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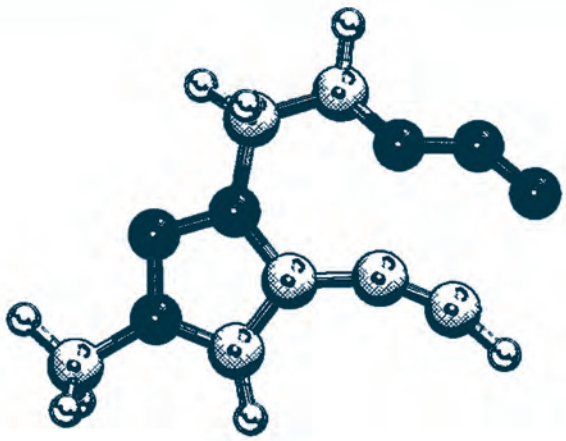

2015


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DEPARTMENT OF ORGANIC CHEMISTRY-I

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Universidad del País Vasco Euskal Herriko Unibertsitatea

# Synthesis, applications and reactivity of 1,2,3-triazolium Salts

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*Agradecimientos*

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Quisiera agradecer la colaboración de Nacho, Javier y Borja (). De verdad, ha sido un placer trabajar con vosotros.

*A mis padres y hermano*

| | |
|---|---|
| AINB | Azobisisobutyronitrile |
| Asc. | Ascorbate (Na Asc.) |
| Boc | *tert*-Butoxycarbonyl |
| cat. | Catalyst |
| CuAAC | Copper-catalyzed azide alkyne cycloaddition |
| D | Debye |
| d | Doublet ($^1$H NMR) |
| dd | Doublet of doublet ($^1$H NMR) |
| DFT | Density functional theory |
| DIPEA | *N*,*N*-Diisopropylethylamine |
| DMAP | 4-*N*,*N*-Dimethylaminopyridine |
| DMF | *N*,*N*-Dimethylformamide |
| DMSO | Dimethylsulfoxide |
| δ | Chemical shift (NMR) |
| $\Delta E^{\ddagger}$ | Activation energy |
| EDG | Electron donating group |
| ESI | Electro spray ionization (Mass spectrometry) |
| Eq. | Equation |
| Equiv. | Equivalent(s) |
| EWG | Electron-withdrawing group |
| FG | Funtionalized groups |
| FMO | Frontier molecular orbital |
| G | Glycine (Gly) |
| $\Delta G^{\ddagger}$ | Activation Gibbs energy |
| h | Hour(s) |
| $\Delta H^{\ddagger}$ | Activation enthalpy |
| HMPA | Hexamethylphosphoramide |
| HOMO | Highest occupied molecular orbital |
| HPLC | High performance liquid chromatography |
| HRMS-HPLC | High resolution mass spectroscopy-High performance liquid chromatography |
| HSQC | Heteronuclear single quantum coherence (NMR) |

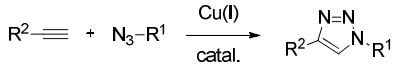
| | |
|---|---|
| Hz | Hertz |
| ICP-MS | Inductively coupled plasma-mass spectrometry |
| IL(s) | Ionic liquid(s) |
| IR | Infrared |
| *J* | Coupling constant (NMR) |
| *k* | Rate constant |
| $k_0$ | Frequency factor |
| $k_B$ | Boltzmann constant |
| KHMDS | Potassium bis(trimethylsilyl)amide |
| LDA | Lithium diisopropylamid |
| LiHMDS | Lithium bis(trimethylsilyl)amide |
| LUMO | Lowest unoccupied molecular orbital |
| M | Metal |
| m | Multiplet (NMR) |
| *m* | Slope |
| Mes | 2,4,6-Trimethylphenyl |
| MIC(s) | Mesoionic carbene(s) |
| mp | Melting point |
| MS | Mass spectrometry |
| NBO | Natural bonding orbital |
| NBS | *N*-Bromosuccinimide |
| NHC | *N*-Heterocyclic carbene |
| NOE | Nuclear Overhauser effect (NMR) |
| q | Quartet (NMR) |
| RMN | Nuclear magnetic resonance |
| ROESY | Rotating frame NOESY (NMR) |
| r.t. | Room temperature |
| RuAAC | Rhutenium-catalyzed azide alkyne cycloaddition |
| $\Delta S^{\ddagger}$ | Activation entropy |
| t | Triplet (NMR) |
| *t* | Time |
| T | Temperature |
| TBTA | Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine |
| CT | Computed tomography |
| TEA | Triethylamine |

| | |
|---|---|
| Tf | Triflyl (trifluoromethanesulfonyl) |
| THF | Tetrahydrofurane |
| TLC | Thin layer chromatography |
| TON | Turnover number |
| Ts | Tosyl (*p*-toluenesulfonyl) |
| UV | Ultraviolet |
| XPS | X-Ray photoelectron spectroscopy |

*Index*

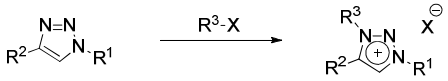
*Resúmen*

En la última década, el empleo y la síntesis de 1,2,3-triazoles ha experimentado una enorme expansión. Esta estructura heterocíclica ya se conocía desde los años 60 del siglo pasado, cuando Huisgen descubrió la cicloadición térmica entre azidas y alquinos. Sin embargo, hasta el año 2001 la reacción ha pasado prácticamente desapercibida. En ese año Meldal y Sharpless, descubrieron independientemente que el catión Cu(I) cataliza la reacción de ciclación de azidas con alquinos a la que pasaron a denominar "Cu-accelerated azide-alkyne cycloaddition" (CuAAC). Además, demostraron que bajo condiciones catalíticas la reacción conduce únicamente a los isómero 1,4-disustituidos.




En esta última década han sido innumerables los logros obtenidos en esta área, así como en la búsqueda de un sistema que permita la obtención de 1,2,3-triazoles de forma totalmente regisoselectiva en ausencia de metales.

Los 1,2,3-triazoles pueden ser alquilados en el nitrógeno 3, proporcionando una carga positiva deslocalizada al 1,2,3-triazol, formando la correspondiente sal de 3-alquil-1,2,3-triazolio. Generalmente, esta reacción sólo funciona satisfactoriamente con agentes alquilantes muy activos, tales como las sales de Meerwein ($R_3O^+BF_4^-$), yoduro de metilo y algunos triflatos de cadena corta.




Las sales de 1,2,3-triazolio poseen importantes aplicaciones como líquidos iónicos (ILs), organocatalizadores, precursores de ligandos de carbenos mesoiónicos o como componentes estructurales en química supramolecular.

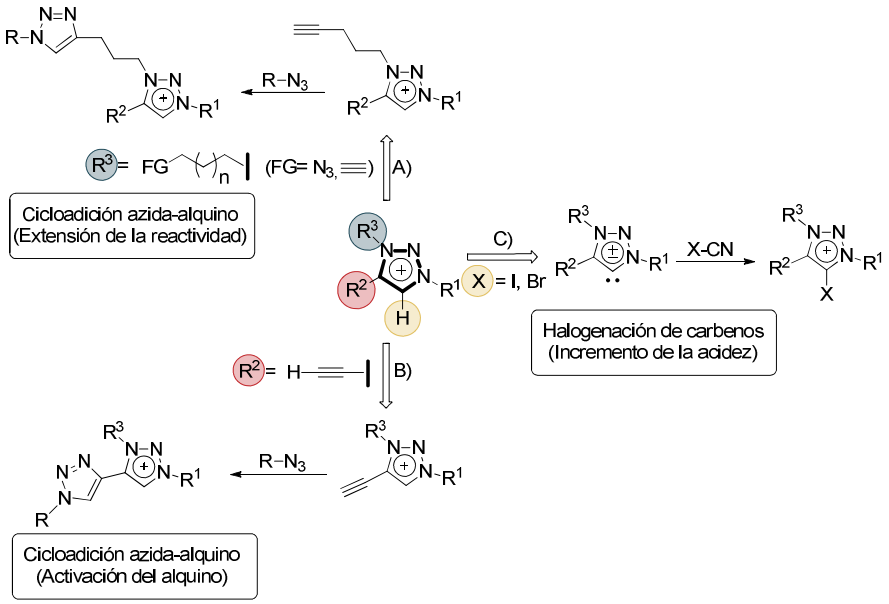
A pesar del rápido desarrollo de las aplicaciones de sales de 1,2,3-triazolio durante los últimos cinco años, apenas existen ejemplos de transformaciones químicas de dichos compuestos que proporcionen productos dereacción que no sean complejos carbénicos de metales de transición.

El objetivo general de esta tesis, es demostrar que el carácter fuertemente electrodeficiente de las sales de 1,2,3-triazolio puede ser aprovechado para llevar a cabo transformaciones en las posiciones C4-, *N*3- y C5- del anillo. Concretamente, se han abordado las siguientes las siguientes reacciones:

En primer lugar, el estudio de nuevos alquinos altamente activados mediante efectos inductivos como consecuencia de la *N*3-alquilación del anillo de triazol, capaces de promover la reacción de cicloadición azida-alquino en ausencia de catalizadores.

Por otro lado, la síntesis de sales *N*3-sustituidas de 1,2,3-triazolio con reactividad latente, la cual a su vez permite llevar a cabo posteriores reacciones en la posición *N*3, creando una gran variedad estructural de sales de 1,2,3-triazolio.

Y finalmente, la síntesis de sales de 5-halo-1,2,3-triazolio 1,3,4-trisustituidas a través de un intermedio carbénico y en presencia de electrófilos.

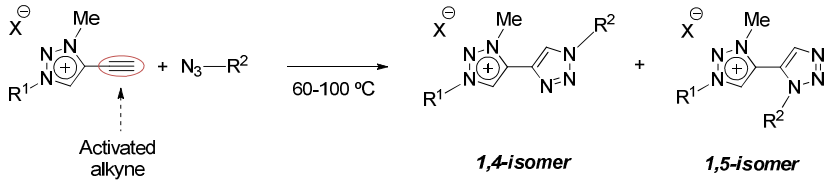



Los resultados más relevantes de cada uno de los apartados, se detallan a continuación:

1. Activación de la reacción de cicloadición azida-alquino promovida por sales de 1,2,3-triazolio

Preparación de sales de 3-alquil-4-alquinil-1,2,3-triazoles mediante una reacción "click" y posterior *N*3-alquilación de 4-alquinil-1,2,3-triazoles por tratamiento con sales de Merweein ($Me_3OBF_4$, $Et_3OBF_4$) o trifluorometanesulfonato de metilo. Reacción que da lugar a los productos deseados con muy buenos rendimientos.

Se observa que la reacción de estos nuevos alquinos triazólicos tanto con azidas aromáticas como alifáticas bajo condiciones térmicas (60-100 ºC) da lugar a sales 1,4-/1,5-sustituidas de 3-metil-4-(1,2,3-triazolil)-1,2,3-triazolio. Estas reacciones ocurren de 40-350 veces más rápido que con los alquinos neutros análogos de 4-alquinil-1*H*-1,2,3-triazol, demostrando el fuerte carácter electrón atractor originado por la alquilación en la posición *N*3 del anillo de triazol.




Además, se confirma que los alquinos triazólicos reaccionan con azidas dando lugar, preferentemente al isómero 1,4- frente al 1,5- (típicamente > 95%) en comparación con su análogo neutro. Estudiando los parámetros termodinámicos de dicha reacción, se observa que la energía de activación $\Delta G^{\neq}$ para el estado de transición del isómero 1,4- es de 2-3 kcal·mol$^{-1}$ menor comparada con la del isómero 1,5- en el caso de los alquinos triazólicos. Por otro lado, esta diferencia es de tan solo 0.4 kcal·mol$^{-1}$ para su análogo neutro.

Cálculos computacionanes DFT confirman que dichos alquinos triazólicos actúan estabilizando el orbital LUMO del dipolarófilo, disminuyendo el salto de energía HOMO-LUMO de la interacción azida-alquino. Este resultado está de acuerdo con la alta regioselectividad 1,4/1,5- observada en el caso de los alquinos triazólicos.

Finalmente, se demuestra que dichos alquinos triazólicos reaccionan con azidas en presencia de cobre(I) (CuAAC) de modo "ultra-rápido" (< 5 min) dando lugar a sales de 4-(1,2,3-triazolil)-3-metil-1,2,3-triazolio con buenos rendimientos.

