, 75.0, and 73.5 (Ph*C*H_2), 69.1 (C-5), 55.3 (CH_3), 50.6 (C-6).

HRMS (ESI/Q-TOF): *m/z* [M + H]$^+$ calcd for $C_{36}H_{38}N_3O_5$: 592.2811; found: 592.2830.

Methyl 2,3,4-Tri-*O*-benzyl-6-deoxy-6-(4-dodecyl-1*H*-1,2,3-triazol-1-yl)-α-D-glucopyranoside (13)

The reaction between 1-tetradecyne (**6**; 43 mg, 0.22 mmol) and methyl 6-azidoglucopyranoside **2** (98 mg, 0.20 mmol) gave, after column chromatography on silica gel (cyclohexane–EtOAc, 4:1), **13** as a solid; yield: 79 mg (58%).

Mp 65–66 °C (MeOH); $[\alpha]_D$ +24.2 (*c* 0.6, $CHCl_3$).

^{1}H NMR (400 MHz): δ = 7.36–7.22 (m, 16 H, Ar, H-5 Tr.), 4.98 and 4.81 (2 d, *J* = 10.8 Hz, 2 H, PhCH_2), 4.90 and 4.73 (2 d, *J* = 10.8 Hz, 2 H, PhCH_2), 4.77 and 4.62 (2 d, *J* = 12.1 Hz, 2 H, PhCH_2), 4.53 (d, $J_{1,2}$ = 3.7 Hz, 1 H, H-1), 4.50 (dd, $J_{5,6a}$ = 3.0 Hz, $J_{6a,6b}$ = 14.3 Hz, 1 H, H-6a), 4.45 (dd, $J_{5,6b}$ = 6.2 Hz, 1 H, H-6b), 4.00 (dd, $J_{2,3}$ = 9.7 Hz, $J_{3,4}$ = 8.9 Hz, 1 H, H-3), 3.95 (ddd, $J_{4,5}$ = 10.0 Hz, 1 H, H-5), 3.42 (dd, 1 H, H-2), 3.18 (s, 3 H, OCH_3), 3.15 (dd, 1 H, H-4), 2.73–2.64 (m, 2 H, CH_2), 1.67–1.58 (m, 2 H, CH_2), 1.36–1.20 (m, 18 H, 9 CH_2), 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3).

^{13}C NMR: δ = 150.4 (C-4 Tr.), 138.4 and 137.9 (C Ar), 129.8, 128.5, 128.2, 128.0, 127.9, 127.7, and 125.6 (CH Ar), 120.1 (C-5 Tr.), 98.0 (C-1), 81.9 (C-3), 79.9 (C-2), 78.0 (C-4), 75.8, 74.9, and 73.4 (Ph*C*H_2), 69.2 (C-5), 55.2 (OCH_3), 50.5 (C-6), 31.9, 29.63, 29.57, 29.4, 29.2, 25.6, and 22.7 (CH_2), 14.1 (CH_3).

HRMS (ESI/Q-TOF): *m/z* [M + H]$^+$ calcd for $C_{42}H_{58}N_3O_5$: 684.4376; found: 684.4391.

Methyl 2,3,4-Tri-*O*-benzyl-6-deoxy-6-[4-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)-1*H*-1,2,3-triazol-1-yl]-α-D-glucopyranoside (14)

The reaction between ethynyl *C*-galactoside **7** (60 mg, 0.11 mmol) and methyl 6-azidoglucopyranoside **2** (49 mg, 0.10 mmol) gave, after column chromatography on silica gel (cyclohexane–EtOAc, 3:1 then 2:1), known[7a] **14** as a solid; yield: 70 mg (68%).

1-(11-Acetamido-3,6,9-trioxaundecyl)-4-phenyl-1*H*-1,2,3-triazole (15)

The reaction between phenylacetylene (**5**; 31 mg, 0.30 mmol) and azide **3** (70 mg, 0.27 mmol) gave, after column chromatography on silica gel (CH_2Cl_2–MeOH, 1:0 → 9:1), **15** as a syrup; yield: 70 mg (72%).

^{1}H NMR (300 MHz): δ = 7.99 (s, 1 H, H-5 Tr.), 7.88–7.84 (m, 2 H, Ar), 7.48–7.42 (m, 2 H, Ar), 7.39–7.33 (m, 1 H, Ar), 6.05 (br s, 1 H, NH), 4.62 (t, *J* = 5.0 Hz, 2 H, CH_2), 3.95 (t, *J* = 5.0 Hz, 2 H, CH_2), 3.70–3.60 (m, 4 H), 3.59–3.54 (m, 4 H), 3.53–3.48 (m, 2 H), 3.44–3.38 (m, 2 H), 1.97 (s, 3 H, CH_3).

