DOI: 10.1002/ejoc.200900779

An Efficient (2-Aminoarenethiolato)copper(I) Complex for the Copper-Catalysed Huisgen Reaction (CuAAC)

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Keywords: Azides / Alkynes / Click chemistry / Cycloaddition / Dendrimers / N ligands

A (2-aminoarenethiolato)copper(I) complex has been used as an efficient catalyst (1 mol-%) for the copper-catalysed Huisgen reaction (CuAAC) of azides and terminal alkynes in an organic solvent. The reaction was also extremely effective in CH_2Cl_2 allowing the complete decoration of dendrimeric scaffolds.

Introduction

The Huisgen reaction, the 1,3-dipolar cycloaddition of azides to terminal alkynes, has probably become one of the most frequently used reactions in organic chemistry, especially after the development by Sharpless and Fokin of a copper-catalysed version (CuAAC).[1] This reaction was the first of a restricted group of reactions generally known by the term "click chemistry".[2] The efficiency of this reaction is demonstrated by the huge number of applications in supramolecular chemistry,[3] peptidomimetics,[4] dendrimer synthesis,[5] bioconjugation, polymer and materials synthesis[6,7] and many other fields.[8]

Such a wide variety of applications requires the reaction to be performed under many different conditions, for example, organic and aqueous solvents, and heterogeneous conditions. Despite this variety of reaction conditions a very limited set of catalysts are available. The use of Cu^{II} salts with a sacrificial reducing agent such as sodium ascorbate is the most common procedure: sodium ascorbate provides the Cu^{I} ions that are needed for the catalytic reaction.[1,9] However, even a copper wire can afford the required Cu^{I} ions by comproportionation of Cu^{II} and Cu^{0}. Simple Cu^{I} salts have also been used, but the thermodynamic instability of Cu^{I} can lead to oxidation to catalytically inactive Cu^{II}. The use of ligands such as tris(1-benzyltriazol-4-ylmethyl)-amine (TBTA)[10] or sulfonated bathophenanthroline[11] improves the rate and efficiency of more delicate reactions. The limited solubility of cuprous salts in organic solvents restricts the choice to soluble preformed coordination complexes of Cu^{I}, for example, under these circumstances $[Cu(PPh_3)_3]Br$[12] and $(EtO)_3PCuI$[13] are the catalysts of choice. The availability of new Cu^{I} complexes, which have been shown to be active in other reactions, allows the efficiency of these compounds to be tested in another useful reaction.

In this work we report the results obtained by using the (aminoarenethiolato)copper(I) complex **1**[14] (Figure 1) as a catalyst in the 1,3-dipolar cycloaddition of azides to terminal alkynes. In (aminoarenethiolato)copper(I) complexes, the copper(I) cation is bonded to a monoanionic, potentially *S*,*N*-bidentate-coordinating 2-aminoarenethiolate ligand. These complexes show excellent solubility in a range of useful solvents. They exist, both in the solid state and in solution, as aggregate species, for example, as dimers, trimers, tetramers or nonamers,[15] and exhibit good thermal stability. In addition, electronic and physical properties can easily be fine-tuned by introducing substituents onto the arene ring or the amino functionality. These (aminoarenethiolato)copper(I) complexes have already been tested as catalysts in allylic substitution,[16] 1,4-[17] and 1,6-addition[18] reactions and aromatic *N*-arylation reactions[19] and have shown good catalytic properties.

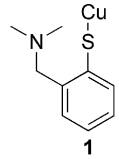

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Figure 1. {[2-(Dimethylamino)methyl]thiophenolato}copper(I) (**1**).

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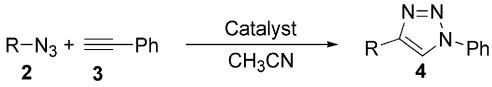
Results and Discussion

As a preliminary test we studied the reaction of phenylacetylene (**3**) with three different azides **2**: an alkyl, a benzyl and an aryl azide. The results are reported in Table 1.

Table 1. Cycloaddition reactions of phenylacetylene (**3**) and diverse azides with two copper catalysts.



R	Yield[a] [%] $CuSO_4$ (5)/Na ascorbate (10)[b]	**1** (1)[c]
C_8H_{17}[d]	quantitative[e]	quantitative[e]
Bn[d]	76	91
Ph	88	81

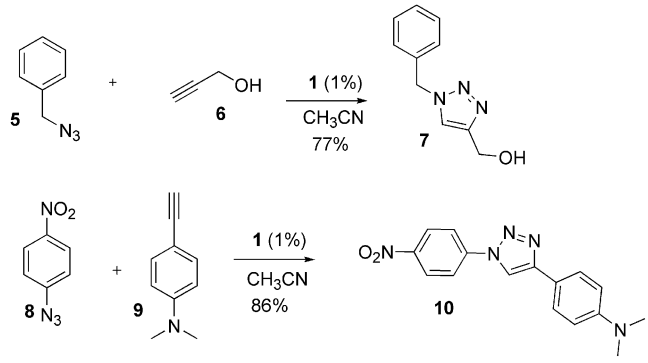
[a] Yield after isolation (column chromatography). [b] Acetonitrile/water (10:1), 1.1 equiv. azide, 18 h, room temp. [c] Dry acetonitrile, 1.1 equiv. azide, 18 h, room temp. [d] See ref.[20]. [e] Conversion determined by ^1H NMR spectroscopy.