La realización de un estudio competitivo de la reacción de cicloadición CuAAC, empleando como dipolarofilos el alquino activado y el alquino neutro confirma la alta reactividad de los primeros, ya que la reacción ocurre a través del alquino catiónico con total selectividad.

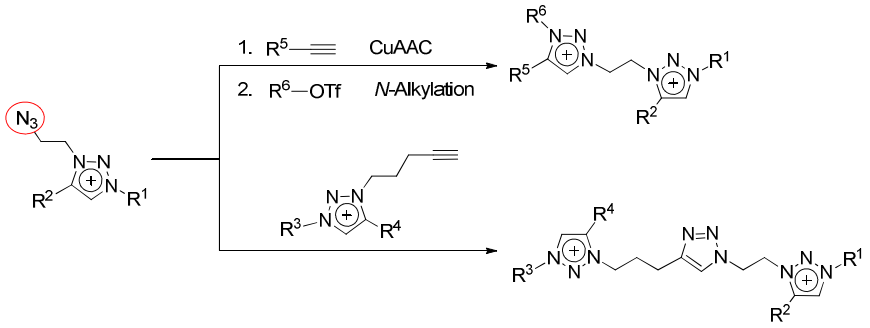
Además, se demuestra que en determinados casos, la sal de 4-(1,2,3-triazolil)-3-metil-1,2,3-triazolio puede ser desmetilada en presencia de tiofenol en medio básico, dando lugar a su análogo neutro.

2. Sales de triazolio con reactividad "click" latente por *N*3-alquilación de 1,2,3-triazoles

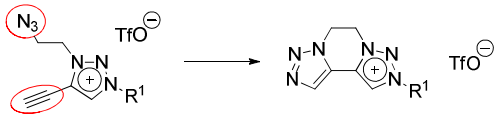
En el tercer capítulo de esta tesis doctoral, se desarrolla una estrategia para preparar sales de 1,2,3-triazolio *N*3-sustituidas a partir de 1,2,3-triazoles 1,4-disustituidos con funcionalidad latente. Dicha transformación se lleva a cabo mediante el empleo de triflatos de alquilo, como agentes alquilantes, y se efectúa en dos etapas. En primer lugar se preparan los correspondientes triflatos a partir de alcoholes funcionalizados y seguidamente se emplean dichos triflatos en la reacción de *N*-alquilación dando lugar a sales de triazolio *N*1,*N*3,C4-trisustituidas con muy buenos rendimientos. Esta metodología es compatible con una gran variedad de grupos funciones.

Esta estrategia se ha aplicado a la síntesis de miméticos de Arg-Gly-Asp (RGD) altamente iodados, los cuales tienen un gran potencial como agentes de contraste para tomografía computarizada de rayos-X.

Con objeto de exterder las aplicaciones de las sales de 1,2,3-triazolio con funcionalidad latente, se han empleado sales de *N*3-(ω-azidoalquil)-1,2,3-triazolio como sustratos de la reacción CuAAC con diferentes alquinos, dando lugar por vez primera a sales de bis(1,2,3-triazolio) multisustituidas y con control posicional total de los sustituyentes.

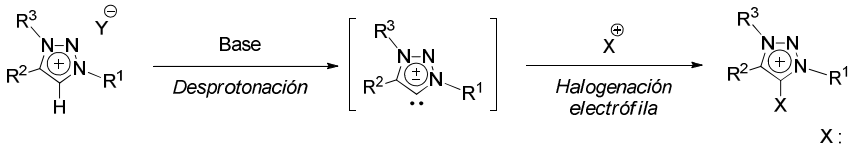



Finalmente, se demuestra que tratando 4-etinil1,2,3-triazoles con triflatos de ω-azidoalquilo, se produce la alquilación del anillo de triazol en la posición N3, seguida de una ciclación térmica [3+2] a consecuencia de la activación del alquino debida al efecto inductivo de la alquilación. Esta estrategia permite obtener un nuevo tipo de sistemas de tipo bis-triazol-triazolio tricíclicos. De acuerdo con los estudios computacionales, la energía de Gibbs para el estado de transición de la ciclación térmica [3+2] es 10 kcal·mol$^{-1}$ menor que su análoga cicloadición intermolecular azida-alquino.



3. <u>Halogenación de sales de 1,2,3-triazolio</u>

Por último, se han diseñado y puesto a punto una nueva metodología para llevar a cabo la halogenación de sales de 1,2,3-triazolio a través de un intermedio carbénico de plata(I) en presencia de haluros de cianógeno, para dar lugar a sales de 5-halo-1,2,3-triazolio 1,3,4-trisustituidas. Se ha llevado a cabo un estudio computacional del mecanismo de reacción que ha permitido identificar un intermedio de reacción altamente electrófilo de tipo I-CN-AgI que es el agente halogenante de carbenos triazólicos.



Por último, se ha estudiado, tanto experimentalmente como teóricamente la reacción de *N*3-desalquilación de sales de 1,2,3-triazolio en la etapa de formación del carbeno por tratamiento con bases fuertes en presencia de yodo cianógeno, dando lugar a 5-halo-1,2,3-triazoles.

# 1

# *General introduction and objectives*

# 1 General introduction and objectives

## 1.1 1,2,3-Triazolium salts and their applications[1]

The spectacular development of the Cu(I)-catalyzed azide-alkyne "click" cycloaddition reaction (CuAAC) has allowed the use of 1,4-disubstituted 1,2,3-triazoles as ubiquitous scaffolds in synthetic chemistry. Owing to this wide availability, structurally complex 1,2,3-triazolium salts can be readily obtained (see **Chapter 3**) from the corresponding 1,2,3-triazoles by *N*-alkylation using alkyl halides, tosylates or triflates, or trialkyl oxonium tetrafluoroborates (Meerwein salts). This transformation often tolerates a wide variety of functional groups at positions *N*1 and C4 of the triazole ring and usually occurs with total *N*3-regioselectivity. Furthermore, 1,2,3-triazolium salts bearing 1,3-diaryl substituents can be obtained directly by [3+2] cycloaddition between alkynes and 1,3-diaza-2-azoniaallene salts[2] or by *N*-arylation with $Ph_2IBF_4$ reagent.[3] Finally, the anionic counterions $X^-$ of triazolium salts can be easily interchanged by simple washing with an excess of an inorganic salt or by using exchange resins.[4]

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1 a) Aizpurua, J.M.; Fratila, R. M.; Monasterio, Z.; Pérez-Esnaola, N.; Andreieff, E.; Irastorza, A.; Sagartzazu-Aizpurua, M. *New J. Chem.* **2014**, *38*, 474-480. "Triazolium cations: from "click" pool to multipurpose applications". b) Schulze, B.; Schubert, U. S. *Chem. Soc. Rev.* **2014**, *43*, 2522-2571. "Beyond click chemistry-supramolecular interactions of 1,2,3-triazoles". c) Yacob, Z.; Liebscher, J. *Top Heterocycl. Chem.* **2015**, *40*, 167-210. "Chemistry of 1,2,3-triazolium salts".

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3 Lv, T.; Wang, Z.; You, J.; Lan, J.; Gao, G. *J. Org. Chem.* **2013**, 78, 5723-5730. "Copper-catalyzed direct aryl quaternization *N*-substituted imidazoles to form imidazolium salts".

4 Dinarès, I.; Mesquida, N.; Ibánez, A.; Alcalde, E. *Arkivoc* **2014**, *ii*, 85-102. "Azolium-based systems: application of an anion exchange resin ($A^-$ form) method and $^1H$ NMR analysis of the charged-assisted $(C\text{-}H)^+\cdot$anion hydrogen bonds".

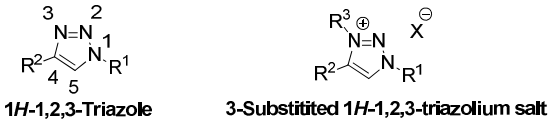


**Figure 1. 1.** General structure for 1*H*-1,2,3-triazoles and 3-substituted 1*H*-1,2,3-triazolium salts.

These results can be rationalized taking into account some fundamental properties of 1*H*-1,2,3-triazoles and their corresponding triazolium salts. Accordingly, the three nitrogen atoms of the 1*H*-1,2,3-triazole ring cause a strong polarization of the aromatic π system and the σ framework. Considering relevant Lewis structures as well as inductive effects, the carbon atoms and the *N*1 nitrogen are expected to be positively charged, while the *N*2, *N*3 atoms show negative partial charges.[5] In agreement with this description, a very large dipole moment (4.38 D) was measured for 1*H*-1,2,3-triazole.[6]

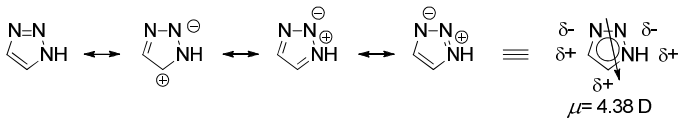


**Figure 1. 2.** Selected contributing Lewis structures, partial charges and dipole moment of the 1*H*-1,2,3-triazole ring.[7]

Comparing the frontier molecular orbitals energies of 1,2,3-triazoles and 1,3-imidazoles reveals that an increasing number of nitrogen atoms leads to a gradual stabilization of both HOMO and LUMO orbitals. 1,2,3-Triazoles feature one *N*-acidic *N*-H bond and two basic nitrogen lone pairs similar to 1,3-imidazole (**Figure 1. 3**). The different

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5 a) Adam, W.; Grimison, A. *Theoret. chim. Acta* **1967**, *7*, 342-351. "Sigma-polarization in 5-membered heterocyclic ring systems". b) Katritzky, A. R.; Ramsden, C. A.; Joule, J. A.; Zhdankin, V. V. *Handbook in Heterocyclic Chemistry* , El servier, Amsterdam, 3rd edn **2010**, 139-209. "Structure of five-membered rings with two or more heteroatoms". c) Weigert, F. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1968**, *90*, 3543-3549. "Nuclear magnetic resonance spectroscopy. Carbon-13 spectra of five-membered aromatic heterocycles".

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7 Jug. K.; Chiodo, S.; Calaminici, P.; Avramopoulos, A.; Papadopoulos, M. G. *J. Phys. Chem. A* **2003**, *107*, 4172-4183. "Electronic and vibrational polarizabilities and hyperpolarizabilities of azoles: a comparative study of the structure-polarization relationship".

base strength of *N*2 and *N*3 positions is reflected by the natural population analysis (NBO) charges of -0.08 for *N*2 and -0.28 for *N*3 which involve a higher basicity for the later.[8]

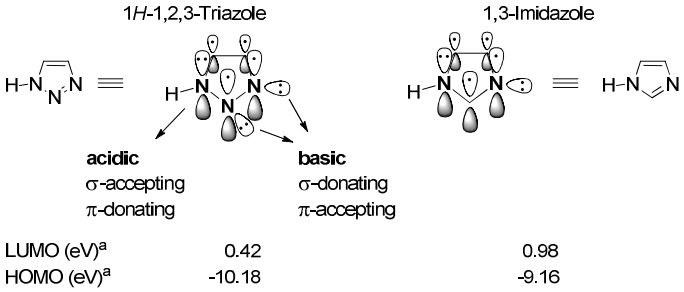



**Figure 1. 3.** Electronic features of 1*H*-1,2,3-triazole and 1,3-imidazole rings ([a]Energies obtained by semi-empirical AM1 calculations).[5b]

Upon alkylation, protonation or metal coordination at *N*3, the polarization of the C-H bond at C4 position is strongly increased in 1,2,3-triazoles, and consequently their acidity. For example, the p$K_a$ value of 1,4-dimethyl-1,2,3-triazole is about 28 in DMSO, whereas its *N*-methyl triazolium salt is 24 (**Figure 1. 4**).