^{13}C NMR: δ = 170.3 (CO), 147.5 (C-4 Tr.), 130.5 (C Ar), 128.7, 128.0, and 125.6 (CH Ar), 120.9 (C-5 Tr.), 70.4, 70.3, 70.2, 69.9, 69.7, 69.3, 50.2, and 39.1 (CH_2), 23.0 (CH_3).

HRMS (ESI/Q-TOF): *m/z* [M + H]$^+$ calcd for $C_{18}H_{27}N_4O_4$: 363.2032; found: 363.2038.

1-(11-Acetamido-3,6,9-trioxaundecyl)-4-dodecyl-1*H*-1,2,3-triazole (16)

The reaction between 1-tetradecyne (**6**; 58.3 mg, 0.30 mmol) and azide **3** (70 mg, 0.27 mmol) gave, after column chromatography on silica gel (CH_2Cl_2–MeOH, 1:0 → 9:1), **16** as an amorphous solid; yield: 107 mg (87%).

^{1}H NMR (300 MHz): δ = 7.43 (s, 1 H, H-5 Tr.), 6.21 (br s, 1 H, NH), 4.51 (t, *J* = 5.3 Hz, 2 H, CH_2), 3.89 (t, *J* = 5.3 Hz, 2 H, CH_2), 3.65–3.52 (m, 10 H, 5 CH_2), 3.49–3.42 (m, 2 H, CH_2), 2.71 (t, *J* = 7.8 Hz, 2 H, CH_2), 2.00 (s, 3 H, CH_3CO), 1.72–1.62 (m, 2 H, CH_2), 1.38–1.24 (m, 18 H, 9 CH_2), 0.88 (t, *J* = 6.7 Hz, 3 H, CH_3).

^{13}C NMR: δ = 170.1 (CO), 148.3 (C-4 Tr.), 121.6 (C-5 Tr.), 70.5, 70.4, 70.1, 69.8, 69.6, 50.0, 39.2, 31.9, 29.6, 29.5, 29.4, 29.3, and 25.7 (CH_2), 23.2 (*C*H_3CO), 22.6 (CH_2), 14.1 (CH_3).

HRMS (ESI/Q-TOF): *m/z* [M + H]$^+$ calcd for $C_{24}H_{47}N_4O_4$: 455.3591; found: 455.3597.

1-(11-Acetamido-3,6,9-trioxaundecyl)-4-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)-1*H*-1,2,3-triazole (17)

The reaction between ethynyl *C*-galactoside **7** (77 mg, 0.14 mmol) and azide **3** (34 mg, 0.13 mmol) gave, after column chromatography on silica gel (CH_2Cl_2–MeOH, 1:0 → 9:1), **17** as a syrup; yield: 86 mg (82%).

$[\alpha]_D$ –6.7 (*c* 0.6, $CHCl_3$).

^{1}H NMR (400 MHz): δ = 7.66 (s, 1 H, H-5 Tr.), 7.39–7.25 (m, 15 H, Ar), 7.21–7.18 (m, 3 H, Ar), 7.03–7.00 (m, 2 H, Ar), 4.98 and

4.64 (2 d, J = 11.5 Hz, 2 H, PhCH_2), 4.78 and 4.73 (2 d, J = 11.7 Hz, 2 H, PhCH_2), 4.72 and 4.36 (2 d, J = 10.7 Hz, 2 H, PhCH_2), 4.52 (d, $J_{1,2}$ = 9.6 Hz, 1 H, H-1), 4.48 (t, J = 5.1 Hz, 2 H, CH_2), 4.46 and 4.40 (2 d, J = 11.9 Hz, 2 H, PhCH_2), 4.24 (dd, $J_{2,3}$ = 9.4 Hz, 1 H, H-2), 4.06 (dd, $J_{3,4}$ = 2.7 Hz, $J_{4,5}$ = 0.5 Hz, 1 H, H-4), 3.86–3.79 (m, 2 H, CH_2), 3.73 (dd, 1 H, H-3), 3.73 (dt, $J_{5,6}$ = 6.5 Hz, 1 H, H-5), 3.58 (d, 2 H, 2 H-6), 3.54–3.44 (m, 10 H, 5 CH_2), 3.38–3.34 (m, 2 H, CH_2), 1.90 (s, 3 H, CH_3).