As shown in Table 1, catalyst **1** is active at a low concentration (1 mol-%) and requires no addition of a tertiary amine. The purification of the crude reaction mixtures is straightforward because the small amount of catalyst is removed simply by filtration through a short pad of silica gel. In comparison with the $CuSO_4$/Na ascorbate couple, the results obtained with catalyst **1** are at least comparable or better. For the $CuSO_4$/Na ascorbate couple we preferred not to compare the yields with those reported in the literature, but rather with experimental results obtained in our laboratory to make a more reliable comparison. Although the catalyst **1** is somewhat sensitive to atmospheric oxygen, it was not necessary to work under an inert atmosphere. Thus, the reactions were performed in sealed vials with no special precautions.

Two other reactions were examined, varying both the azide and the alkyne (Scheme 1). Again the catalyst was revealed to be extremely efficient, affording high yields of the products, which were purified by filtration through a short pad of silica gel (**7**) or by simple vacuum filtration (**10**). The use of acetonitrile as the solvent was initially dictated by the in situ formation of the starting aromatic azides, for example, the azide **8**, which was obtained from 4-nitroaniline.[21]

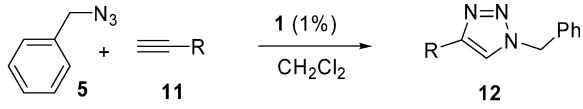
The choice of solvent is, however, important: for example, whereas no reaction was observed in water, dichloromethane was found to be a good solvent, as demonstrated by the results reported in Table 2.

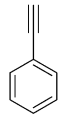
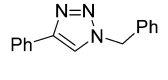
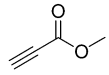
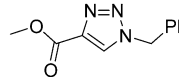
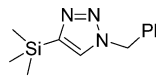
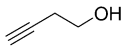
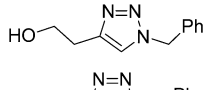
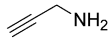
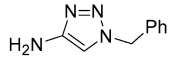
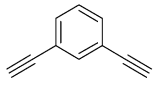
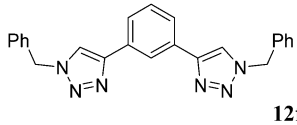
The new reactions performed in CH_2Cl_2 were found to be efficient and afforded simple compounds in high yields. The use of CH_2Cl_2 or acetonitrile appears to be equivalent for these simple reactions, but it is rather fundamental in the case of more complex substrates.



Scheme 1.

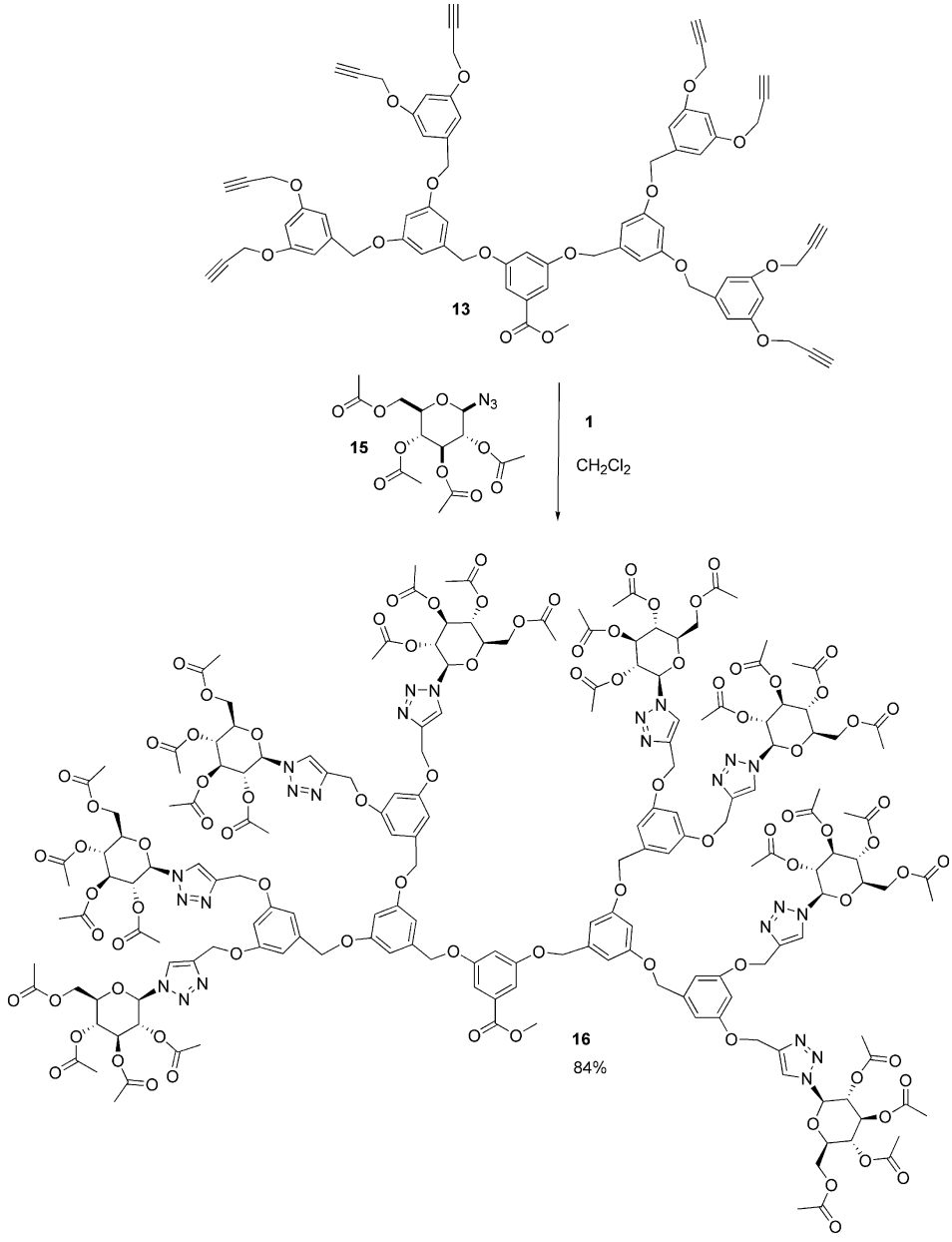
Table 2. Cycloaddition reactions of benzyl azide (**5**) with several dipolarophiles.