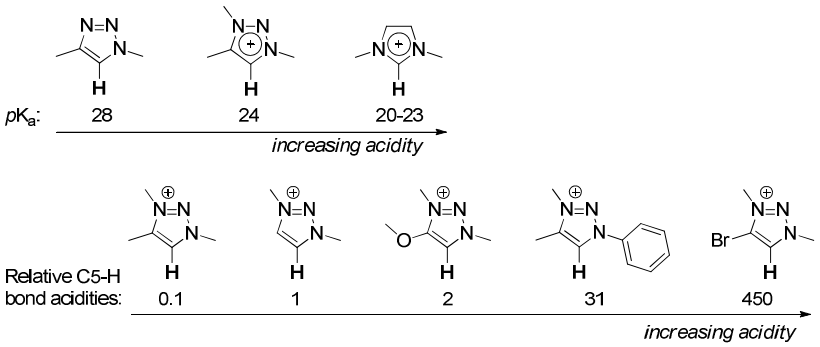



**Figure 1. 4.** p$K_a$ ranges for selected azoliums and influences of inductive substituent effects on the relative CH-acidity determined by H/D-exchange kinetics.[9]

Imidazolium salts are known to be slightly more acidic than analogous triazolium salts.[10] Nevertheless, replacement of the methyl group at C4 position in 1,2,3-triazolium salts

[8] Mindt, T. L.; Struthers, H.; Brans, L.; Anguelov, T.; Schweinsberg, C.; Maes, V.; Tourwé, D.; Schibli, R. *J. Am. Chem. Soc.* **2006**, *128*, 15096-15097. “”Click to chelate”: synthesis and installation of metal chelates into biomolecules in a single step”.

[9] Begtrup, M. *Acta Chem. Scand.* **1971**, *25*, 249-259. “Reactions between azolium salts and nucleophilic reagents. II. Bromo-1,2,3-triazolium salts and sodium hydroxide”.

by electrodonating and electrowithdrawing substituents may enhance the acidity by a factor ranging from several units to hundreds. Alternatively, the substitution of the *N*-methyl group by a phenyl group also increases the acidity about 30 times.

1,2,3-Triazolium salts have found important applications (**Figure 1. 5**) as ionic liquids by incorporating at least one flexible substituent ($R^2$) and a bulky hydrophobic anion ($BF_4$,TfO, $PF_6$, $NTf_2$) to difficult crystalline accommodation. In addition, the introduction of chiral substituents ($R^1$) provides polar structures potentially suitable to promote asymmetric organocatalysis. Upon deprotonation at C5, 1,2,3-triazolium salts form mesoionic *N*-heterocyclic aromatic carbenes which strongly coordinate to transition metals. Finally, their acidic C5–H bond can be preserved to participate in supramolecular hydrogen bonding with anion acceptors.

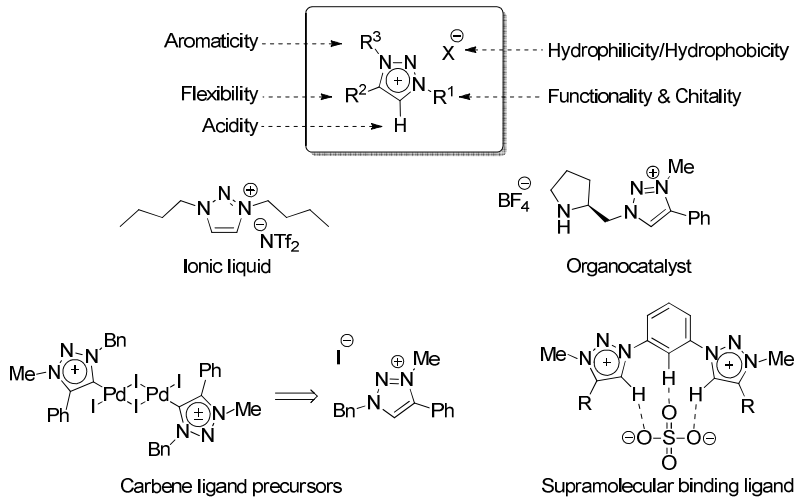



**Figure 1. 5.** Some examples of 1,2,3-triazolium salts and their applications.

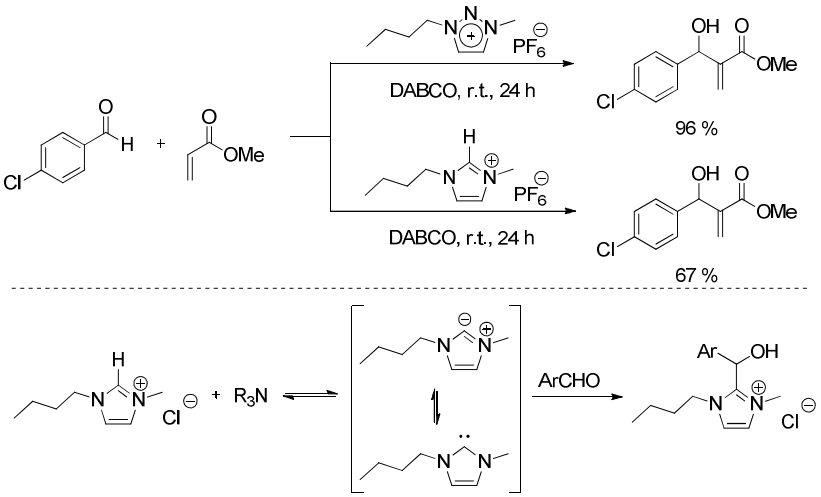
### 1.1.1 Triazolium salts as ionic liquids

Ionic liquids (ILs) are organic salts characterized by melting points below 100 °C, negligible vapour pressure, thermal and chemical stability, high polarity and conductivity, moderate viscosity, and ability to dissolve a wide range of organic and inorganic compounds.

[10] Donnelly, K. F.; Petronilho, A.; Albrecht, M. *Chem. Commun.* **2013**, *49*, 1145-1159. "Application of 1,2,3-triazolylidenes as versatile NHC-type ligands: synthesis, properties, and application in catalysis and beyond".

Despite their ionic nature and high polarity, most ILs containing the triflamide anion ($NTf_2$) are totally immiscible with water. The diversity in properties make ILs suitable for a plethora of applications, including "green" solvents for (bio)organic chemistry or catalysis, energy storage and materials science and nanotechnology.

Unquestionably, the most popular ILs are the 1,3-imidazole-based salts, which have become commercially available in bulk quantities. An important limitation of 1,3-imidazole-based "classical" ILs is the easy deprotonation at C2 position even under mild basic conditions. For example, unsubstituted C4 and C5 triazolium salts have shown to be superior to imidazole ILs as chemically inert solvents for the Baylis-Hillman reaction of methyl acrylate and acrylonitrile with aromatic aldehydes (**Scheme 1. 1**).[11,12]




**Scheme 1. 1.** Comparison of a Baylis-Hillman reaction conducted in triazolium IL and imidazolium IL solvents. Below: carbene-aldehyde adduct formation from imidazolium salts.

Bicyclic 1,2,3-triazolium ionic liquids **I** developed by Chu[13] were used advantageously over DMF as solvents in the synthesis of the natural product rutaecarpine under microwave irradiation. These fully substituted 1,3,4,5-tetraalquil-triazolium analogues,

[11] Jeong, Y.; Ryu, J.-S. *J. Org. Chem.* **2010**, *75*, 4183-4191. "Synthesis of 1,3-dialkyl-1,2,3-triazolium ionic liquids and their applications to the Baylis-Hillman reaction".

[12] Aggarwal, V. K.; Emme, I.; Mereu, A. *Chem. Commun.* **2002**, 1612-1613. "Unexpected side reactions of imidazolium-based ionic liquids in the base-catalysed Baylis-Hillman reaction".

[13] Tseng, M.-C.; Cheng, H.-T.; Shen M.-J.; Chu, Y.-H. *Org. Lett.* **2011**, *13*, 4434-4437. "Bicyclic 1,2,3-triazolium ionic liquids: synthesis, characterization, and application to rutaecarpine synthesis".

displayed superior chemical stability. Sasai[14] has reported the gram scale synthesis of spiro bis(1,2,3-triazolium) salts **II** as chiral ionic liquids. Preliminary studies revealed the chiral discrimination ability of these triazolium ILs, suggesting their potential as asymmetric induction tools in catalysis (**Figure 1. 6**).

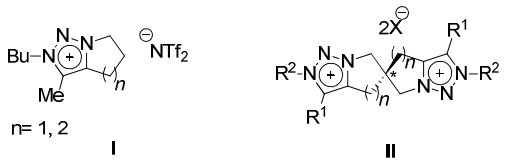



**Figure 1. 6.** Bicyclic **I** and tricyclic **II** 1,2,3-triazolium ionic liquids.

### 1.1.2 Triazolium salts as organonocatalysts

1,2,3-Triazolium salts can be covalently fixed to an organocatalytic chiral unit in order to enable affective recycling of the catalyst. Liebscher developed this concept and carried out the synthesis of the first chiral 1,2,3-triazolium salts derived from (*S*)-prolinol[15] **III**, 4-hydroxy-L-proline[16,17] **IV** and L-lysine[18] **V**, and studied their catalytic properties in several asymmetric reactions (**Scheme 1. 2**).

Chiral triazolium salts **III**-**V** behave as efficient and easily recyclable organocatalysts (in some instances 4-5 cycles) in the asymmetric Michael addition of enols to β-nitrostyrenes,[15b,16] the aldol reaction[16,18] and the asymmetric α-aminoxylation of carbonyl compounds with nitrosobenzene.[17]

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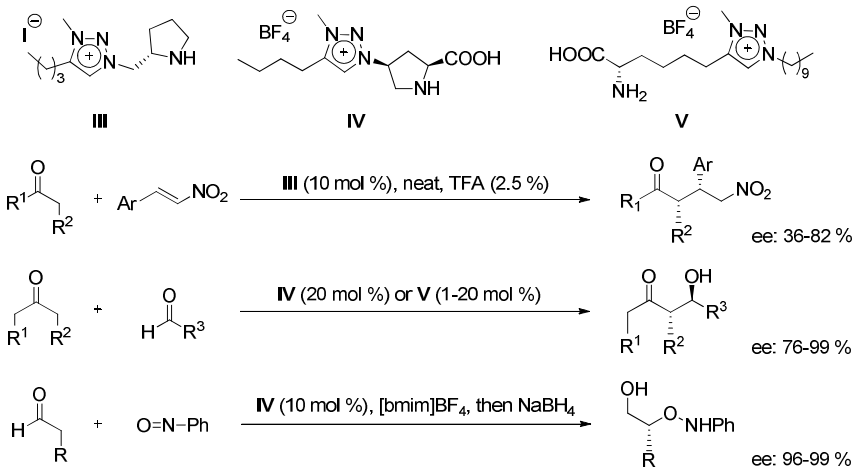
[14] a) Yoshida, Y.; Takizawa, S.; Sasai, H. *Tetrahedron Lett.* **2011**, *52*, 6877-6879. "Synthesis of spiro bis(1,2,3-triazolium) salts as chiral ionic liquids". b) Yoshida, Y.; Takizawa, S.; Sasai, H. *Tetrahedron: Asymmetry* **2012**, *23*, 843-851. "Design and synthesis of spiro bis(1,2,3-triazolium) salts as chiral ionic liquids".

[15] a) Hanelt, S.; Liebscher, J. *Synlett* **2008**, 1058-1060. "A novel and versatile access to task-specific ionic liquids based on 1,2,3-triazolium salts". b) Yacob, Z.; Shah, J.; Leistner, J.; Liebscher, J. *Synlett* **2008**, 2342-2344. "(S)-Pyrrolidin-2-ylmethyl-1,2,3-triazolium salts-ionic liquid supported organocatalysts for enantioselective Michael additions to β-nitrostyrenes".

[16] Shah, J.; Khan, S. S.; Blumenthal, H.; Liebscher, J. *Synthesis* **2009**, 3975-3982. "1,2,3-Triazolium-tagged prolines and their application in asymmetric aldol and Michael reactions".

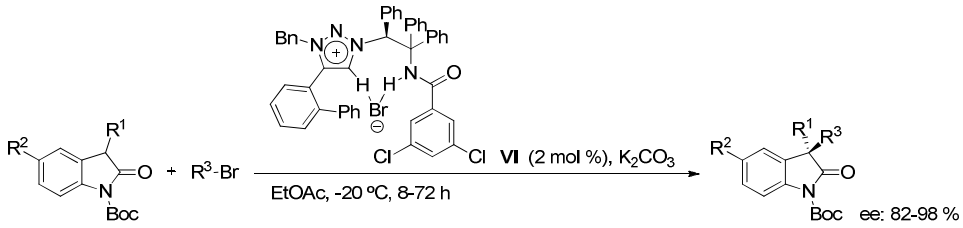
[17] Khan, S. S.; Shah, J.; Liebscher, J. *Tetrahedron* **2011**, *67*, 1812-1820. "Ionic-liquid tagged prolines as recyclable organocatalysts for enantioselective α-aminoxylations of carbonyl compounds".