^{13}C NMR: δ = 170.2 (CO), 145.9 (C-4 Tr.), 138.8, 138.3, and 137.8 (C Ar), 128.4, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, and 127.4 (CH Ar), 123.7 (C-5 Tr.), 84.4 (C-3), 78.4 (C-2), 77.4 (C-5), 74.9 (PhCH_2), 74.7 (PhCH_2, C-1), 74.0 (C-4), 73.5 and 72.5 (PhCH_2), 70.5, 70.4, 70.3, 70.1, 69.7, and 69.4 (CH_2), 68.7 (C-6), 50.2 and 39.2 (CH_2), 23.1 (CH_3).

HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{46}H_{57}N_4O_9$: 809.4126; found: 809.4166.

6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-α-D-galactopyranose (18)

The reaction between phenylacetylene (**5**; 22.5 mg, 0.22 mmol) and 6-azidogalactopyranose **4** (57 mg, 0.20 mmol) gave, after column chromatography on silica gel (cyclohexane–EtOAc, 4:1 → 2:1), known[19] **18** as a solid; yield: 74 mg (95%).

6-Deoxy-6-(4-dodecyl-1*H*-1,2,3-triazol-1-yl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (19)

The reaction between 1-tetradecyne (**6**; 43 mg, 0.22 mmol) and 6-azidogalactopyranose **4** (57 mg, 0.20 mmol) gave, after column chromatography on silica gel (cyclohexane–EtOAc, 2:1), **19** as an amorphous solid; yield: 86 mg (90%).

$[\alpha]_D$ –38.0 (c 0.6, $CHCl_3$).

^{1}H NMR (400 MHz): δ = 7.46 (s, 1 H, H-5 Tr.), 5.52 (d, $J_{1,2}$ = 4.9 Hz, 1 H, H-1), 4.63 (dd, $J_{2,3}$ = 2.6 Hz, $J_{3,4}$ = 7.9 Hz, 1 H, H-3), 4.60 (dd, $J_{5,6a}$ = 4.1 Hz, $J_{6a,6b}$ = 14.1 Hz, 1 H, H-6a), 4.40 (dd, $J_{5,6b}$ = 8.1 Hz, 1 H, H-6b), 4.32 (dd, 1 H, H-2), 4.20–4.14 (m, 2 H, H-4, H-5), 2.71 (t, J = 7.7 Hz, 2 H, CH_2), 1.69–1.61 (m, 2 H, CH_2), 1.50, 1.38, 1.36, and 1.29 (4 s, 12 H, 4 CH_3), 1.34–1.22 (m, 18 H, 9 CH_2), 0.87 (t, J = 6.7 Hz, 3 H, CH_3).

^{13}C NMR: δ = 148.5 (C-4 Tr.), 122.3 (C-5 Tr.), 110.0 and 109.3 (OCO), 96.5 (C-1), 71.5 (C-4), 71.0 (C-3), 70.6 (C-2), 67.6 (C-5), 50.8 (C-6), 32.2, 29.9, 29.8, 29.7, 29.6, and 29.4 (CH_2), 26.2 (CH_3), 26.0 (CH_2), 25.1 and 24.6 (CH_3), 22.9 (CH_2), 14.4 (CH_3).

HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{26}H_{46}N_3O_5$: 480.3437; found: 480.3442.

6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-[4-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)-1*H*-1,2,3-triazol-1-yl]-α-D-galactopyranose (20)

The reaction between ethynyl C-galactoside **7** (60 mg, 0.11 mmol) and 6-azidogalactopyranose **4** (29 mg, 0.10 mmol) gave, after column chromatography on silica gel (cyclohexane–EtOAc, 4:1 → 2:1), **20** as an amorphous solid; yield: 74 mg (89%).

$[\alpha]_D$ –26.7 (c 0.6, $CHCl_3$).

