‘Click’ Synthesis of Nonsymmetrical 4,4′-Bis(1,2,3-triazolium) Salts

Jesus M. Aizpurua,*[a] Maialen Sagartzazu-Aizpurua,[a] Itxaso Azcune,[a] José I. Miranda,[a] Zaira Monasterio,[a] Eva García-Lecina,[b] Raluca M. Fratila[c]

[a] Departamento de Química Orgánica-I, Universidad del País Vasco UPV/EHU, Joxe Mari Korta R&D Center, Avda Tolosa-72, 20018 San Sebastián, Spain
Fax +34(943)015959; E-mail: jesusmaria.aizpurua@ehu.es

[b] Departamento de Tratamientos de Superficie, CIDETEC-ik4, Paseo Miramón-196, 20009 San Sebastián, Spain

[c] Faculty of Science and Technology, SupraMolecular Chemistry & Technology (SMCT), University of Twente, 7500 AE Enschede, The Netherlands

Received 5 March 2011

Abstract: Nonsymmetrically substituted 4,4′-bis(1,2,3-triazolium) salts were prepared in a totally site-specific manner by copper(I)-catalyzed ‘click’ [2+3] cycloaddition of 3-alkyl-4-ethynyl-1,2,3-triazolium salts with alkyl and aryl azides. Competition experiments demonstrated that triazolium alkynes were more reactive than their triazole counterparts in CuAAC reactions, especially with aromatic azides. The N-alkylation site integrity was maintained in all the triazolium salts prepared.

Key words: alkylation, catalysis, cycloaddition, heterocycles, 1,2,3-triazolium salts

Interest in 3-alkyl-1,2,3-triazolium salts **1** (Figure 1) has increased dramatically during recent years, and this has paralleled the improved preparation of 1,4-disubstituted 1,2,3-triazoles using copper(I)-catalyzed alkyne–azide ‘click’ cycloaddition reactions (CuAAC).[1] Among various promising applications, triazolium salts **1** have been proposed as ionic liquids,[2] catalysts for asymmetric synthesis,[3] switch elements for nanomachines,[4] and as precursors of mesoionic carbene ligands.[5]

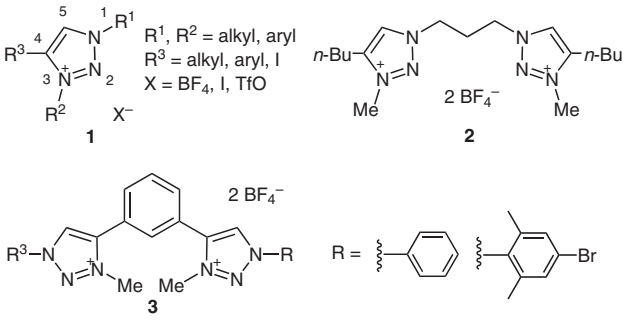
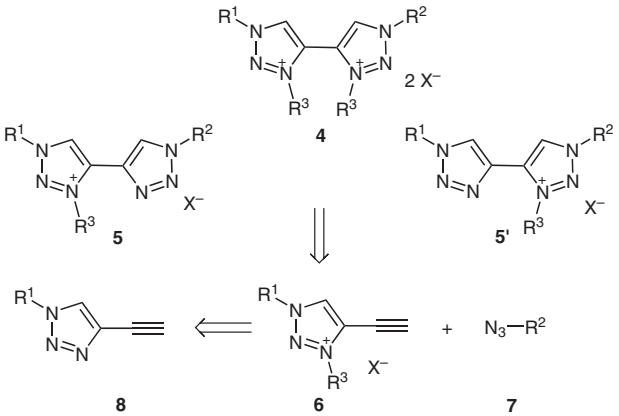


Figure 1 1,2,3-Triazolium salts **1** and symmetrically substituted bis(1,2,3-triazolium) salts **2** and **3**

Owing to their pincer-type nature, poly-triazolium molecules are particularly suited for metal cation chelation or for supramolecular polydentate interactions. Developing this concept, Liebscher[6] has recently reported the preparation of the first bis(1,2,3-triazolium) salt **2**, incorporating a propylidene bridge between the 1,1′-nitrogen atoms. Similarly, Schubert[7] has demonstrated the proton-donating ability of the bis(1,2,3-triazolium) salts **3**, tethered at the 4,4′ positions with an aromatic ring, towards sulfate anions. In both instances, however, the substitution pattern of the triazolium heterocycles was limited to symmetrical groups.

With the exception of a single example of chemoselective N-monomethylation of a bis-triazole of type **3**,[7] to the best of our knowledge, no general method exists to prepare mixed substituted bis(triazolium) salts.

During the course of our investigation on the synthesis of 1,2,3-triazole-scaffolded glycopeptide hybrids,[8] we became interested in the preparation of nonsymmetrically substituted 4,4′-bis(1,2,3-triazoles).[9,10] A logical extension of the work was the synthesis of the unprecedented bis(1,2,3-triazolium) salts **4** and their corresponding mono-N-alkylated counterparts **5** and **5′** (Scheme 1). Herein, we disclose our results on the synthesis of such compounds from the key 3-alkyl-5-ethynyl-1,2,3-triazolinium salts **6** and different azides, using CuAAC chemistry.