[18] Khan, S. S.; Shah, J.; Liebscher, J. *Tetrahedron* **2010**, *66*, 5082-5088. "Synthesis of new ionic-liquid-tagged organocatalysts and their application in stereoselective direct aldol reactions".




**Scheme 1. 2.** Chiral *N*-alkyl-1,2,3-triazolium-based organocatalysts derived from α-amino acids and their use in several asymmetric reactions.

In another example of the potential of triazolium salts to design organocatalysts, very low loads (2 mol %) of the of the L-phenylalanine-derived triazolium catalyst **VI** were shown to promote a highly efficient asymmetric alkylation of oxindoles under mild reaction conditions (**Scheme 1. 3**).[19]




**Scheme 1. 3.** Asymmetric alkylation of oxindoles promoted by chiral *N*-alkyl-1,2,3-triazolium organocatalysts.

The preceding examples show that 1,2,3-triazolium-based organocatalysts enjoy a much wider structural variety than the "classical" 1,3-imidazole salts and a similar or superior catalytic ability in most instances. More elaborated and specific organocatalysts are expected to be prepared in coming years.

[19] Ohmatsu, K.; Kiyokawa, M.; Ooi, T. *J. Am. Chem. Soc.* **2011**, *133*, 1307-1309. "Chiral 1,2,3-triazoliums as new cationic organic catalysts with anion-recognition ability: application to asymmetric alkylation of oxindoles".

### 1.1.3 Triazolium salts as carbene ligands precursors

In a pioneering paper, Albrecht showed that 3-alkyl-1,2,3-triazolium salts can serve as precursors of transition metal complexes carrying 1,2,3-triazol-5-ylidene ligands,[20] also referred to as *N*-heterocyclic carbenes (NHCs). As no canonical resonance forms containing a carbene can be drawn for free ligands **VII** without additional charges, they are known as mesoionic carbenes (MICs) (**Figure 1. 7**). MICs are more σ-donating ligands than classical 1,3-imidazole carbenes, which opens up interesting perpectives for their application to prepare very stabilized transition metal complexes.

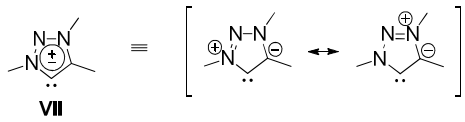
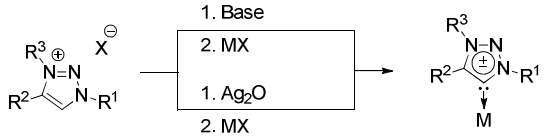



**Figure 1. 7.** Canonical resonance structures of *N*-alkyl-1,2,3-triazole mesoionic carbenes MIC (**VII**).

Bertrand isolated and characterized by X-ray diffraction the first free 1,2,3-triazole mesoionic carbene synthetized by deprotonation of a 3-methyl-1,2,3-triazolium salt with $KN(SiMe_3)_2$.[21] Recently, the same group has demonstrated that MIC´s can support simultaneously two adjacent carbon carbenes in the same structure.[22] Alternatively, triazolylidene complexes can be prepared by transmetalation of silver carbenes obtained by the reaction of triazolium salts with $Ag_2O$.[23]




**Scheme 1. 4.** Preparation of MICs from *N*-alkyl-1,2,3-triazolium salts.

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[20] Mathew, P.; Neels, A.; Albrecht, M. *J. Am. Chem. Soc.* **2008**, *130*, 13534-13535."1,2,3-Triazolylidenes as versatile abnormal carbene ligands for late transition metals".

[21] Guisado-Barrios, G.; Bouffard, J.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 4759-4762. "Crystalline 1*H*-1,2,3-triazol-5-ylidenes: New stable mesoionic carbenes (MICs)"

[22] Yan, X.; Bouffard, J.; Guisado-Barrios, G.; Donnadieu, B.; Bertrand, G. *Chem. Eur. J.* **2012**, *18*, 14627-14631. "Anionic 1,2,3-triazole-4,5-diylidene: A 1,2-dihapto ligand for the construction of bimetallic complexes".

[23] a) Wang, H. M.J.; Lin, I. J. B. *Organometallics* **1998**, *17*, 972-975. "Facile synthesis of silver(I)-carbene complexes. Useful carbene transfer agents". b) Garrison, J. C.; Youngs, W. J. *Chem. Rev.* **2005**, *105*, 3978-4008. "Ag(I) *N*-Heterocyclic carbene complexes: synthesis, structure, and application". c) Lin, I. J. B.; Vasam, C. S. *Coord. Chem. Rev.* **2007**, *251*, 642-670. "Preparation and application of *N*-heterocyclic carbene complexes of Ag(I)".

MICs can form a wide variety of complexes depending on the coordination ability of the carbene ligand, the number of triazole units included in the ligand, and the chelating or open character of the coordination bonds formed with the metal. Accordingly, triazole carbene ligands can be classified as monodentate, polydentate and bridged, polydentated bis(triazolylidenes)[24] and bidentated 4,4´-bis(1,2,3-triazolylidenes)[25] (**Figure 1. 8**).

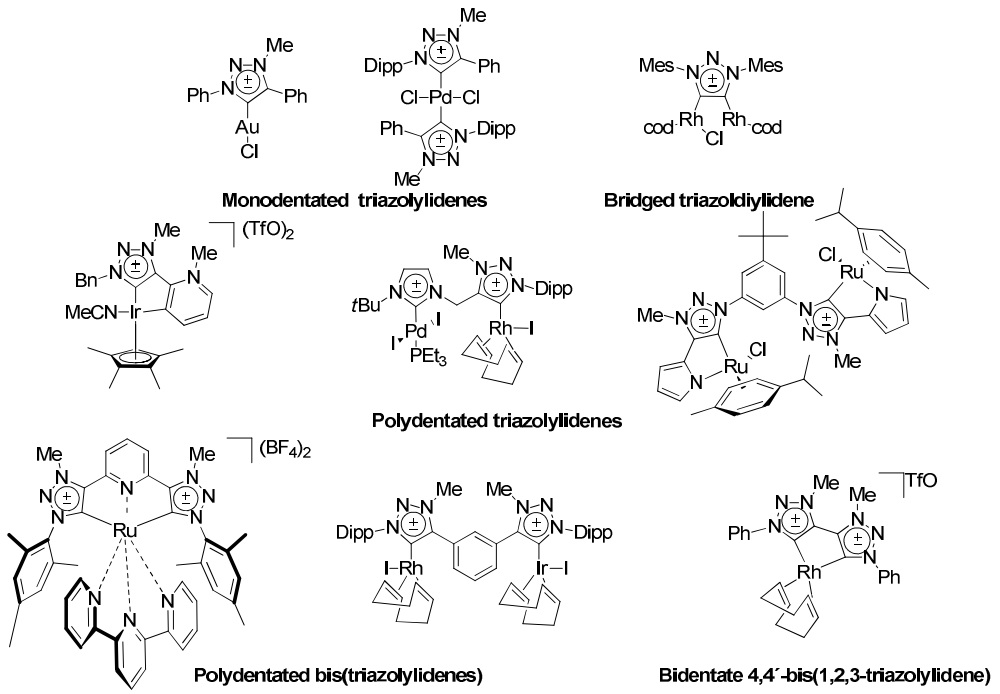



**Figure 1. 8.** Main structural motifs of metal carbene complexes containing 1,2,3-triazolylidene ligands.

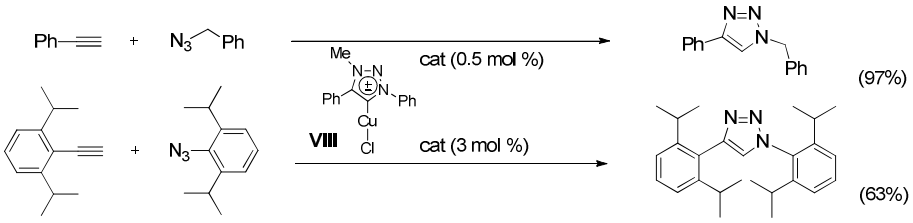
MIC complexes have important applications as catalysts. For example, Fukuzawa and coworkers have described the first synthesis of copper complexes bearing a 1,2,3-triazole carbene ligand,[26,27] demonstrating that they are efficient catalysts for azide-alkyne

[24] a) Zamora, M. T.; Ferguson, M. J.; Cowie, M. *Organometallics* **2012**, *31*, 5384-5395. "Di-mesoionic carbene-bridged complexes of $Rh_2$, $Ir_2$ and RhIr: a stepwise metalation strategy for the synthesis of di-MIC-bridged mixed-metal systems". b) Keske, E. C.; Zenkina, O. V.; Wang, R.; Crudden, C. M. *Organometallics*, **2012**, *31*, 456-461. "Synthesis and structure of silver and rhodium 1,2,3-triazol-5-ylidene mesoionic carbene complexes".

[25] Guisado-Barrios, G.; Bouffard, J.; Donnadieu, B.; Bertrand, G. *Organometallics* **2011**, *30*, 6017-6021. "Bis(1,2,3-triazol-5-ylidenes) (i-bitz) as stable 1,4-bidentate ligands based on mesoionic carbenes (MICs)".

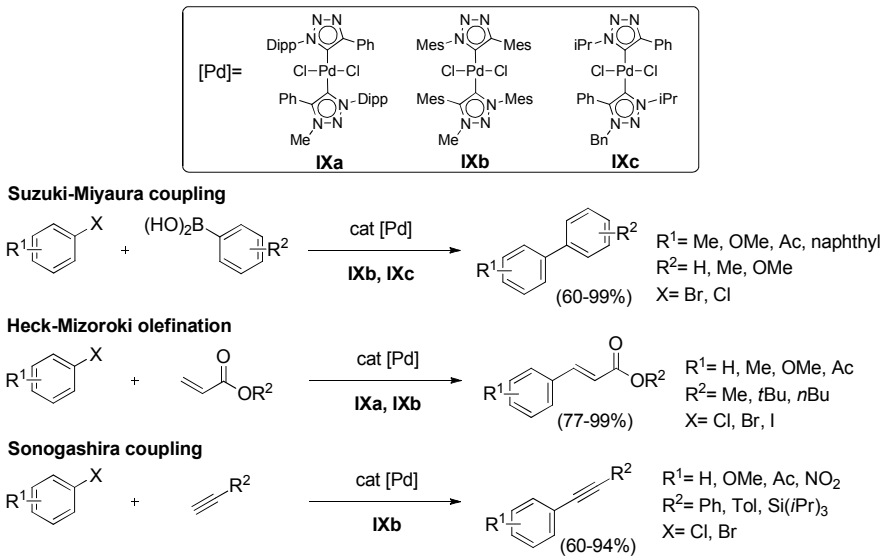
[26] Nakamura, T.; Terashima, T.; Ogata, K.; Fukuzawa S.-I. *Org. Lett.* **2011**, *13*, 620-623. "Copper(I) 1,2,3-triazol-5-ylidene complexes as efficient catalysts for click reactions of azides with alkynes".

[3+2] cycloaddition reactions at very low loads of catalyst (typically 0.5 mol%).[26] In addition, complex **VIII**, was more active than other known Cu(I) catalysts and performed well in reactions where classical catalysts failed. For example, the coupling of sterically bulky alkynes with bulky azides (e.g., Dipp-C≡CH with Dipp-$N_3$) proceeded with high conversion in the presence of 3 mol% of MIC complex **VIII** (**Scheme 1. 5**).




**Scheme 1. 5.** CuAAC reaction catalyzed with copper(I) 1,2,3-triazolylidene complex **VIII**.

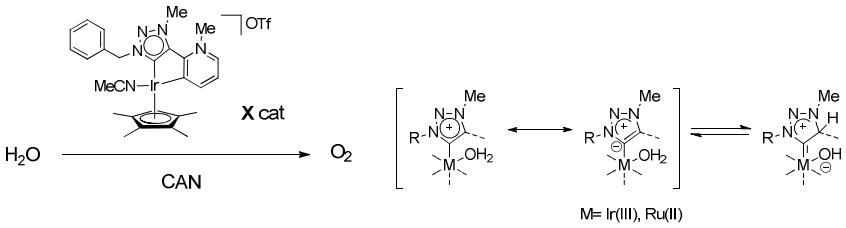
Palladium(II) biscarbene complexes **IX** proved to be very effective for cross-coupling reaction catalysis, with important implementations in the Suzuki-Miyaura, Sonogashira and Heck reactions (**Scheme 1. 6**).