Entry	Alkyne	Yield[a]	
1		91%[b]	 **12a**
2		93%[b]	 **12b**
3		82%[b]	 **12c**
4		24%[b]	 **12d**
5		>95%[b,c]	 **12e**
6		90%[d]	 **12f**

[a] Isolated yield after column chromatography. [b] Dichloromethane, 1.1 equiv. benzyl azide, 1 equiv. alkyne, 1 mol-% catalyst **1**. [c] Isolated as the hydrochloride. [d] Dichloromethane, 2.2 equiv. benzyl azide, 1 equiv. alkyne, 2 mol-% catalyst **1** (1 mol-% with respect to reaction sites).

The real breakthrough offered by the introduction of click chemistry is the possibility of functionalizing complex systems in a single, simple step. This challenge is provided by the possibility of decorating dendrimers with a high number of peripheral substituents. Therefore we tested the efficiency of catalyst **1** in the reactions of dendrons **13**[22,23] and **14** with the commercial sugar derivative **15** (Schemes 2 and 3).



Scheme 2.

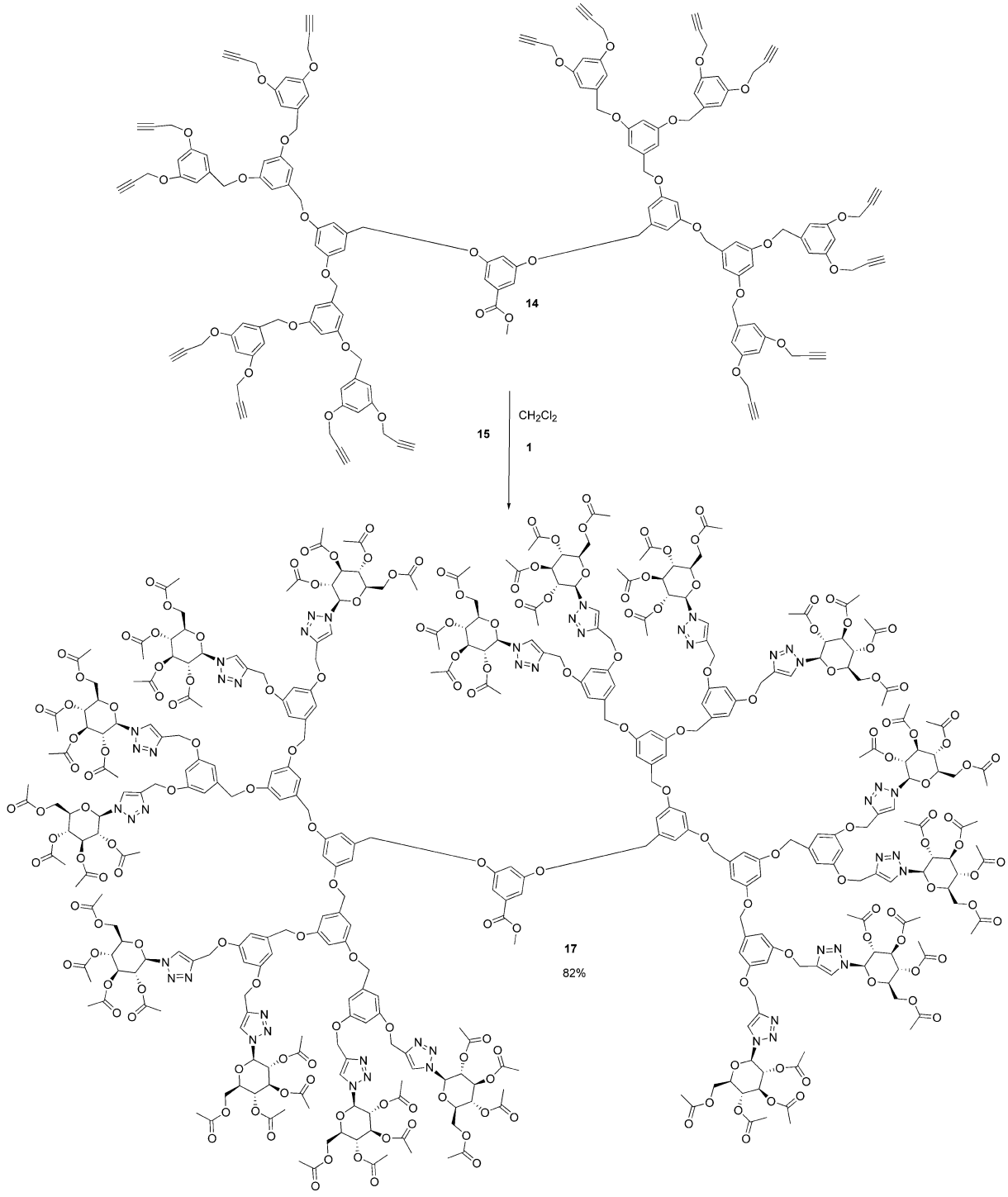
The reaction performed in CH_3CN was not efficient and only the use of 10 mol-% (per triple bond) of catalyst **1** induced the disappearance of the starting materials. Although in the reaction performed in CH_3CN, ^1H NMR signals at δ = 8.5 ppm suggested the presence of more than one compound, the spectrum of the crude mixture derived from the reaction in CH_2Cl_2 showed a single sharp signal for the 8 equiv. triazolic protons (Figure 2).

The use of 1 mol-% of catalyst **1** (with respect to the azide counterpart) in CH_2Cl_2 afforded compounds **16** and **17** in 84 and 82% yields, respectively. The reactions were performed at room temp. in 18 h without the need of MW irradiation. In both cases the ^1H NMR spectra confirmed the monodipersion of the compounds through a proper integration of signals (see Figure 3).