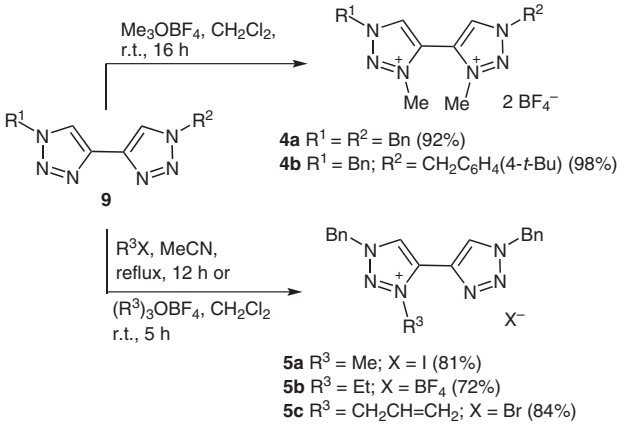


Scheme 1 Retrosynthetic analysis of mixed N-alkylated 4,4′-bis(1,2,3-triazolium) salts **4** and **5**

We first screened a range of alkylating reagents for the N-alkylation of 4,4′-bis(1,2,3-triazoles) **9**, which were readily prepared following reported procedures.[10] In line with previous observations[7] (Scheme 2, top), trimethyloxoni-

SYNTHESIS 2011, No. 17, pp 2737–2742
Advanced online publication: 09.06.2011
DOI: 10.1055/s-0030-1260061; Art ID: C25211SS

um tetrafluoroborate (Meerwein's salt) proved to be a very powerful reagent, affording N,N′-dimethylated 4,4′-bis(triazolium) salts **4** in good isolated yields. The reactions were completely regioselective and only 3,3′-dialkylated compounds were observed, despite some reports outlining the possible formation of regioisomeric 2- and 3-alkyl triazolium salts from monocyclic 1,2,3-triazoles.[11] Owing to their strongly polar nature, these dicationic salts were insoluble in dichloromethane and acetonitrile solvents, but were soluble in methanol, and a single precipitation of the crude products from mixtures of these solvents was sufficient for purification.



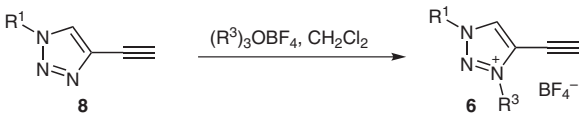
Scheme 2 N-Alkylation of symmetrical bis(1,2,3-triazoles)

Because of the extended π-conjugation of the 4,4′-bis(1,2,3-triazole) system, it was anticipated that 3N-alkylation of one of the heterocyclic rings could strongly decrease the electron density at the 3N′-position of the contiguous ring, thus rendering the chemoselective mono-N-alkylation of 4,4′-bis(1,2,3-triazoles) feasible in a clean manner. Indeed, this effect was observed (Scheme 2, bottom) when Meerwein's methyl salt was replaced by either the less electrophilic methyl iodide or the more sterically demanding reagents triethyloxonium tetrafluoroborate and allyl bromide. Accordingly, mono-N-alkylated triazolium-triazole derivatives **5a–c** were obtained in a single operation without the need for separation steps. Furthermore, quantitative counter-anion exchange from iodide or bromide to tetrafluoroborate for **5a** and **5c** could be performed by treatment with silver tetrafluoroborate in methanol.[2b]

After successful monoalkylation of symmetrically 1,1′-disubstituted 4,4′-bis(triazoles) **5**, the preparation of non-symmetrically 1,1′-disubstituted analogs was addressed following a two-operation procedure starting from 4-ethynyl-1,2,3-triazoles **8**.[10] First, 3-alkyl-4-ethynyl-1,2,3-triazolium tetrafluoroborates **6** were prepared (Table 1), then 'clicked' with azides to provide the target mixed triazolium-triazole salts **5** (Table 2).

N-Alkylation of 4-ethynyl-1,2,3-triazoles **8a–d** to give tetrafluroborates **6** occurred uneventfully upon reaction with Meerwein's salt reagents (Table 1), and the reaction

Table 1 N-Alkylation of 4-Ethynyl(1,2,3-triazoles) **8**

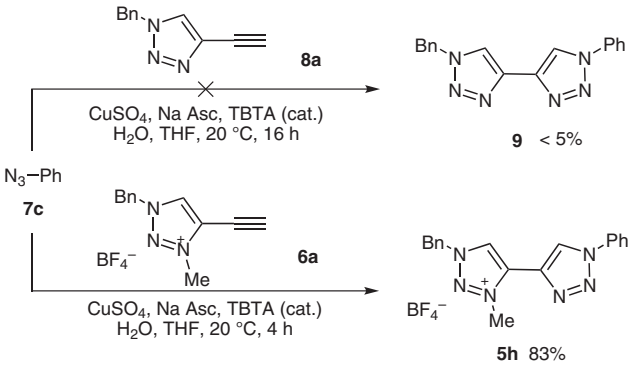


Entry	R^1	R^3	Triazole[a]	Product	Yield (%)[b]
1	Bn	Me	**8a**	**6a**	77
2	Bn	Et	**8a**	**6b**	72
3	4-*t*-BuC$_6$H$_4$CH$_2$	Me	**8b**	**6c**	80
4	4-NCC$_6$H$_4$	Me	**8c**	**6d**	72
5	4-NCC$_6$H$_4$	Et	**8c**	**6e**	78

[a] Prepared as described by Aizpurua et al.[10]
[b] Isolated pure product.