**Scheme 1. 6.** Catalytic activity of palladium(II) bis(triazolylidene) complexes **IX** in cross-coupling reactions.

[27] Inomata, H.; Ogata, K.; Fukuzawa, S.-I.; Hou, Z. *Org. Lett.* **2012**, *14*, 3986-3989. "Direct C-H carboxylation with carbon dioxide using 1,2,3-triazol-5-ylidene copper(I) complexes".

Apart from forming C-C bonds, triazole-based complexes are also excellent oxidation catalysts. Currently, finding efficient methodologies for water oxidation is one of the biggest challenges in the field of sustainable energy. Iridium complexes comprising triazolylidene carbene ligands are among the most efficient catalytic systems for water oxidation in the presence of Ce(IV) as sacrificial oxidant. The turnover numbers (TON= 10.000) achieved using the bidentate triazole carbene **X** is the highest reported to date for such oxidation. This exceptional catalytic activity was attributed to the abnormal character of the triazolylidene ligand, which can assist the oxidation by enabling a proton-coupled electron transfer process indicated in **Scheme 1. 7**.




**Scheme 1. 7.** Water oxidation catalysis using iridium and ruthenium triazolylidene complexes.

On the other hand, 1,2,3-triazol-5-ylidenes MICs have important applications aside from catalytic applications. For example, in ruthenium 1,2,3-triazol-5-ylidenes, the introduction of a carbene ligand triggers a response from the Ru(II) electron donor site, resulting in a substantial reduction of the gap between the HOMO and LUMO orbitals of the carbene complex. This lowered gap can facilitate the charge separation processes, with beneficial consequences for photovoltaic applications.[28]

[28] a) Schulze, B.; Escudero, D.; Friebe, C.; Siebert, R.; Görls, H.; Köhn, U.; Altuntas, E.; Baumgaertel, A.; Hager, M. D.; Winter, A.; Dietzek, B.; Popp, J.; González, L.; Schubert, U. S. *Chem. Eur. J.* **2011**, *17*, 5494-5498. "A heteroleptic bis(tridentate) ruthenium(II) complex of a click-derived abnormal carbene pincer ligand with potential for photosensitzer application". b) Brown, D. G.; Schauer, P. A.; Borau-Garcia, J.; Fancy, B. R.; Berlinguette, C. P. *J. Am. Chem. Soc.* **2013**, *135*, 1692-1695. "Stabilization of ruthenium sensitizers to $TiO_2$ surfaces through cooperative anchoring groups". c) Leigh, V.; Ghattas, W.; Lalrempuia, R.; Müller-Bunz, H.; Pryce, M. T.; Albrecht, M. *Inorg. Chem.* **2013**, *52*, 5395-5402. "Synthesis, photo-, and electrochemistry of ruthenium bis(bipyridine) complexes comprising a *N*-heterocyclic carbene ligand".

### 1.1.4 Triazolium salts in supramolecular chemistry[29]

Owing to the slightly polarized nature of the C5-H bond, 1,2,3-triazoles have rapidly gained recognition as excellent hydrogen donors for selective anion binding. Recently, the groups of Sessler and Hay evaluated the binding of chloride by simple triazole and triazolium models. According to their calculations, the triazolium chloride complex is much more stable ($\Delta G$= -89.2 Kcal mol$^{-1}$) than the corresponding triazole chloride complex ($\Delta G$= -12.4 Kcal mol$^{-1}$) in vacuo (**Figure 1. 9**).[30]

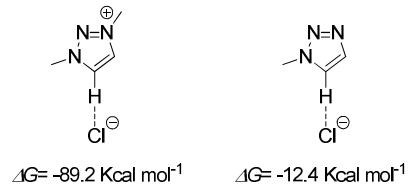



**Figure 1. 9.** Comparison of the calculated (MP2/aug-cc-pVDZ) Gibbs energies, $\Delta G$, for the formation of a chloride complex with the triazolium cation and triazole in vacuum.

Pandey applied for the first time this concept to cyclic and acyclic bistriazolium complexes,[31] which showed a high recognition preference for the biologically meaningful $H_2PO_4^-$ anion when compared to halide anions.[31a] The chelating ability of the triazolium ligands for different anions can be easily tuned by transforming them into multidentate structures[32] such as **XI-XII**[33] or by creating multivalent macrocycles like **XIII**[34] (**Figure 1. 10**).

---

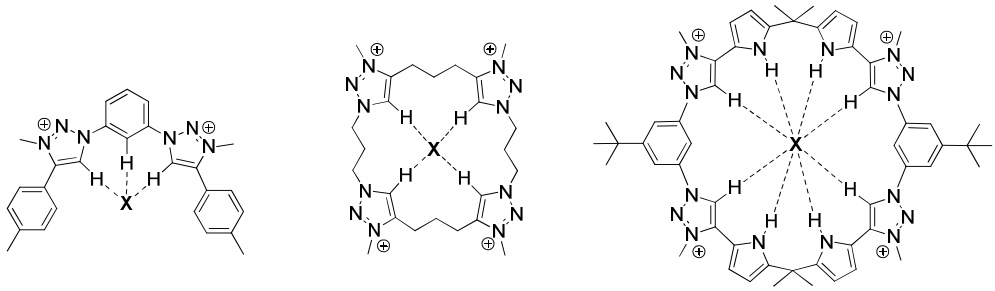
29 a) Coutrot, F.; Busseron, E. *Chem. Eur. J.* **2008**, *14*, 4784-4787. "A new glycorotaxane molecular machine based on an anilinium and a triazolium station". b) Jiang, Y.; Guo, J.-B.; Chen, C.-F. *Org. Lett.* **2010**, *12*, 4248-4251. "A new [3]rotaxane molecular machine based on a dibenzylammonium ion and a triazolium station". 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*, 11893-11895. "Enhancement of anion recognition exhibited by a halogen-bonding rotaxane host system".

30 Cai, J.; Hay, B. P.; Young, N. J.; Yang, X.; Sessler, J. L. *Chem. Sci.* **2013**, *4*, 1560-1567. "A pyrrole-based triazolium-plane with NH and cationic CH donor groups as a receptor for tetrahedral oxyanions that functions in polar media".

31 a) Kumar, A.; Pandey, P. S. *Org. Lett.* **2008**, *10*, 165-168. "Anion recognition by 1,2,3-triazolium receptors: application of click chemistry in anion recognition". b) Chhatra, R. K.; Kumar, A.; Pandey, P. S. *J. Org. Chem.* **2011**, *76*, 9086-9089. "Synthesis of a bile acid-based click-macrocycle and its application in selective recognition of chloride ion"

32 Cao, Q.-Y.; Pradhan, T.; Lee, M. H.; No, K.; Kim, J. S. *Analyst* **2012**, *137*, 4454-4457. "Ferrocene-based anion receptor bearing amide and triazolium donor groups".

33 Schulze, B.; Friebe, C.; Hager, M. D.; Günther, W.; Köhn, U.; Jahn, B. O.; Görls, H.; Schubert, U. S. *Org. Lett.* **2010**, *12*, 2710-2713. "Anion complexation by triazolium "ligands": Mono- and bis-tridentate complexes of sulfate".




**XI** **XII** **XIII**

**Figure 1. 10.** Triazolium-based cleft and macrocyclic anion receptors and association constants with selected anions.

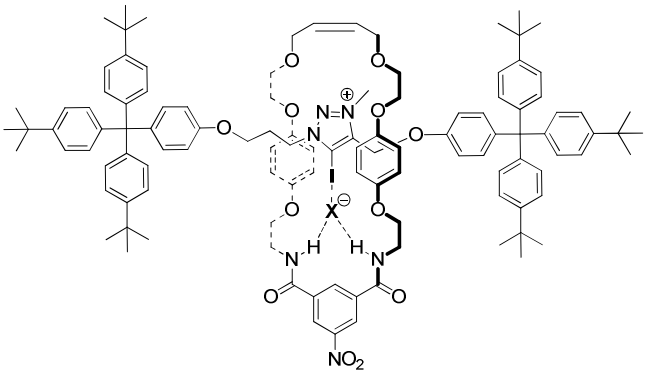
1,2,3-Triazolium salts have also been widely used for the synthesis of catenane and rotaxane supramolecular structures using a diverse range of recognition motifs, such as electron-rich or electron-poor π-stacking systems, hydrogen bonding and metal ion coordination.[35]

Beer reported the first example of exploiting the 1,2,3-triazolium group in the anion template formation of rotaxane assemblies.[36] Attractive halogen bond interactions can arise in solution from the terminal positive polarization of the C5–I bond in 5-iodo-1,2,3-triazolium salts to give stringent linear binding with halides. Beer has demonstrated for the first time this concept to control and facilitate the assembly of the interlocked rotaxane structure **XIV**.[29c] The iodotriazolium axle significantly enhances the rotaxane's anion-recognition properties in comparison with the hydrogen-bonding analogue, providing unusual selectivity for iodide in aqueous medium.

[34] White, N. G.; Carvalho, S.; Félix, V.; Beer, P. D. *Org. Biomol. Chem.* **2012**, *10*, 6951-6959. "Anion binding in aqueous media by a tetra-triazolium macrocycle".

[35] Hänni, K. D.; Leigh, D. A. *Chem. Soc. Rev.* **2010**, *39*, 1240-1251. "The application of CuAAC "click" chemistry to catenane and rotaxane synthesis".

[36] Mullen, K. M.; Mercurio, J.; Serpell, C. J.; Beer, P. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 4781-4784. "Exploiting the 1,2,3-triazolium motif in anion-templated formation of a bromide-selective rotaxane host assembly".

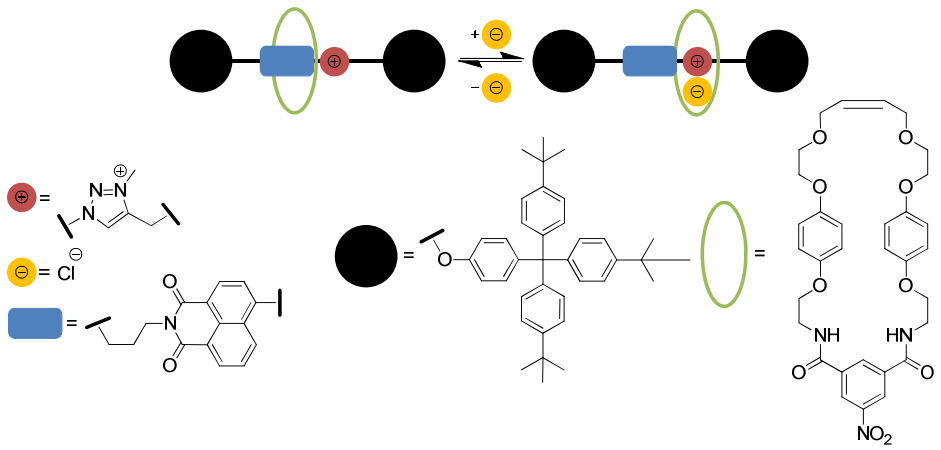


XIV

| $X^{\ominus}$ | Ka ($M^{-1}$) |
|---|---|
| Cl | 457 |
| Br | 1251 |
| I | 2228 |

**Figure 1. 11.** Selective recognition of halide anions with *N*-alkyl-1,2,3-triazolium-based receptors through C5-I···X halogen bond interactions.