This result appears to be particularly significant compared with the outcome obtained from the use of the $CuSO_4$/Na ascorbate catalyst with the same reagents, which in a CH_3CN/water mixture afforded no products.

Unfortunately this efficient catalyst was not able to catalyse the 1,3-dipolar cycloaddition reactions of benzyl azide with internal alkynes either at room temperature or at 60 °C or under MW irradiation.[24]

Finally, to complete this preliminary survey of the application of this class of catalyst we performed a kinetic resolution[25] of a racemic (1-azidoethyl)benzene by using a chi-



Scheme 3.

ral and enantiopure analogue of compound **1**, that is, compound **18** bearing a methyl group on the benzylic position (Figure 4). Despite varying the solvent, reagent ratio and temperature, no significant *ee*s were obtained in the different attempts. It is likely that the simple chiral environment of **18** is unable to differentiate the two reaction paths. Other studies with more complex substrates are necessary to explore the scope of this catalyst.

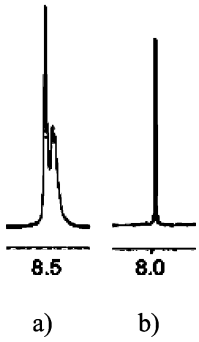


Figure 2. Signals of the triazolic protons of the crude reaction mixtures of **16** obtained in a) CH_3CN (^1H NMR in [D_6]DMSO) and b) CH_2Cl_2 (^1H NMR in $CDCl_3$).

Conclusions

Compound **1** has been shown to be an efficient and general catalyst for the copper-catalysed Huisgen reaction (CuAAC) reaction, affording good yields of the cycloaddition products, and has also been found to be very useful in more challenging cases, for example, in the complete decoration of dendrimeric structures. Dichloromethane was the solvent of choice for this reaction, although CH_3CN also afforded good results. The long term stability and efficiency of compound **1** make it a useful and practical alternative to other commercially available copper(I) complexes.