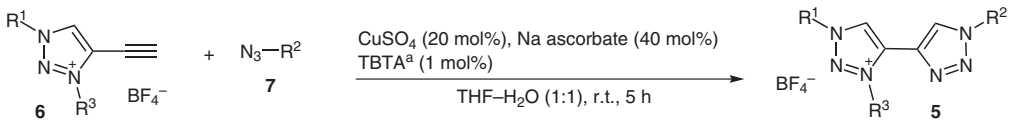
was tolerant of some additional functional groups (e.g., nitrile). The reactivity of 4-ethynyl-3-alkyl-1,2,3-triazolinium salts **6** towards different azides **7** was then assessed under several CuAAC conditions (Table 2). Either the base-free copper(I) tetrakis(acetonitrile) catalyst (entry 1), the stoichiometric copper(I) iodide/*N*,*N*-diisopropylethylamine system (entry 2) or the Sharpless' copper(II) sulfate/sodium ascorbate catalyst (entry 3) demonstrated similar efficiency in promoting the cycloaddition reactions at room temperature. Because of its low load in copper metal and more convenient operational conditions, we selected the latter procedure as the method of choice to carry out the transformation. The reaction was effective both for aliphatic (entries 1–6) and aromatic azides (entry 7), and it was tolerant of α-amino acids and sugar residues (entries 8 and 9).

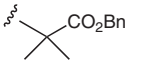
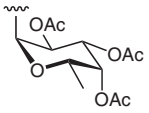
The reactivity observed for aromatic azides deserves some comment. As previously noted by us[10] and others,[11,12] electron-rich heterocyclic alkynes often fail to react or give poor yields with aromatic or electron-deficient azides (see Scheme 3, transformation **8a** → **9**). As outlined above, N-alkylation of 4-ethynyl-1,2,3-triazoles to generate the triazolium analogs (**6a**) greatly increased the alkyne CuAAC reactivity, likely because of the activating effect of the conjugated electron-deficient triazolium moi-



Scheme 3 CuAAC reactivity of 4-ethynyl-1,2,3-triazole **8a** and its N-methylated salt **6a** towards phenyl azide **7c**

Table 2 Copper(I)-Catalyzed Cycloaddition of 4-Ethynyl-(1,2,3-triazoles) **6** with Azides

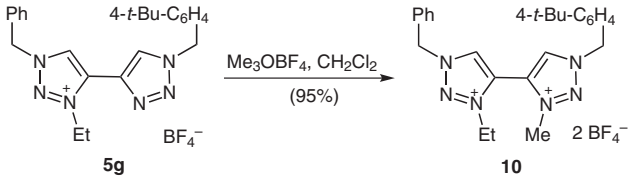


Entry	R^1	R^2	R^3	**7**	Cu(I) catalyst; conditions[a]	**5**	Yield (%)[b]
1	Bn	Bn	Me	**7a**	$Cu(MeCN)_4PF_6$ (5 mol%), MeCN, 50 °C, 16 h	**5d**	92
2	Bn	Bn	Me	**7a**	CuI (1.2 equiv), DIPEA (1.2 equiv), MeCN, r.t., 5 h	**5d**	78
3	Bn	Bn	Me	**7a**	$CuSO_4$, Na Asc, TBTA	**5d**	95
4	4-*t*-$BuC_6H_4CH_2$	Bn	Me	**7a**	$CuSO_4$, Na Asc, TBTA	**5e**	88
5	Bn	$CH_2C_6H_4$-*t*-Bu	Me	**7b**	$CuSO_4$, Na Asc, TBTA	**5f**	93
6	Bn	$CH_2C_6H_4$-*t*-Bu	Et	**7b**	$CuSO_4$, Na Asc, TBTA	**5g**	75
7	Bn	Ph	Me	**7c**	$CuSO_4$, Na Asc, TBTA	**5h**	83
8	4-NCC_6H_4		Me	**7d**	$CuSO_4$, Na Asc, TBTA	**5i**	80
9	4-NCC_6H_4		Et	**7e**	$CuSO_4$, Na Asc, TBTA	**5j**	70

[a] Na Asc: sodium ascorbate; TBTA: tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine.
[b] Isolated yield after chromatography.

ety on the alkyne group. This result is currently being development further in our laboratory to achieve an alkyne-chemoselective[13] click reaction from triazolium diynes.