^{1}H NMR (400 MHz): δ = 7.66 (s, 1 H, H-5 Tr.), 7.39–7.25 (m, 15 H, Ar), 7.22–7.18 (m, 3 H, Ar), 7.10–7.06 (m, 2 H, Ar), 5.44 (d, $J_{1,2}$ = 5.0 Hz, 1 H, H-1), 5.00 and 4.66 (2 d, J = 11.5 Hz, 2 H, PhCH_2), 4.77 and 4.72 (2 d, J = 11.7 Hz, 2 H, PhCH_2), 4.70 and 4.39 (2 d, J = 10.8 Hz, 2 H, PhCH_2), 4.54 (dd, $J_{5,6a}$ = 5.4 Hz, $J_{6a,6b}$ = 14.2 Hz, 1 H, H-6a), 4.53 (d, $J_{1',2'}$ = 9.7 Hz, 1 H, H-1′), 4.52 (dd, $J_{2,3}$ = 2.7 Hz, $J_{3,4}$ = 7.8 Hz, 1 H, H-3), 4.45 and 4.39 (2 d, J = 12.0 Hz, 2 H, PhCH_2), 4.43 (dd, $J_{5,6b}$ = 7.8 Hz, 1 H, H-6b), 4.30 (dd, $J_{2',3'}$ = 9.8 Hz, 1 H, H-2′), 4.28 (dd, 1 H, H-2), 4.22 (ddd, $J_{4,5}$ = 1.8 Hz, 1 H, H-5), 4.06 (dd, $J_{3',4'}$ = 2.7 Hz, $J_{4',5'}$ = 0.6 Hz, 1 H, H-4′), 4.02 (dd, 1 H, H-4), 3.72 (dd, 1 H, H-3′), 3.72 (ddd, $J_{5',6'a}$ = 6.7 Hz, $J_{5',6'b}$ = 6.3 Hz, 1 H, H-5′), 3.60 (dd, $J_{6'a,6'b}$ = 9.5 Hz, 1 H, H-6′a), 3.58 (dd, 1 H, H-6′b), 1.48, 1.36, 1.27, and 1.23 (4 s, 12 H, 4 CH_3).

^{13}C NMR: δ = 145.7 (C-4 Tr.), 138.9, 138.4, and 137.9 (C Ar), 128.4, 128.15, 128.07, 128.0, 127.7, 127.5, and 127.4 (CH Ar), 124.0 (C-5 Tr.), 109.7 and 109.0 (OCO), 96.2 (C-1), 84.5 (C-3′), 78.6 (C-2′), 77.4 (C-5′), 75.0 (PhCH_2), 74.5 (PhCH_2, C-1′), 74.0 (C-4′), 73.5 and 72.5 (PhCH_2), 70.9 (C-4), 70.7 (C-3), 70.3 (C-2), 68.7 (C-6′), 66.9 (C-5), 50.1 (C-6), 26.0, 25.9, 24.8, and 24.4 (CH_3).

HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{48}H_{56}N_3O_{10}$: 834.3966; found: 834.3970.

5,11,17,23-Tetrakis[3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propyl]-25,26,27,28-tetrapropoxycalix[4]arene (22)

The reaction between phenylacetylene (**5**; 20.4 mg, 0.20 mmol) and tetraazidocalixarene **21** (46 mg, 0.05 mmol) gave, after column chromatography on silica gel (acetone), **22** as an amorphous solid; yield: 54 mg (81%).

^{1}H NMR (300 MHz): δ = 7.78–7.74 (m, 8 H, Ar), 7.75 (s, 4 H, 4 H-5 Tr.), 7.39–7.27 (m, 12 H, Ar), 6.51 (s, 8 H, Ar), 4.42 and 3.09 (2 d, J = 13.1 Hz, 8 H, 4 ArCH_2Ar), 4.18 (t, J = 7.1 Hz, 8 H, 4 Ar$CH_2CH_2CH_2$), 3.82 (t, J = 7.5 Hz, 8 H, 4 $CH_3CH_2CH_2O$), 2.29 (t, J = 7.2 Hz, 8 H, 4 Ar$CH_2CH_2CH_2$), 2.06–1.90 (m, 16 H, 4 Ar$CH_2CH_2CH_2$, 4 $CH_3CH_2CH_2O$), 1.00 (t, J = 7.5 Hz, 12 H, 4 $CH_3CH_2CH_2O$).

^{13}C NMR: δ = 154.8 (C Ar), 147.3 (C-4 Tr.), 134.8, 133.3, and 130.6 (C Ar), 128.8, 128.1, 128.0, and 125.5 (CH Ar), 120.0 (C-5 Tr.), 76.8 ($CH_3CH_2CH_2O$), 49.4 (Ar$CH_2CH_2CH_2$), 31.9 and 31.7 (Ar$CH_2CH_2CH_2$, Ar$CH_2CH_2CH_2$), 30.8 (ArCH_2Ar), 23.2 ($CH_3CH_2CH_2O$), 10.3 ($CH_3CH_2CH_2O$).

HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{84}H_{93}N_{12}O_4$: 1333.7443; found: 1333.7405.

5,11,17,23-Tetrakis[3-(4-dodecyl-1*H*-1,2,3-triazol-1-yl)propyl]-25,26,27,28-tetrapropoxycalix[4]arene (23)

The reaction between 1-tetradecyne (**6**; 39 mg, 0.20 mmol) and tetraazidocalixarene **21** (46 mg, 0.05 mmol) gave, after column chromatography on silica gel (EtOAc–cyclohexane, 1:1 → 1:0), **23** as amorphous solid; yield: 64 mg (75%).

^{1}H NMR (300 MHz): δ = 7.29 (s, 4 H, 4 H-5 Tr.), 6.47 (s, 8 H, Ar), 4.41 and 3.08 (2 d, J = 13.1 Hz, 8 H, 4 ArCH_2Ar), 4.18 (t, J = 7.2 Hz, 8 H, 4 Ar$CH_2CH_2CH_2$), 3.82 (t, J = 7.5 Hz, 8 H, 4 $CH_3CH_2CH_2O$), 2.68 (t, J = 7.8 Hz, 8 H, 4 CH_2), 2.30 (t, J = 7.2 Hz, 8 H, 4 Ar$CH_2CH_2CH_2$), 2.06–1.88 (m, 16 H, 4 Ar$CH_2CH_2CH_2$, 4 $CH_3CH_2CH_2O$), 1.75–1.60 (m, 8 H, 4 CH_2), 1.40–1.20 (m, 72 H), 1.00 (t, J = 7.3 Hz, 12 H, 4 $CH_3CH_2CH_2O$), 0.90 (t, J = 6.6 Hz, 12 H, 4 CH_3).

^{13}C NMR: δ = 154.9 (C Ar), 148.3 (C-4 Tr.), 134.8 and 133.3 (C Ar), 128.0 (CH Ar), 120.7 (C-5 Tr.), 76.8 ($CH_3CH_2CH_2O$), 49.3 (Ar$CH_2CH_2CH_2$), 31.9, 30.9, 29.7, 29.6, 29.4, 29.3, 25.8, 23.2, and 22.7 (CH_2), 14.1 (CH_3), 10.3 ($CH_3CH_2CH_2O$).

HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{108}H_{173}N_{12}O_4$: 1702.3703; found: 1702.3801.

25,26,27,28-Tetrapropoxy-5,11,17,23-tetrakis{3-[4-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)-1*H*-1,2,3-triazol-1-yl]propyl}calix[4]arene (24)

The reaction between ethynyl C-galactoside **7** (72 mg, 0.13 mmol) and tetraazidocalixarene **21** (30 mg, 0.03 mmol) gave, after column chromatography on silica gel (cyclohexane–EtOAc, 3:1 → 2:1), known[7b] **24** as a syrup; yield: 75 mg (74%).

1-(1-Adamantyl)-4-dodecyl-1*H*-1,2,3-triazole (26)

The reaction between 1-tetradecyne (**6**; 72 mg, 0.37 mmol) and 1-adamantyl azide (**25**; 60 mg, 0.34 mmol) gave, after column chro-

matography on silica gel (cyclohexane–EtOAc, 15:1 → 5:1), **26** as a syrup in 57% (using toluene, containing DIPEA) and 62% (using IL **8**) yield.

^{1}H NMR (300 MHz): δ = 7.34 (s, 1 H, H-5 Tr.), 2.72 (t, *J* = 7.7 Hz, 2 H, CH_2), 2.30–2.22 (m, 9 H), 1.86–1.76 (m, 6 H), 1.72–1.62 (m, 2 H, CH_2), 1.40–1.24 (m, 18 H), 0.90 (t, *J* = 6.7 Hz, 3 H, CH_3).

^{13}C NMR: δ = 147.5 (C-4 Tr.), 116.8 (C-5 Tr.), 59.1 (C), 43.0, 36.0, 31.9 (CH_2), 29.64 and 29.56 (CH_2), 29.46 (CH), 29.3, 25.9, and 22.7 (CH_2), 14.1 (CH_3).

HRMS (ESI/Q-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{42}N_3$: 372.3379; found: 372.3370.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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