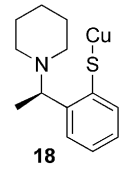


Figure 4. Structure of the enantiopure compound **18**.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded with a Varian Mercury 400 (^1H: 400 MHz) or Gemini 200 (^1H: 200 MHz; ^{13}C: 50 MHz) spectrometer with tetramethylsilane as the internal reference. The chemical shifts (δ) and coupling constants (J) are expressed in ppm and hertz, respectively. IR spectra were recorded with a Perkin–Elmer 881 FT-IR spectrophotometer as KBr pellets. Merck silica gel (0.040–0.063 mm) and MP EcoChrom silica gel (32–63, 60 Å) were used for flash chromatography. TLC was performed on Merck silica gel 60 F_{254} plates. Elemental analyses were performed with a Perkin–Elmer 240 C,H,N Analyzer. Mass spectra were recorded with a Carlo Erba QMD 1000 spectrometer for EI–MS (70 eV), with a Thermo LTQ spectrometer for ESI–MS and with a Bruker Ultraflex III TOF/TOF spectrometer for MALDI MS. [α] values were measured with a Jasco DIP 370 instrument. Gas chromatographic analysis of chiral mixtures were performed with a Shimadzu-GC2014 instrument equipped with a Shimadzu AOC-20i auto-sampler (isothermal 95 °C; Supelco β-DEX 120 chiral column 30 m × 0.25 mm i.d., d_f = 0.25 μ). All commercially available reagents and solvents were purchased from Sigma Aldrich

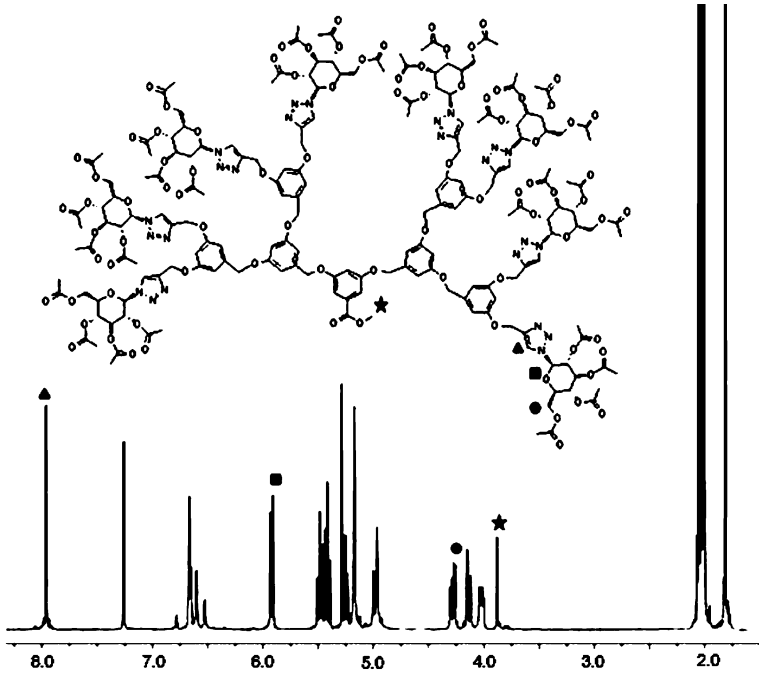


Figure 3. ^1H NMR spectrum (400 MHz, $CDCl_3$) of compound **16** (diagnostic signals and their assignments are shown).

and used as received unless otherwise specified. Azide **15** was purchased from Acros Organics. For the synthesis of catalyst **1** see ref.[14], for catalyst **18** see ref.[26] for the synthesis of the ligand; the copper complex was obtained by following the same procedure for the synthesis of **1**. Products whose characterizations are not reported here have previously been synthesized and characterization data has been reported in the literature.[27] For the synthesis and characterization of **13** see ref.[22,23] for the general procedures for the synthesis of acetylenic dendrimers.

Safety Warning: Azides are potentially explosive. Maximum care must be taken especially when manipulating large-scale reactions.

General Procedure for the Copper(I)-Catalysed Huisgen Reaction (Azide/Alkyne Cycloaddition: CuAAC)

Aminoarenethiolate Catalyst: The alkyne (1 equiv.) and azide (1.1 equiv.) were dissolved in the solvent (acetonitrile or dichloromethane, 2 mL per 100 mg of azide). The catalyst **1** (0.01 equiv.) was added and the suspension was stirred for 18 h at room temp. The solvent was evaporated to dryness and the crude product purified by column chromatography on silica eluting with CH_2Cl_2 or CH_2Cl_2/CH_3OH, 20:1 (for more polar products).

Na Ascorbate/$CuSO_4$: The alkyne (1 equiv.) and azide (1.1 equiv.) were dissolved in acetonitrile (2 mL per 100 mg of azide) and $CuSO_4$ (1 M solution in water, 0.05% equiv.) was added. Sodium ascorbate (0.1 equiv.) was dissolved in acetonitrile (0.2 mL) and added to the solution. This mixture was stirred at room temp. for 18 h, evaporated to dryness and purified by column chromatography on silica.