Finally, the synthetic versatility and full structural control of the method was illustrated by the synthesis of the bis(1,2,3-triazolium) salt **10**, containing four different substituents at 1,1′- and 3,3′-positions (Scheme 4). The dicationic product **10** was readily prepared in 95% isolated yield after treatment of the bis(1,2,3-triazoline) monocation **5g** with two equivalents of trimethyloxonium tetrafluoroborate in dichloromethane. This result clearly indicates that our approach can generate a much larger chemical diversity of triazolium compounds than other existing methods.



Scheme 4 Synthesis of a bis(1,2,3-triazolium) salt carrying four different substituents

In summary, it has been shown that 1,1′-unsymmetrically substituted 4,4′-bis(1,2,3-triazolium) salts can be obtained through click chemistry. Key steps of this protocol were the copper(I)-catalyzed [3+2] cycloaddition of 3-alkyl-4-ethynyl-1,2,3-triazolium salts with azides and the N-alkylation of the resulting triazoles with trialkyloxonium tetrafluoroborates, alkyl iodides, or alkyl bromides. The former reaction is compatible with multifunctional aliphatic and/or aromatic azides to produce 1,2,3-triazolium/1,2,3-triazole mixed bis-heterocyclic compounds. It has also been found that the method permits the site-controlled N-alkylation of bis(1,2,3-triazole) at the 3,3′-positions to provide both symmetrically and nonsymmetrically quaternized bis(1,2,3-triazolium) salts. Experiments are underway in our laboratories to establish the suitability for carbene-formation of the novel bis-triazolium salts.

All reactions were carried out under an atmosphere of nitrogen in oven- or flame-dried glassware with magnetic stirring. Solvents were distilled prior to use. MeCN and CH_2Cl_2 were distilled from calcium hydride. MeOH was dried over magnesium metal and iodine. Purification of reaction products was carried out by flash chromatography using silica gel 60 (230–400 mesh, from Merck 60F PF254). Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60-F plates. Melting points were measured with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded with a Shimadzu IR-435 spectrophotometer using neat samples. ^1H and ^{13}C NMR spectra were recorded with Bruker Avance DPX300 and Bruker Avance500 spectrometers and are reported as δ values (ppm) relative to residual $CHCl_3$ (^1H NMR: δ = 7.26 ppm) and $CDCl_3$ (^{13}C NMR: δ = 77.16 ppm) as internal standards, respectively. Mass spectra were obtained with an Agilent HP 5973 mass spectrometer using a TOF analyzer (GCT Micromass). Compounds **8a–c**, **9a**, **9b**, **7d**, and **7e** were prepared as previously described.[10]

Synthesis of 1,2,3-Triazolium Tetrafluoroborates 4, 5b, 6, and 10; General Procedure

The corresponding bis(1,2,3-triazole) **9** (0.25 mmol), 4-ethynyl-(1,2,3-triazole) (0.50 mmol), or 1,2,3-triazolium tetrafluoroborate salt **5g** (0.50 mmol) was added under nitrogen to a solution of the corresponding trialkyloxonium tetrafluoroborate (0.60 mmol) in anhydrous CH_2Cl_2 (5 mL), and the mixture was stirred at r.t. for 5 h. The volatiles were evaporated in vacuo, the residue was redissolved in anhydrous MeOH (5 mL), and the resulting mixture was stirred overnight at r.t. and evaporated. The crude product was purified by precipitation from Et_2O or by column chromatography (silica gel; CH_2Cl_2–MeOH, 9:1).

1,1′-Dibenzyl-3,3′-dimethyl-4,4′-bis(1*H*-1,2,3-triazol)-3,3′-diium Ditetrafluoroborate (4a)

Yield: 92%; white crystals; mp 243–244 °C (MeOH–CH_2Cl_2).

IR: 3396, 3121, 2495, 1454 (triazole), 1034 (BF_4) cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 9.47 (s, 2 H), 7.65–7.41 (m, 10 H), 6.04 (s, 4 H), 4.33 (s, 6 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 133.5, 133.1, 130.0, 129.7, 129.6, 127.5, 57.3, 39.9.

HRMS (ESI+): *m*/*z* $[M]^{2+}$ calcd for $C_{20}H_{22}N_6^{2+}$: 346.1895; found: 346.1897.

1-Benzyl-1′-(4-*tert*-butylbenzyl)-3,3′-dimethyl-4,4′-bis(1*H*-1,2,3-triazol)-3,3′-diium Ditetrafluoroborate (4b)

Yield: 98%; white crystals; mp 229–231 °C (MeOH–CH_2Cl_2).

IR: 3140, 2968, 1739, 1455 (triazole), 1035 (BF_4) cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 9.47 (s, 2 H), 7.66–7.42 (m, 9 H), 6.03 (s, 2 H), 5.98 (s, 2 H), 4.32 (d, *J* = 2.6 Hz, 6 H), 1.28 (s, 9 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 152.2, 132.9, 132.8, 132.6, 129.7, 129.5, 129.1, 129.0, 127.0, 127.0, 125.9, 56.7, 56.5, 34.5, 30.9, 30.7.

HRMS (ESI+): *m*/*z* $[M]^{2+}$ calcd for $C_{24}H_{30}N_6^{2+}$: 402.2521; found: 402.2517.