The ability of mechanically interlocked molecules to undergo controlled, reversible molecular motion through changes in the relative positions of their constituent parts is receiving an ever increasing amount of interest due to the promise of potential nano-



**Scheme 1. 8.** Schematic representacion of the anion-induced molecular shuttling exhibed by a triazolium rotaxane.

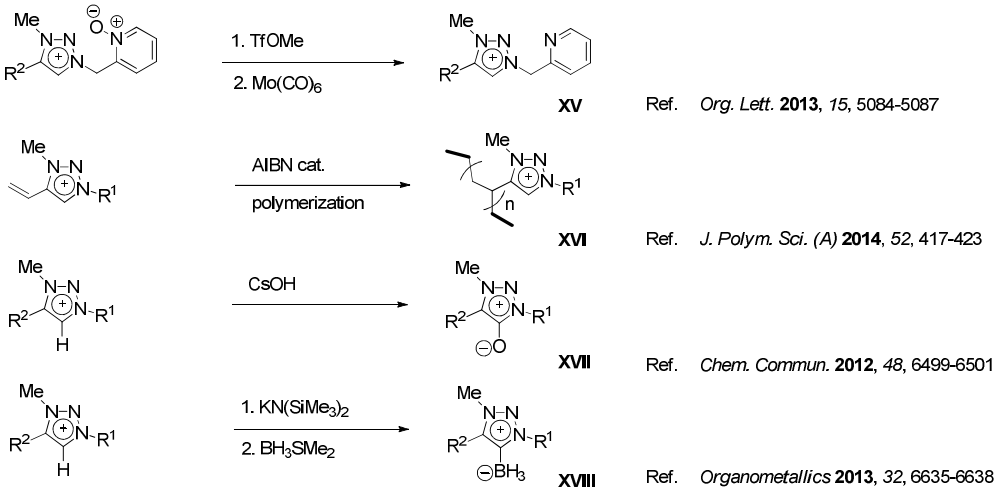
technological applications as molecular switches and machines. Although the investigation of 1,2,3-triazolium-based molecular machines is still in its infancy, several triazolium-

containing rotaxanes have been shown to be capable of controlled, reversible shuttling induced by the addition of coordinating anions (**Scheme 1. 8**)[37].

The examples disclosed above illustrate the remarkable growth experienced by the chemistry of 3-*N*-alkyl-1,2,3-triazolium salts during the last five years, boosted by their easy "click" assembly from structurally complex azides and alkynes. Despite this successful and fast development, some important aspects of the chemistry of 1,2,3-triazolium cations remain unexplored and will constitute the main subject of this PhD thesis.

## 1.2 Transformation reactions of 1,2,3-triazolium salts

With the exception of the conversion of 3-alkyl-1,2,3-triazolium salts into their corresponding transition metal carbene complexes,[38] (see Section 1.1.3) and the hydrogenolytic deprotections of benzyl ester groups in proline-containing triazolium organocatalyst precursors,[15-18] there are very few examples of chemical transformations of 1,2,3-triazolium salts to form metal-free compounds (**Scheme 1. 9**).

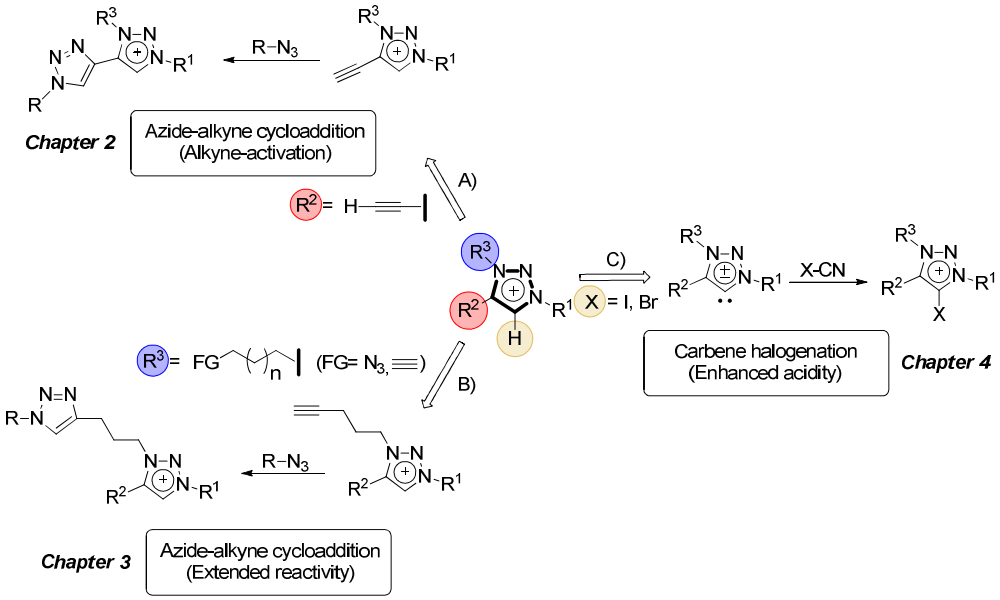



**Scheme 1. 9.** Transformation reactions of *N*-alkyl-1,2,3-triazolium salts to metal-free compounds described in prior works.

[37] Spence, G. T.; Pitak, M. B.; Beer, P. D. *Chem. Eur. J.* **2012**, *18*, 7100-7108. "Anion-induced shuttling of a naphthalimide triazolium rotaxane".

[38] For a recent review, see: Aizpurua, J.M.; Sagartzazu-Aizpurua, M.; Monasterio, Z. "Mesoionic 1,2,3-triazoles and 1,2,3-triazole carbenes" in Chemistry of 1,2,3-triazoles, *Topics in Heterocyclic Chemistry*, **2014**, *40*, 211-268. Eds. Dehaen, W.; Bakulev, V.A.; Springer-Verlag; Heidelberg.

Recently, the pyridyl *N*-oxide substituent attached at the *N*1 position of several 1,2,3-triazolium salts has been deprotected to the mixed triazolium-amine ligands **XV** using molibdenum hexacarbonyl.[39] Triazolium cations have shown to be inert to radical polymerization conditions, as illustrated by the easy conversion of the 4-vinyl-1,2,3-triazolium monomers into the corresponding polyionic liquids **XVI**.[40] Finally, upon deprotonation of the C5-H position, 3-alkyl-1,2,3-triazolium cations have been oxidized to the mesoionic oxides **XVII**[41] or transformed into the highly stable triazolium-borane ylides **XVIII**.[42]




**Scheme 1. 10.**Transformation reactions of *N*-alkyl-1,2,3-triazolium salts investigated in this PhD thesis.

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39 Bolje, A.; Kosmrlj, J. *Org. Lett.* **2013**, *19*, 5084-5087. "A selective approach to pyridine appended 1,2,3-triazolium salts".

40 Adzima, B. J.; Taylor, S. C.; He, H.; Luebke, D. R.; Matyjaszewski, K.; Nulwala, H. B. *J. Polym. Sci., Part A: Polym. Chem.* **2014**, *52*, 417-423. "Vinyl-triazolium monomers: versatile and new class of radically polymerizable ionic monomers".

41 Petronilho, A.; Müller-Bunz, H.; Albrecht, M. *Chem. Commun.* **2012**, *48*, 6499-6501. "Mesoionic oxides: facile Access from triazolium salts or triazolylidene copper precursors, and catalytic relevance".

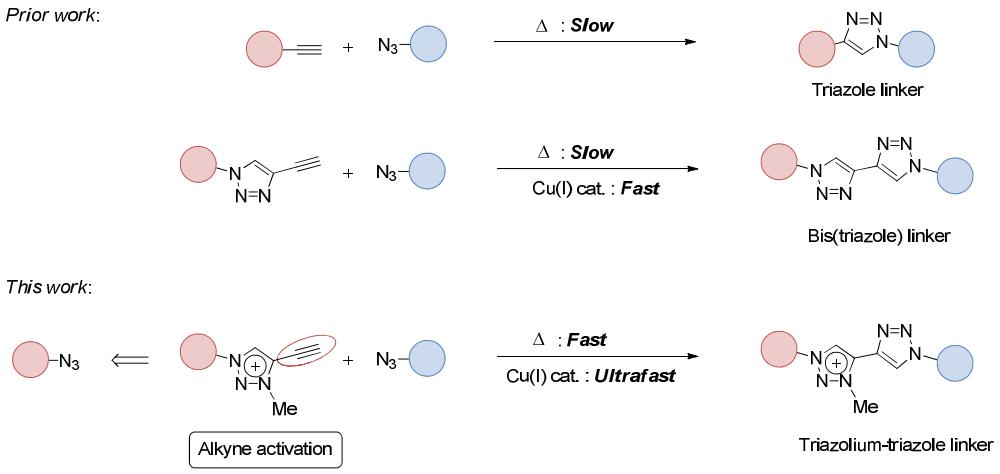
42 Oliveira Freitas, L. B.; Eisenberger, P.; Crudden, C. M. *Organometallics* **2013**, *32*, 6635-6638. "Mesoionic carbene-boranes".

In view of the scarce number of chemical reactions involving 1,2,3-triazolium salts as substrates, we planned to conduct several transformations at three of the substitution positions of the 1,2,3-triazolium ring (**Scheme 1. 10**). Furthermore, we selected such transformations to take advantage of the electronic activation provided by the triazolium system to some suitable neighboring groups.

We established the following general objectives for our research plan:

### 1.2.1 Triazolium cation-activated azide-alkyne cycloaddition reactions

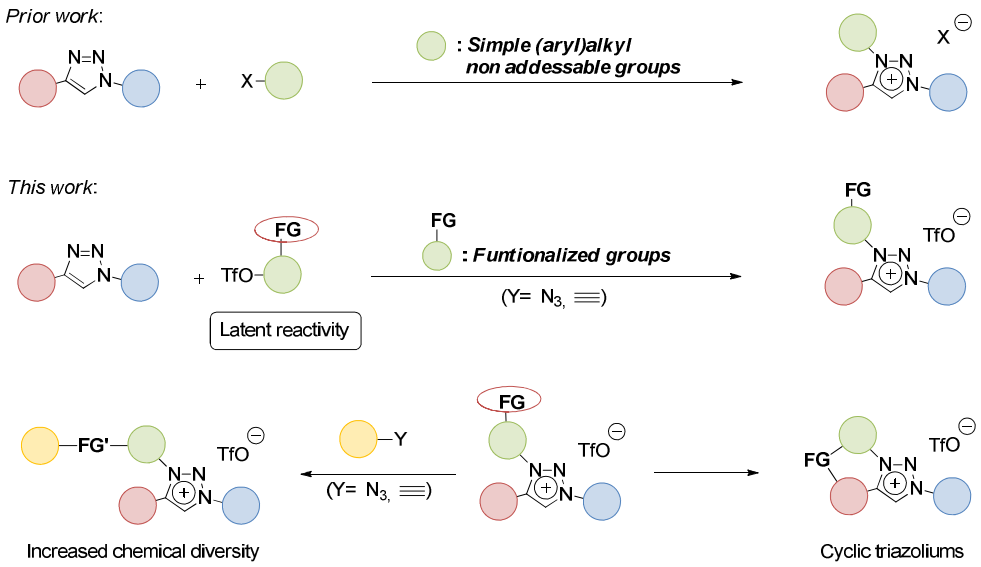
Activation of the Huisgen azide-alkyne [3+2] cycloaddition reaction using the strongly electronwithdrawing triazolium ring to alter the HOMO/LUMO energy levels of alkynes, might provide a novel entry to conjugated molecules bonded by a polar triazolium-triazole linker (**Scheme 1. 11**). Hybrid constructs could be formed following this approach starting from different organic azides, either in the absence or the presence of Cu(I) catalysts. In the later case, the strongly increased acidity of the triazolium acetylenes compared to the conventional ones, can anticipate an ultrafast CuAAC reaction rate. Detailed results related to this topic will be disclosed in Chapter 2.




**Scheme 1. 11.** "Click" azide-alkyne [3+2] cycloaddition reactions activated by *N*-alkyl-1,2,3-triazolium salts.

### 1.2.2 Triazolium salts with latent reactivity by *N*3-alkylation of 1,2,3-triazoles

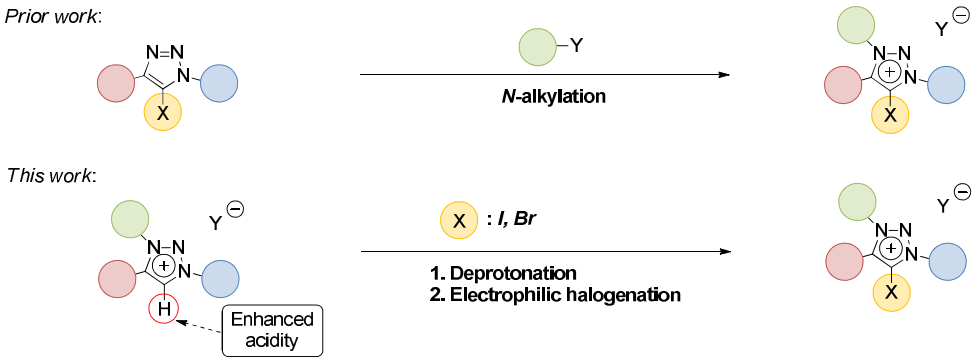
As discussed in section 1.1.1, triazolium salts carrying complex substituents at *N*1 and C4 positions from the starting azides and alkynes are well known materials. In contrast, introduction of complex (functional) groups by *N*3-alkylation into 1,2,3-triazoles remains an unsolved problem. This approach would increase considerably the scope of complex triazolium salts available, providing a synthetic entry to unprecedented complex and cyclic triazolium structures. Detailed results related to this topic will be disclosed in Chapter 3.