***N*,*N*-Dimethyl-4-[1-(4-nitrophenyl)-1*H*–1,2,3-triazol-4-yl]aniline (10):** 1-Azido-4-nitrobenzene was generated in situ from 4-nitroaniline following a procedure reported previously:[21] 4-nitroaniline (0.73 mmol, 0.1 g, 1.1 equiv.) was dissolved in dry acetonitrile (5 mL) and cooled to 0 °C. *tert*-Butyl nitrite was added (0.99 mmol, 0.102 g, 117 μL, 1.5 equiv.) followed by trimethylsilyl azide (0.79 mmol, 0.091 g, 104 μL, 1.2 equiv.) dropwise. This solution was stirred at room temp. for 2 h. Then 4-ethynyl-*N*,*N*-dimethylaniline (0.66 mmol, 0.096 g, 1 equiv.) dissolved in the minimum quantity of acetonitrile was added, followed by catalyst **1** (6.6×10^{-3} mmol, 1.5 mg, 0.01 equiv.). The reaction was stirred at room temp. for 18 h. The resulting suspension was filtered and the insoluble solid was washed with CH_2Cl_2 (2 mL), petroleum ether (10 mL) and diethyl ether (10 mL). A brown waxy solid (0.177 g, 86) was obtained. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.28 (s, 1 H, triazole), 8.46 (d, J = 9.2 Hz, 2 H, aromatic ring), 8.23 (d, J = 9.2 Hz, 2 H, aromatic ring), 7.5 (d, J = 8.8 Hz, 2 H, aromatic ring), 6.81 (d, J = 8.8 Hz, 2 H, aromatic ring), 2.94 (s, 6 H, NMe_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 150.1 (s), 149.0 (s), 146.9 (s), 139.8 (s), 126.8 (d, triazole), 126.1 (d, 2 C), 120.6 (d, 2 C), 118.2 (d, 2 C), 117.8 (s), 112.8 (d, 2 C), 41.3 (q, NMe_2) ppm. IR (KBr): $\tilde{\nu}$ = 3105 (m), 3083 (m), 2964 (w), 2921 (w), 2857 (w), 2803 (w), 1621 (m), 1594 (m), 1518 (s), 1502 (s), 1405 (m), 1341 (s), 1223 (m), 1035 (m), 860 (m), 857 (m), 825 (m), 804 (m), 750 (m), 690 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 309.1 (28.1) [M]$^+$, 281.2 (49.5), 268 (21.3), 237.1 (100), 235 (57.3), 161.1 (50.5), 159.1 (45.4), 158 (39), 143.1 (16.7), 132.1(12.4), 125.8 (17.1), 117 (57.3), 113.1 (19.1), 112.1 (29.7), 103.5 (29.2), 99.1 (70.9), 98.1 (25.8), 91.1 (52.9), 57.1 (44.3), 56.1 (61.8), 55.1 (81.3). $C_{16}H_{15}N_5O_2$ (309.32): calcd. C 62.13, H 4.89, N 22.64; found C 62.22, H 4.93, N 22.70.

1,3-Bis(1-benzyl-1*H*-1,2,3-triazol-4-yl)benzene (12f): Benzyl azide (0.1 g, 0.75 mmol, 2.2 equiv.), 1,3 diethynylbenzene (0.043 g, 0.34 mmol, 1.0 equiv.) and catalyst **1** (3.2 mg, 0.0068 mmol, 0.02 equiv., 1% molar ratio to triple bonds) were dissolved in dichloromethane (2 mL) and stirred for 18 h. The solvent was evaporated to dryness and the crude product purified by column chromatography on silica starting elution with CH_2Cl_2 then increasing the polarity to CH_2Cl_2/MeOH (20:1) to afford a white glass (0.120 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1 H, central aromatic ring), 7.77 (d, J = 7.6 Hz, 2 H, central aromatic ring), 7.72 (s, 2 H, triazole), 7.44–7.35 (m, 7 H, aromatic rings), 7.32–7.28 (m, 4 H, aromatic rings), 5.51 (s, 4 H, CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 147.4 (s, 2 C, triazole), 134.2 (s, 2 C), 130.7 (s, 2 C), 129.0 (d, 2 C, triazole), 128.8 (d, 1 C), 128.5 (d, 4 C), 127.8 (d, 4 C), 125.0 (d, 2 C), 122.4 (d, 2 C), 119.6 (d, 1 C), 54.0 (t, 2 C, CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3105 (m), 3083 (m), 3029 (m), 2943 (s), 1610 (m), 1588 (w), 1497 (s), 1454 (s), 1438 (m), 1411 (m), 1411 (w), 1352 (w), 1342 (m), 1223 (m), 1212 (m), 1083 (m), 1072 (m), 1051 (s), 1029 (m), 1002 (m), 970 (w), 884 (w), 836 (w), 803 (s), 793 (s), 750 (m), 723 (s), 707 (s), 691 (s) 583 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 392.2 (14) [M]$^+$, 363.3 (12), 335.2 (13), 273.2 (52.3), 245.2 (21.3), 217. 2 (8), 154 (20.3), 127.1 (7.4), 91.1 (100), 65.1 (18). $C_{24}H_{20}N_6$ (392.46): calcd. C 73.45, H 5.14, N 21.41; found C 73.21, H 5.30, N 21.51.