1,1′-Dibenzyl-3-ethyl-4,4′-bis(1*H*-1,2,3-triazol)-3-ium Tetrafluoroborate (5b)

Yield: 72%; white crystals; mp 108–109 °C (CH_2Cl_2).

IR: 3136, 1629, 1498, 1457 (triazole), 1029 (BF_4) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.02 (s, 1 H), 8.69 (s, 1 H), 7.56–7.30 (m, 10 H), 5.73 (s, 2 H), 5.57 (s, 2 H), 5.02 (q, *J* = 7.2 Hz, 2 H), 1.67 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, CD_3CN): δ = 134.8, 134.3, 131.7, 131.7, 129.8, 129.3, 129.1, 128.8, 128.4, 127.7, 126.2, 117.3, 57.3, 54.1, 49.3, 13.4.

HRMS (ESI+): *m*/*z* $[M]^+$ calcd for $C_{20}H_{21}N_6^+$: 345.1822; found: 345.1824.

1-Benzyl-4-ethynyl-3-methyl-1*H*-1,2,3-triazol-3-ium Tetrafluoroborate (6a)

Yield: 77%; white solid; mp 99–102 °C (CH_2Cl_2).

IR: 3237 (≡C–H), 3150, 3110, 2130 (C≡C), 1568, 1497, 1449 (triazole), 1026.1 (BF_4) cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 8.96 (s, 1 H), 7.50 (m, 5 H), 5.84 (s, 2 H), 4.97 (s, 1 H), 4.35 (s, 3 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 133.7, 133.0, 130.9, 130.4, 127.9, 95.8, 65.4, 58.8, 39.3.

HRMS (ESI+): *m*/*z* $[M]^+$ calcd for $C_{12}H_{12}N_3^+$: 198.1026; found: 198.1030.

1-Benzyl-3-ethyl-4-ethynyl-1*H*-1,2,3-triazol-3-ium Tetrafluoroborate (6b)

Yield: 72%; oil.

IR: 3244 (≡C–H), 3151, 3105, 2136 (C≡C), 1738, 1564, 1457 (triazole), 1030 (BF_4) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.60 (s, 1 H), 7.45 (ddd, *J* = 67.7, 5.6, 3.2 Hz, 5 H), 5.74 (s, 2 H), 4.60 (q, *J* = 7.3 Hz, 2 H), 4.26 (s, 1 H), 1.60 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 132.6, 131.0, 130.0, 129.8, 129.5, 125.3, 94.7, 64.1, 58.0, 48.6, 13.8.

1-(4-*tert*-Butylbenzyl)-4-ethynyl-3-methyl-1*H*-1,2,3-triazol-3-ium Tetrafluoroborate (6c)

Yield: 80%; colorless crystals; mp 119–121 °C (CH_2Cl_2).

IR (KBr): 3405 (≡C–H), 2961, 1463 (triazole), 1030 (BF_4) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.59 (s, 1 H), 7.46 (d, *J* = 8.0 Hz, 2 H), 7.40 (d, *J* = 8.1 Hz, 2 H), 5.70 (s, 2 H), 4.27 (s, 3 H), 1.27 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.3, 132.2, 129.6, 128.1, 126.4, 126.3, 94.9, 64.3, 57.7, 38.9, 34.8, 31.2.

HRMS (ESI+): *m*/*z* $[M]^+$ calcd for $C_{16}H_{20}N_3^+$: 254.1652; found: 254.1646.

1-(4-Cyanophenyl)-4-ethynyl-3-methyl-1*H*-1,2,3-triazol-3-ium Tetrafluoroborate (6d)

Yield: 72%; white crystals; mp 196–198 °C (CH_2Cl_2).

IR: 3237 (≡C–H), 3151, 3112, 2926, 2237 (C≡N), 2135 (C≡C), 1729, 1606, 1569, 1445 (triazole), 1035 (BF_4) cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 10.04 (s, 1 H), 8.30 (d, *J* = 8.8 Hz, 2 H), 8.21 (d, *J* = 8.8 Hz, 2 H), 4.46 (s, 3 H), 3.28 (s, 1 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 137.7, 134.3, 131.3, 127.4, 122.7, 116.7, 115.7, 95.3, 63.8, 38.5.

1-(4-Cyanophenyl)-3-ethyl-4-ethynyl-1*H*-1,2,3-triazol-3-ium Tetrafluoroborate (6e)

Yield: 78%; white solid; mp 153–156 °C (CH_2Cl_2).

IR: 3239 (≡C–H), 3159, 3113, 2231 (C≡N), 2137 (C≡C), 1737, 1603, 1565, 1436 (triazole), 1035 (BF_4) cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 10.05 (s, 1 H), 8.34–8.20 (m, 4 H), 4.83 (q, *J* = 7.3 Hz, 2 H), 2.09 (s, 1 H), 1.65 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 137.5, 134.7, 132.3, 127.5, 122.5, 117.5, 114.5, 97.1, 64.7, 48.7, 13.3.

1-Benzyl-1′-(4-*tert*-butylbenzyl)-3-ethyl-3′-methyl-4,4′-bis(1*H*-1,2,3-triazol)-3,3′-diium Ditetrafluoroborate (10)

Yield: 95%; white crystals; mp 130 °C (dec).