**Scheme 1. 12.** Complex 1,2,3-triazolium salts by *N*-alkylation with functionalized triflates.

### 1.2.3 C-Halogenation of triazolium salts through carbene intermediates

C5-Halotriazolium salts are currently available from 1*H*-1,2,3-triazoles bearing a previously installed halogen atom at C5 position by *N*3-alkylation reaction. At present there is no method to convert structurally complex *N*-alkyl-1,2,3-triazolium salts into their corresponding 5-halo derivatives. We hypothetised that mesoionic carbenes, readily available by C5-deprotonation of triazolium salts, could react with suitable electrophilic halogen sources reagents to provide 5-halo-1,2,3-triazolium salts. Detailed results related to this topic will be disclosed in Chapter 4.




**Scheme 1. 14.** C5-Halogenation of *N*-alkyl-1,2,3-triazolium salts.

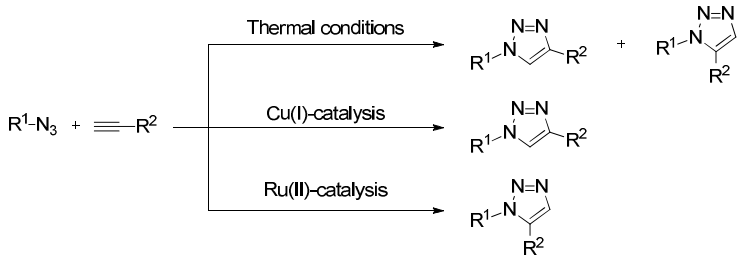
# 2

*1,2,3-Triazolium cation-activated azide-alkyne cycloaddition reactions*

# 2 Triazolium cation-activated azide-alkyne cycloaddition reactions

## 2.1 Introduction

The Huisgen[43] 1,3-dipolar cycloaddition reaction between azides and terminal or internal alkynes usually requires prolonged heating and results in mixtures of 1,4- and 1,5-regioisomers. In 2001, the groups of Meldal[44] and Sarpless[45] independently discovered that copper(I) drastically accelerates the 1,3-dipolar cycloaddition between azides and terminal alkynes (CuAAC), yielding regioselectively 1,4-disubstituted 1,2,3-triazoles. Later on, was discovered the regioselective synthesis of 1,5-disubstituted triazoles catalyzed by rhutenium(II) (RuAAC).[46] The formation of 1,5-diarylsubstituted triazoles can also be promoted by strong bases[47] (**Scheme 2. 1**).




**Scheme 2. 1.** 1,3-Dipolar cycloaddition of azides and alkynes under thermal conditions provides mixtures of 1,4- and 1,5-disubstituted 1,2,3-triazoles. The Cu(I) and Ru(II) catalysis gives single 1,4 and 1,5 diastereoisomers respectively.

As mentioned in the introduction chapter, the first general objective of this PhD thesis was to study the reaction of 4-alkynyl-1,2,3-triazolium salts with azides to form bis-

[43] a) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 633-645. "Kinetics and mechanism of 1,3-dipolar cycloadditions". b) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 565-598. "1,3-Dipolar cycloadditions. Past and future".

[44] Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem*. **2002**, *67*, 3057-3064. "Peptidotriazoles on solid phase: (1,2,3)-triazoles by regiospecific copper(I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides".

[45] Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed*. **2002**, *41*, 2596-2599. "A stepwise Huisgen cycloaddition process: copper(I)-catalyzed regioselective ligation of azides and terminal alkynes".

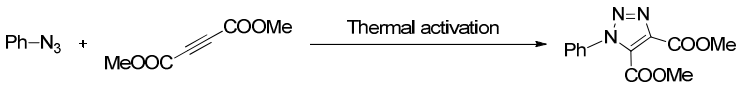
[46] Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998-15999. "Ruthenium-catalyzed cycloaddition of alkynes and organic azides".

[47] Kwok, S. W.; Fotsing, J. R.; Fraser, R. J.; Rodionov, V. O.; Fokin, V. V. *Org. Lett.* **2010**, *19*, 4217-4219. "Transition-metal-free catalytic synthesis of 1,5-diaryl-1,2,3-triazoles".

triazolium products under either thermal or catalytic conditions using cationic triazolium alkynes. To address this subject, we will survey in the subsequent sections the mechanistic details of such reactions, focusing on the electronic factors that govern their reaction rate and regioselectivity.

### 2.1.1 Thermally activated azide-alkyne 1,3-dipolar cycloadditions[48]

In 1893, Michael[49] discovered the addition reaction of phenyl azide and dimethyl acetylenedicarboxylate to form a 1,2,3-triazole (**Scheme 2. 2**). Since then, different theories have been developed to explain and rationalize the factors governing the activation and regioselectiviy of such kind of reactions.




**Scheme 2. 2.** Cycloaddition of phenyl azide and dimethyl acetylenedicarboxylate.

Huisgen classified this reaction as [3+2] 1,3-dipolar cycloaddition, the concerted addition of a 1,3-dipole azide to an alkyne triple bond. Later, Woodward and Hofmann classified the reaction as an example of pericyclic cycloaddition which is thermally allowed due to symmetrically and geometrically favorable [$_{\pi}4_{s}$ + $_{\pi}2_{s}$] molecular orbital interactions.[50] Despite this progresses, reaction rates and regisolectivity were difficult to predict until Sustmann[51] and Houk[52] applied the frontier molecular orbital (FMO) computational model to

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48 Schulze, B.; Schubert, U. S. *Chem. Soc. Rev.* **2014**, *43*, 2522-2571."Beyond click chemistry-supramolecular interactions of 1,2,3-triazoles".

49 Michael, A. J. *Prakt. Chem.* **1893**, *48*, 94-95. "Ueber die Einwirkung von Diazobenzolimid auf Acetylendicarbonsauremethylester".

50 Woodward, R. B.; Hoffmann, R. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781-853. "The conservation of orbital symmetry".

51 a) Sustmann, R. *Tetrahedron Lett.* **1971**, *12*, 2717-2720. "Simple model for substituent effects in cycloaddition reactions. I. 1,3-Dipolar cycloadditions". b) Sustmann, R.; Trill H. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 838-840. "Substituent effects in 1,3-dipolar cycloadditions of phenyl azide". c) Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569-593. "Orbital energy control of cycloaddition reactivity"

52 a) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361-369. "Frontier molecular orbital theory of cycloaddition reactions". b) Houk, K. N.; Sims, J.; Duke, R. E.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287-7301. "Frontier molecular orbitals of 1,3 dipoles and dipolarophiles". c) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301-7315. "Origin of reactivity, regioselectivity, and periselectivity in 1,3-dipolar cycloadditions".

the reaction.[53,54,55] When the dipole has a high-lying HOMO which overlaps with the LUMO of the dipolarophile, the azide is referred to as *HOMO controlled dipole* or nucleophilic dipole. In this case, HOMO-raising electron-donating groups (EDG) as well as a LUMO-lowering electron-withdrawing groups (EWG) will increase the reaction rate favouring the 1,4-isomer.[51b,c] Conversely, when the dipole has a low-lying LUMO which overlaps with the HOMO of the dipolarophile, the azide is referred to as *LUMO-controlled dipole* or electrophilic dipole, favouring the 1,5-isomer. If both the HOMO and the LUMO of the dipole can overlap simultaneously with the complementary frontier orbitals of the dipolarophile, the azide is referred to as *HOMO-LUMO-controlled dipole* or ambiphilic dipole. This kind of interaction is observed, for example, in the cycloaddition of phenyl azide and phenylacetylene which yields a mixture of 1,4- and 1,5-substituted 1,2,3-triazoles in roughly 1:1 ratio (**Figure 2. 1**).[56]

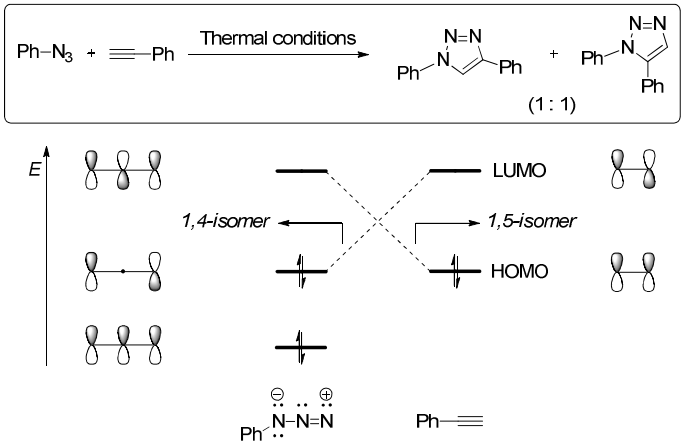


**Figure 2. 1.** Ambiphilic dipole FMO interactions for the 1,3-dipole cycloaddition of phenyl azide and phenylacetylene.[51c,57]

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53 a) Fukuzi, K. *Science* **1982**, *218*, 747-754. "Role of frontier orbitals in chemical reactions". b) Fukuzi, K.; Yonezawa, T.; Shingu, H. *J. Chem. Phys.* **1952**, *20*, 722-725. "A molecular orbital theory of reactivity in aromatic hydrocarbons".

54 a) Herndon, W. C. *Chem. Rev.* **1972**, *72*, 157-179. "Theory of cycloaddition reactions". b) Klopman, G. *J. Am. Chem. Soc.* **1968**, *90*, 223-234. "Chemical reactivity and the concept of charge- and frontier-controlled reactions". c) Salem, L. *J. Am. Chem. Soc.* **1968**, *90*, 553-566. "Intermolecular orbital theory of the interaction between conjugated systems. II. Thermal and photochemical cycloadditions".

55 Dewar, M. J. S. *THEOCHEM* **1989**, *200*, 301-323. "A critique of frontier orbital theory".

56 Kirmse, W.; Horner, L. *Liebigs Ann. Chem.* **1958**, *614*, 1-3. "Reaction of phenylacetylene with azides and diazo compounds".

57 Fleming, I. Frontier Orbitals and Organic Chemical Reactions, John Wiley & Sons, Chichester, **1976**.

In general, the quantitative Huisgen reaction rate change is well predicted by the FMO model as a function of the azide and alkyne substituents. However, the observed regioselectivity is frequently in opposition to expectations based on FMO model, in particular for varying azide substituents.[55] This lack of quantitative predictive accuracy promoted the development of sophisticated computational methods to include the distortion of the azide dipole during the interaction with the alkyne.

In an alternative approach, Houk[58] proposed a distortion/interaction model based on high-accuracy quantum chemical methods to explain the cycloaddition rate increase observed for strained cycloalkynes. **Figure 2. 2** ilustrates how the distortion, interaction and activation energies ($\Delta E^{\neq}$) required to transform the reactants into their transition-state geometries are related. The distortion alters the electronic properties by narrowing the HOMO-LUMO gap of the 1,3-dipole and increasing the charge-transfer compared to the ground state. At the transition state, the destabilizing distortion ($\Delta E_d^{\neq}$) is compensated by the stabilizing orbital interactions ($\Delta E_i^{\neq}$) enabling the formation of the cycloadduct upon further movement along the reaction coordinate. If the distortion energy is comparable for the formation of both regioisomers, orbital interactions might control the regioselectivity.