Acet$_{16}$-G4-COOCH$_3$ (14): Acet$_8$-G3-Br[22,23] (0.1 g, 0.079 mmol 1 equiv.), methyl 3,5-dihydroxybenzoate (0.0066 g, 0.0395 mmol, 0.5 equiv.), K_2CO_3 (0.065 g, 0.474 mmol, 6 equiv.) and 18-crown-6 (5 mg) were suspended in acetone (10 mL). The mixture was heated at reflux under nitrogen for 48 h then evaporated to dryness and partitioned between water and dichloromethane. The organic layer was dried with Na_2SO_4, evaporated and purified by column chromatography on silica eluting with chloroform, then increasing the polarity to chloroform/diethyl ether (20:1). A waxy solid (0.094 g, 94%) was obtained. ^{1}H NMR (400 MHz,$CDCl_3$): δ = 7.27 (d, J = 4 Hz, 2 H, central aromatic ring), 6.77 (t, J = 4 Hz, 1 H, central aromatic ring), 6.69–6.59 (m, 28 H), 6.58–6.49 (m, 14 H), 5.02–4.92 (m, 28 H, CH_2), 4.63 (d, J = 2.4 Hz, 32 H, CH_2), 3.87 (s, 3 H, CH_3), 2.49 (t, J = 2.4 Hz, 16 H, alkynyl protons) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.9 (s, C=O), 159.8 (s, 16 C), 159.2 (s, 8 C), 158.7 (s, 6 C), 139.3 (s, 12 C), 139.1 (s, 2 C), 132 (s), 106.8 (d, 2 C), 106.5 (d, 28 C), 101.8 (d, 15 C), 78.4 (s, 16 C, alkynyl group), 75.9 (d, 16 C, alkynyl group), 69.8 (t, 14 C, CH_2), 56.0 (t, 16 C, CH_2), 51.2 (q, CH_3) ppm. MS (ESI): *m*/*z* (%) = 2523.7 (88) [M + K]$^+$, 2507.8 (65) [M + Na]$^+$, 1217.8 (32), 861.4 (36), 773.5 (50), 757.64 (94), 713.55 (100). $C_{154}H_{124}O_{32}$ (2486.61): calcd. C 74.38, H 5.03; found C 74.22, H 5.01.

Glu$_8$-G3-COOCH$_3$ (16): 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide (**15**; 0.1 g, 0.268 mmol, 8.8 equiv.), the dendritic core **13** (0.036 g, 0.03 mmol, 1 equiv.) and catalyst **1** (5.5×10^{-4} g, 0.0024 mmol, 0.08 equiv., 1% molar ratio to triple bonds) were added to dichloromethane (2 mL) and the mixture was stirred for 18 h. The mixture was evaporated and the crude product purified on a silica column eluting with dichloromethane/methanol (40:1) to yield the product (0.126 g, 84%). The same reaction performed in acetonitrile led to a mixture of products (see Results and Discussion). $[\alpha]_D^{25}$ = –56.1 (*c* = 0.25, chloroform). ^{1}H NMR (400 MHz,$CDCl_3$): δ = 7.96 (s, 8 H, triazole), 7.27 (d, J = 2.0 Hz, 2 H, central aromatic ring), 6.78 (t, J = 2.0 Hz, 1 H, central aromatic ring), 6.67 (d, J = 2.4 Hz, 8 H), 6.65 (d, J = 2.0 Hz, 4 H), 6.60 (t, J = 2.4 Hz, 4 H), 6.52 (d, J = 2.0 Hz, 2 H), 5.92 (d, J = 9.2 Hz, 8 H), 5.48 (t, J = 9.2 Hz, 8 H), 5.42 (t, J = 9.2 Hz, 8 H), 5.26 (t, J = 9.2 Hz, 8 H), 5.17 (s, 16 H, CH_2), 5.00 (s, 4 H, CH_2), 4.97 (s, 8 H, CH_2), 4.28 (dd, J = 12.4, 4.8 Hz, 8 H, diastereotopic, Glu-CH_2-OAc), 4.13 (dd, J = 12.4, 2.0 Hz, 8 H, diastereotopic, Glu-CH_2-OAc), 4.02 (ddd, J = 9.2, 4.8, 2.0 Hz, 8 H), 3.88 (s, 3 H,