IR: 3570, 2968, 1738, 1458 (triazole), 1026 (BF_4) cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 9.44 (s, 1 H), 9.40 (s, 1 H), 7.59–7.45 (m, 9 H), 6.04 (s, 2 H), 5.97 (s, 2 H), 4.63 (q, *J* = 7.2 Hz, 2 H), 4.31 (s, 3 H), 1.56 (t, *J* = 7.2 Hz, 3 H), 1.28 (s, 9 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 152.1, 133.1, 132.9, 132.4, 129.6, 129.4, 129.1, 129.0, 126.6, 126.4, 125.9, 56.8, 56.5, 48.3, 39.8, 34.4, 30.9, 13.1.

HRMS (ESI+): *m*/*z* $[M]^{2+}$ calcd for $C_{25}H_{32}N_6^{2+}$: 416.2677; found: 416.2670.

Synthesis of 1,2,3-Triazolium Salts 5a and 5c

A solution of the corresponding bis(1,2,3-triazole) **9** (0.2 mmol) and alkyl halide (2 mmol) in anhydrous MeCN (5 mL) was heated to re-

flux for 12 h. The volatiles were removed under reduced pressure and the crude product was purified by precipitation with Et_2O or by column chromatography (silica gel; CH_2Cl_2–MeOH, 9:1).

1,1′-Dibenzyl-3-methyl-4,4′-bis(1*H*-1,2,3-triazol)-3-ium Iodide (5a)
Yield: 81%; white crystals; mp 140–142 °C (CH_2Cl_2/MeOH).

IR: 3436 (≡C–H), 3034, 1629, 1454 (triazole) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 10.07 (s, 1 H), 9.26 (s, 1 H), 7.66–7.25 (m, 10 H), 5.90 (s, 2 H), 5.61 (s, 2 H), 4.57 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 134.3, 133.5, 131.3, 130.8, 129.9, 129.5, 129.3, 129.0, 128.9, 128.8, 128.3, 127.2, 57.7, 54.5, 40.9.

HRMS (ESI+): *m*/*z* $[M-I]^+$ calcd for $C_{19}H_{19}N_6^+$: 331.1666; found: 331.1657.

3-Allyl-1,1′-dibenzyl-3-methyl-4,4′-bis(1*H*-1,2,3-triazol)-3-ium Bromide (5c)
Yield: 84%; oil.

IR: 3403 (≡C–H), 3033, 2188, 1625 (C=C), 1456 (triazole) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 10.60 (s, 1 H), 9.41 (s, 1 H), 7.68–7.21 (m, 9 H), 6.04 (ddt, *J* = 16.5, 10.2, 6.2 Hz, 1 H), 5.94 (s, 2 H), 5.63 (d, *J* = 6.2 Hz, 2 H), 5.61 (s, 2 H), 5.42–5.35 (m, 2 H), 5.27 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 133.7, 133.5, 131.6, 131.1, 129.9, 129.6, 129.4, 129.3, 129.0, 128.8, 128.3, 128.1, 127.6, 122.8, 57.7, 55.7, 54.5.

4-(1,2,3-Triazol-4-yl)-(3-methyl-1,2,3-triazol-3-ium) Tetrafluoroborates 5; General Procedure
To a solution of the corresponding 4-ethynyl-3-alkyl-1*H*-1,2,3-triazol-3-ium tetrafluroborate **6** (0.20 mmol), azide **7** (0.22 mmol) and TBTA (0.002 mmol) in *t*-BuOH–THF (1:1, 2 mL) kept under a nitrogen atmosphere, was added a deoxygenated aqueous solution (1 mL) containing sodium ascorbate (0.08 mmol) and $CuSO_4·H_2O$ (0.04 mmol). The homogeneous solution was stirred for 4–5 h, then the organic solvents were evaporated under reduced pressure and aqueous 10% ammonia (3 mL) was added and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic phases were dried (Na_2SO_4) and the product was purified by column chromatography (silica gel; CH_2Cl_2–MeOH, 9:1).

1,1′-Dibenzyl-3-methyl-4,4′-bis(1*H*-1,2,3-triazol)-3-ium Tetrafluoroborate (5d)
Yield: 95%; oil.

IR: 3136, 1456 (triazole), 1029 (BF_4) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.00 (s, 1 H), 8.67 (s, 1 H), 7.55–7.30 (m, 9 H), 5.71 (s, 2 H), 5.55 (d, *J* = 13.5 Hz, 2 H), 4.55 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 134.7, 133.7, 131.7, 131.0, 130.1, 129.5, 129.5, 129.1, 128.9, 128.4, 128.2, 126.8, 57.9, 54.6, 40.5.

1′-Benzyl-1-(4-*tert*-butylbenzyl)-3-methyl-4,4′-bis(1*H*-1,2,3-triazol)-3-ium Tetrafluoroborate (5e)
Yield: 88%; white crystals; mp 137–139 °C (Et_2O).