CH_3), 2.05 (s, 24 H, CH_3), 2.03 (s, 24 H, CH_3), 2.01 (s, 24 H, CH_3), 1.81 (s, 24 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 169.9, 169.4, 168.9, 166.7, 160, 159.7, 159.5, 144.6, 139.6, 139, 132, 121.5, 108.5, 107.1, 106.7, 106.5, 101.6, 101.2, 87.9, 85.7, 77.2, 75.1, 72.7, 70.3, 69.7, 67.7, 61.8, 61.5, 52.2 ppm. IR (KBr): $\tilde{\nu}$ = 3183 (w), 3107 (w), 2951 (m), 2909 (m), 2844 (w), 2121 (w), 1756 (s), 1597 (s), 1456 (m), 1371 (s), 1253 (s), 1227 (s), 1151 (m), 1101 (m), 1029 (s), 921 (m), 815 (br), 683 (w), 596 (m) cm^{-1}. MS (MALDI-TOF): calcd. 4189.285; found 4189.263. $C_{186}H_{212}N_{24}O_{88}$ (4191.78): calcd. C 53.29, H 5.10, N 8.02; found C 53.21, H 5.09, N 8.00.

Glu_{16}-G4-$COOCH_3$ (17): The procedure used for the synthesis of **16** was followed using the following quantities: 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (**16**; 0.1 g, 0.268 mmol, 18 equiv.), acetylenic core **14** (0.037 g, 0.0149 mmol, 1 equiv.), catalyst **1** (5.5×10^{-4} g, 0.00238 mmol, 0.16 equiv., 1% ratio to triple bonds) and dichloromethane (2 mL). Column chromatography on silica with dichloromethane/methanol (40:1) gave the product (0.103 g, 82%). $[a]_D^{26}$ = –36.6 (*c* = 1, chloroform). ^1H NMR (400 MHz,$CDCl_3$): δ = 7.99 (s, 16 H, triazole), 7.25 (m, 2 H, central aromatic ring), 6.79 (br. t, 1 H, central aromatic ring), 6.70–6.44 (m, 42 H), 5.92 (d, *J* = 9.2 Hz, 16 H), 5.49 (t, *J* = 9.2 Hz, 16 H), 5.41 (t, *J* = 9.2 Hz, 16 H), 5.26 (t, *J* = 9.2 Hz, 16 H), 5.14 (s, 32 H, CH_2-O), 5.04–4.88 (m, 28 H, CH_2-O), 4.27 (dd, *J* = 12.8, 4.8 Hz, 16 H diastereotopic, Glu-CH_2-OAc), 4.12 (br. d, *J* = 12.8 Hz, 16 H, diastereotopic, Glu-CH_2-OAc), 4.07–3.98 (m, 16 H), 3.85 (s, 3 H, CH_3), 2.05 (s, 48 H, CH_3), 2.03 (s, 48 H, CH_3), 2.01 (s, 48 H, CH_3), 1.81 (s, 48 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 169.9, 169.4, 168.8, 160.1, 159.9, 159.4, 144.6, 139.6, 121.7, 106.7, 106.5, 101.2, 85.6, 77.2, 75, 72.7, 70.3, 69.7, 67.7, 61.8, 61.5, 56, 20.6, 20.5, 20.48, 20 ppm. IR (KBr): $\tilde{\nu}$ = 3184 (w), 3105 (w), 2954 (m), 2911 (m), 2846 (w), 2120 (w), 1755 (s), 1595 (s), 1459 (m), 1373 (s), 1255 (s), 1228 (br s), 1153 (m), 1099 (m), 1034 (br s), 922 (m), 814 (b), 680 (w), 594 (m) cm^{-1}. MS (MALDI-TOF): calcd. 8454.602; found 8453.243. $C_{378}H_{428}N_{48}O_{176}$ (8459.66): calcd. C 53.67, H 5.10, N 7.95; found C 53.51, H 5.08, N 7.92.

Kinetic Resolution Studies: (1-Azidoethyl)benzene was synthesized following the method reported in the literature[28] starting from the racemic alcohol; it was then treated[25] with phenylacetylene and catalyst **18** (1 mol-%) in three different solvents (2 mL of solvent per 100 mg azide). A thermostatted bath was used to achieve a constant temperature (–12 °C). All the reactions gave quantitative yields; the disappearance of phenylacetylene was determined by NMR and TLC of the reaction mixtures. After the reaction, the residual azide was isolated and recovered by column chromatography on silica, eluting with hexane/ethyl acetate (10:1). A sample was analysed by GC on a Supelco chiral column to determine the enantiomeric excess.

Acknowledgments

Funding from the Italian Ministero dell'Università e della Ricerca – Fondo Investimenti per la Ricerca di Base (FIRB) (FIRB 2004, "Molecular compounds and hybrid nanostructured materials with resonant and non-resonant optical properties for photonic devices", contract no. RBNE033KMA) and from the European Community (contract no. RIII-CT-2003-506350) is acknowledged. Mrs. Brunella Innocenti and Mr. Maurizio Passaponti are acknowledged for technical assistance.

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Received: July 13, 2009
Published Online: September 21, 2009