IR: 2961, 1738, 1455 (triazole), 1032 (BF_4) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.90 (s, 1 H), 8.65 (s, 1 H), 7.61–7.22 (m, 9 H), 5.67 (s, 2 H), 5.54 (s, 2 H), 4.47 (s, 3 H), 1.30 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.3, 134.6, 133.9, 131.8, 129.2, 129.1, 128.9, 128.6, 128.4, 128.3, 127.2, 126.4, 57.5, 54.5, 40.4, 34.7, 31.1.

HRMS (ESI+): *m*/*z* $[M]^+$ calcd for $C_{23}H_{27}N_6^+$: 387.2292; found: 387.2294.

1-Benzyl-1′-(4-*tert*-butylbenzyl)-3-methyl-4,4′-bis(1*H*-1,2,3-triazol)-3-ium Tetrafluoroborate (5f)
Yield: 93%; white foam; mp 45–48 °C (Et_2O).

IR: 3135, 2962, 1458 (triazole), 1046 (BF_4) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.98 (s, 1 H), 8.66 (s, 1 H), 7.57–7.25 (m, 9 H), 5.73 (s, 2 H), 5.55 (s, 2 H), 4.56 (s, 3 H), 1.28 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.1, 134.8, 131.7, 131.1, 130.8, 130.1, 129.5, 128.2, 128.2, 126.7, 126.1, 57.9, 54.4, 40.5, 34.6, 31.2.

1-Benzyl-1′-(4-*tert*-butylbenzyl)-3-ethyl-4,4′-bis(1*H*-1,2,3-triazol)-3-ium Tetrafluoroborate (5g)
Yield: 75%; oil.

IR: 3136, 2963, 1738, 1458 (triazole), 1047 (BF_4) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.07 (s, 1 H), 8.70 (s, 1 H), 7.59–7.24 (m, 9 H), 5.57 (s, 2 H), 5.32 (s, 2 H), 5.05 (q, *J* = 7.3Hz, 2 H), 1.68 (t, *J* = 7.3 Hz, 3 H), 1.30 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.1, 134.0, 131.7, 131.1, 130.7, 130.0, 129.5, 129.4, 128.3, 128.2, 126.8, 126.1, 57.9, 54.4, 49.5, 34.8, 31.1, 14.4.

1-Benzyl-3-methyl-1′-phenyl-4,4′-bis(1*H*-1,2,3-triazol)-3-ium Tetrafluoroborate (5h)
Yield: 83%; white crystals; mp 183–185 °C (CH_2Cl_2–MeOH).

IR: 3163, 3128, 1644, 1595, 1457 (triazole), 1022 (BF_4) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.33 (s, 1 H), 9.24 (s, 1 H), 7.91–7.81 (m, 2 H), 7.64–7.44 (m, 7 H), 5.78 (s, 2 H), 4.69 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.9, 134.6, 132.2, 130.8, 130.3, 130.0, 129.8, 129.7, 129.5, 128.9, 125.0, 120.6, 58.2, 40.7.

HRMS (ESI+): *m*/*z* $[M]^+$ calcd for $C_{18}H_{17}N_6^+$: 317.1509; found: 317.1513.

1′-[1-(Benzyloxycarbonyl)isopropyl]-1-(4-cyanophenyl)-3-methyl-4,4′-bis(1*H*-1,2,3-triazol)-3-ium Tetrafluoroborate (5i)
Yield: 80%; white crystals; mp 205–208 °C (CH_2Cl_2–MeOH).

IR: 3013, 2970, 2230 (C≡N), 1737 (C=O), 1457 (triazole), 1042 (BF_4) cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 10.16 (s, 1 H), 9.26 (s, 1 H), 8.31 (s, 4 H), 7.46–7.23 (m, 5 H), 5.23 (s, 2 H), 4.64 (s, 3 H), 2.09 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.5, 137.5, 135.5, 135.3, 134.7, 131.0, 128.5, 128.3, 127.6, 127.0, 125.5, 122.3, 117.5, 114.4, 67.4, 65.4, 30.7, 25.0.

3-Ethyl-1-(4-cyanophenyl)-1′-(2,3,4-tri-*O*-acetyl-α-L-fucosyl)-4,4′-bis(1*H*-1,2,3-triazol)-3-ium Tetrafluoroborate (5j)
Yield: 70%; white crystals; mp 190–192 °C (CH_2Cl_2); $[\alpha]_D^{20}$ –50.5 (*c* 0.10, CH_2Cl_2).

IR: 3137, 2991, 2235 (C≡N), 1744 (C=O), 1371 (triazole), 1215, 1061 (BF_4) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.61 (s, 1 H), 8.88 (s, 1 H), 8.22 (d, *J* = 8.9 Hz, 2 H), 7.95 (d, *J* = 8.8 Hz, 2 H), 6.40 (d, *J* = 5.9 Hz, 1 H), 6.10 (dd, *J* = 10.9, 3.4 Hz, 1 H), 5.67 (dd, *J* = 11.0, 5.9 Hz, 1 H), 5.55 (d, *J* = 2.9 Hz, 1 H), 5.32 (s, 1 H), 5.24 (q, *J* = 7.3 Hz, 2 H), 4.69 (q, *J* = 6.3 Hz, 1 H), 2.28 (s, 3 H), 2.06–2.01 (m, 3 H), 1.91 (s, 3 H), 1.85 (t, *J* = 7.3 Hz, 3 H), 1.25–1.19 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.5, 170.3, 169.8, 137.4, 134.4, 131.8, 130.5, 130.1, 127.2, 122.3, 116.9, 116.0, 83.6, 70.5, 69.9, 68.0, 65.9, 50.6, 20.7, 20.6, 20.2, 16.1, 14.6.

Acknowledgment

This work was supported by the Ministerio de Ciencia e Innovación (MICINN, Spain) (Project: CTQ2010–21625-C02–01), UPV/EHU and Gobierno Vasco (ETORTEK-inanoGUNE IE-09/243). Grants from Gobierno Vasco to M.S.-A and I.A. are acknowledged. We thank SGIker UPV/EHU for NMR facilities.

References

(1) (a) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596. (c) Meldal, M.; Tornoe, C. W. *Chem. Rev.* **2008**, *108*, 2952.

(2) (a) Hanelt, S.; Liebscher, J. *Synlett* **2008**, 1058. (b) Khan, S. S.; Hanelt, S.; Liebscher, J. *ARKIVOC* **2009**, *(xii)*, 193. (c) Jeong, Y.; Ryu, J.-S. *J. Org. Chem.* **2010**, *75*, 4183. (d) Fletcher, J. T.; Keeney, M. E.; Walz, S. E. *Synthesis* **2010**, 3339. (e) Nakamura, T.; Ogata, K.; Fukuzawa, S.-I. *Chem. Lett.* **2010**, *39*, 920. (f) Yacob, Z.; Shah, J.; Leistner, J.; Liebscher, J. *Synlett* **2008**, 2342. (g) Shah, J.; Khan, S. S.; Blumenthal, H.; Liebscher, J. *Synthesis* **2009**, 3975.

(3) Khan, S. S.; Shah, J.; Liebscher, J. *Tetrahedron* **2010**, *66*, 5082.

(4) (a) Coutrot, F.; Busseron, E. *Chem. Eur. J.* **2008**, *14*, 4784. (b) Jiang, Y.; Guo, J.-B.; Chen, C.-F. *Org. Lett.* **2010**, *12*, 4248. (c) Kilah, N. L.; Wise, M. D.; Serpell, C. J.; Thompson, A. L.; White, N. G.; Christensen, K. E.; Beer, P. D. *J. Am. Chem. Soc.* **2010**, *132*, 11893.

(5) (a) Mathew, P.; Neels, A.; Albrecht, M. *J. Am. Chem. Soc.* **2008**, *130*, 13534. (b) Guisado-Barrios, G.; Bouffard, J.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 4759. (c) Lalrempuia, R.; McDaniel, N. D.; Müller-Bunz, H.; Bernhard, S.; Albrecht, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 9765. (d) Kilpin, K. J.; Paul, U. S. D.; Lee, A.-L.; Crowley, J. D. *Chem. Commun.* **2011**, *47*, 328. (e) Prades, A.; Peris, E.; Albrecht, M. *Organometallics* **2011**, *30*, 1162. (f) Poulain, A.; Canseco-Gonzalez, D.; Hynes-Roche, R.; Müller-Bunz, H.; Schuster, O.; Stoeckli-Evans, H.; Neels, A.; Albrecht, M. *Organometallics* **2011**, *30*, 1021.

(6) Khan, S. S.; Liebscher, J. *Synthesis* **2010**, 2609.

(7) Schulze, B.; Friebe, C.; Hager, M. D.; Günther, W.; Köhn, U.; Jahn, B. O.; Görls, H.; Schubert, U. S. *Org. Lett.* **2010**, *12*, 2710.

(8) Palomo, C.; Aizpurua, J. M.; Balentova, E.; Azcune, I.; Santos, J. I.; Jimenez-Barbero, J.; Cañada, J.; Miranda, J. I. *Org. Lett.* **2008**, *10*, 2227.

(9) For the first synthesis of nonsymmetrically substituted 4,4′-bis(1,2,3-triazoles), see: Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A.; Capuzzola, F. *Tetrahedron* **2009**, *65*, 10573.

(10) Aizpurua, J. M.; Azcune, I.; Fratila, R. M.; Balentova, E.; Sagartzazu-Aizpurua, M.; Miranda, J. I. *Org. Lett.* **2010**, *12*, 1584.

(11) Wamhoff, H. *1,2,3-Triazoles and their Benzo Derivatives,* In *Comprehensive Heterocyclic Chemistry*, Vol. 5; Katritzky, A. R.; Rees, C. W.; Pott, K. T., Eds.; Pergamon Press: Oxford, **1984**, 669.

(12) Schubert, U. S.; Hoogenboom, R.; Hager, M. D.; Winter, A.; Friebe, C.; Happ, B. *Chem. Asian J.* **2009**, *4*, 154.

(13) Elamari, H.; Meganem, F.; Herscovici, J.; Girard, C. *Tetrahedron Lett.* **2011**, *52*, 658.