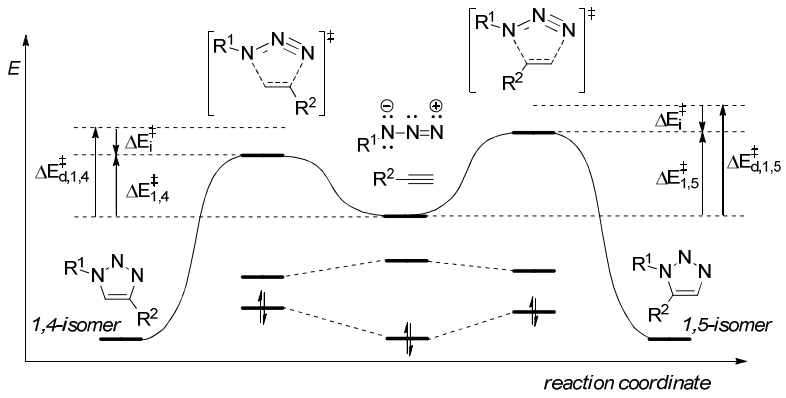


**Figure 2. 2.** The distortiton/interaction model for the azide-alkyne cycloaddition reaction.

[58] a) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 10646-10647. "Distortion/interaction energy control of 1,3-dipolar cycloaddition reactivity". b) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10187-10198. "Theory of 1,3-dipolar cycloaddition/interaction and frontier molecular orbitals models".

In view of Houk´s distortion/interaction model, it is plausible that the introduction of strain to the alkyne ground state (cyclooctyne,[58a] benzyne[59]) causes a rate enhancement in 1,3-dipolar cycloadditions (strain-promoted azide-alkyne cycloaddition, SPAAC).

### 2.1.2 Copper-catalyzed azide-alkyne cycloadditions[48,60,61]

As mentioned above, the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) yields 1,2,3-triazoles about $10^6$ times faster than conventional thermal cycloadditions and virtually complete 1,4- regioselectivity. Currently accepted CuAAC mechanism is supported by a collection of computational and experimental studies (**Scheme 2. 3**). Firstly, a Cu(I) species undergoes π coordination of the triple bond of the alkyne (**step A**). This coordination greatly increases the CH-acidity of the therminal alkyne ($pk_a$ drops from ≈25 to ≈15) and allows the subsequent formation of a σ-coordinated Cu(I) acetylide with the activated alkyne (**step B**) in aqueous media even without an additional amine base. Some studies have shown that the reaction is second order with respect to Cu(I), thus a second Cu(I) remains π-coordinated at the α-carbon of the σ-bound acetylide resembling the known μ-coordination mode of Cu(I) acetylides. In the next step, the π-coordinated Cu(I) center activates the azide by coordinating with the lone pair electrons of the nitrogen (**step C**). According to this, the azide and the acetylide are not coordinated to the same copper atom. This effect is supported by the fact that no triazole formation occurs when a preformed σ-bound Cu(I) acetylide is used as substrate without additional Cu(I).[62]

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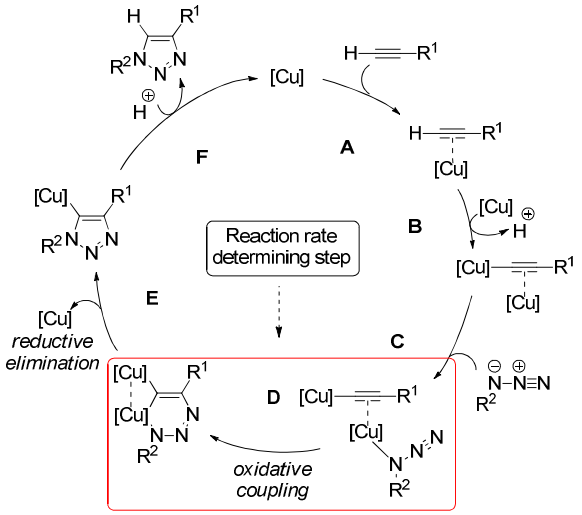
59 a) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409-2412. "Benzyne click chemistry: synthesis of benzotriazoles from benzynes and azides". b) Campbell-Verduyn, L.; Elsinga, P. H.; Mirfeizi, L.; Dierckx, R. A.; Feringa, B. L. *Org. Biomol. Chem.* **2008**, *6*, 3461-3463. "Copper-free 'click': 1,3-dipolar cycloaddition of azides and arynes".

60 Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302-1315. "Copper-catalyzed azide-alkyne cycloaddition (CuAAC) and beyond: new reactivity of copper(I) acetylides".

61 Buckley, B. R.; Heaney, H. *Top Heterocycl. Chem.* **2012**, *28*, 1-30, Springer-Verlag Berlin Heidelberg. "Mechanistic investigations of copper(I)-catalysed alkyne-azide cycloaddition reactions".

62 Worrell, B. T.; Malik, J. A.; Fokin, V. V. *Science* **2013**, *340*, 457-460. "Direct evidence of a dinuclear copper intermediate in Cu(I)-catalyzed azide-alkyne cycloadditions".




**Scheme 2. 3.** Proposed mechanism of the CuAAC ([Cu] denotes a copper fragment that varies in the number of ligands and in the formal oxidation state).

In principle, coordination of the organic azide can occur *via* both the substituted or the terminal nitrogen, but, in contrast to the π-accepting terminal nitrogen, the π-donating substituted nitrogen is expected to increase the electron density on the metal center, which would facilitate the subsequent oxidative coupling (**step D**). The observed selectivity for the 1,4-regioisomer may be explained by the preference for Cu(I) π coordination at the α-carbon of the acetylide, which directs a nucleophilic attack of the β-carbon at the terminal, electrophilic nitrogen of the coordinated azide upon oxidative coupling. As a result of the latter, rate-limiting step, a six-membered metalacycle is formed including a μ-alkenylidene. According to computational studies, this intermediate is stabilized by a geminal bimetallic coordination. Recently, the transient formation of the bimetallic cupra-cycle was corroborated by a $Cu^{63}/Cu^{65}$ crossover experiment and furthermore, improved activity has been observed when using a bimetallic, mixed-valent Cu(II)/Cu(I) catalytic system.[63] Ultimately, ring contraction and Cu(I) extrusion via reductive elimination (**step E**) affords the Cu(I)-bound triazolide in a highly exothermic process. In aqueous media, the Cu(I) triazolide then readily undergoes protonolysis (**step F**) liberating the free triazole and allowing the Cu(I) to re-enter the catalytic cycle.

[63] Kuang, G.-C.; Guha, P. M.; Brotherton, W. S.; Simmons, J. T.; Stankee, L. A.; Nguyen, B. T.; Clark, R. J.; Zhu, L. *J. Am. Chem. Soc.* **2011**, *133*, 13984-14001. "Experimental investigation on the mechanism of chelation-assisted, copper(II) acetate-accelerated azide-alkyne cycloaddition".

The addition of Cu(I)-stabilizing ligands (nitrogen-type donors) result in rate acceleration and avoid the formation of an inactive Cu(I) complex. It should be noted that Cu(I) acetylides tend to aggregate, which can stall the catalytic cycle, this is prevented by preparing the Cu(I) acetylides in the presence of the organic azide and by the addition of a polydentated hemilabile ligand.[64] A wide range of Cu(I) species have been reported in presence or not of nitrogen ligands as catalysts. However, when $CuSO_4$/sodium ascorbate is used as a Cu(I) source in aqueous media, the CuAAC is highly efficient in most cases.[45,60,64]

### 2.1.3 Reactivity of the azide substrate

As shown before, the azide taking part in a 1,3-dipolar cycloaddition reaction is characterized by the presence of an electrophilic nitrogen atom with an electron sextet and a formal positive charge, as well as a nucleophilic nitrogen atom with an electron octet and a formal negative charge placed, respectively, at 1- and 3-positions (see **Figure 2. 3**).[43b]

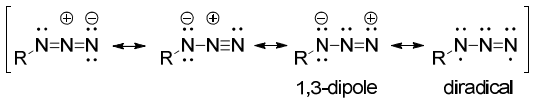
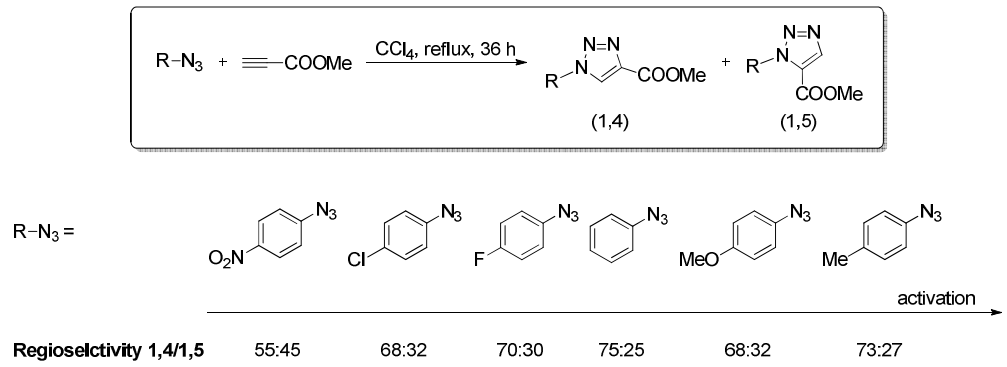



**Figure 2. 3.** Selected contributing resonance structures of an organic azide.

The rates and regioselectivities of thermal cycloaddition reaction observed for different azides can be partially modulated by placing adequate groups in their structures (**Scheme 2. 4**). Thus, electron-donating groups attached to the ring of aromatic azides slightly increase the relative cycloaddition reaction and 1,4-regioselectivity preference, whereas electron-withdrawing groups play the opposite role. As expected, aliphatic azides behave as better nucleophilic dipoles, giving rise to faster reactions and higher 1,4-regioselectivities than aromatic azides.

[64] Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952-3015. "Cu-catalyzed azide-alkyne cycloaddition".




**Scheme 2. 4.** Azide substituent effect on the activation and regioselectivity of 1,3-dipolar cycloaddition reactions with methyl propiolate.

According to the mechanism proposal for the CuAAC reaction disclosed above, electron-rich azides also accelerate the metal-catalyzed reaction by facilitating the Cu(I) π coordination at the disubstituted nitrogen atom of the azide, which would increase the electron density on the metal center, facilitating the subsequent oxidative coupling (**Scheme 2. 3**, step **C**). As expected, steric hindrance of both azide and alkyne substrates is detrimental for the reaction rate either under thermal cycloaddition conditions or under CuAAC catalysis.

### 2.1.4 Reactivity of activated alkynes

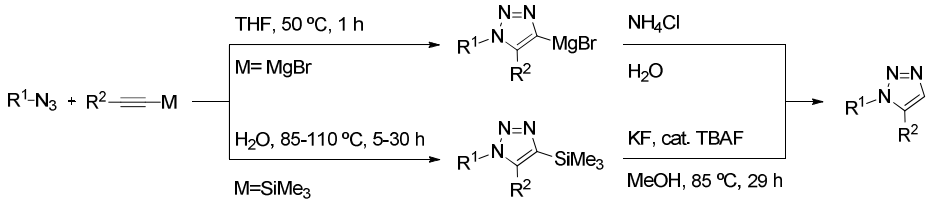
In general, azides do not react easily with alkynes in the absence of a metal catalysts since they are poor 1,3-dipolar acceptors. Therefore, different approaches have been developed to increase the reactivity of the alkyne groups to promote metal-free azide-alkyne cycloadditions under mild conditions and improved regioselectivity.

The synthesis of 1,4- or 1,5-disubstituted triazoles can be carried out by modulating the electronic properties of alkynes. Thus, 1,5-isomers can be prepared with total regioselectivity when alkynes with strong electron-donating groups (EDG) are used, such as magnesium acetylides[65] or silylacetylenes[66] (**Scheme 2. 5**). Importantly, in the trimethylsilyl directed azide-alkyne cycloadditions (SiAAC), the very high regioselectivity is only marginally affected when azide and alkyne are substituted with sterically demanding or

[65] Krasinski, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237-1240. "Direct synthesis of 1,5-disubstituted-4-magnesio-1,2,3-triazoles, revisited".

[66] Kloss, F.; Köhn, U.; Jahn, B. O.; Hager, M. D.; Görls, H.; Schubert, U. S. *Chem. Asian J.* **2011**, *6*, 2816-2824. "Metal-free 1,5-regioselective azide-alkyne [3+2]-cycloaddition".

electron-withdrawing/donating groups with the lowest 1,5-regioselectivity being about 90 % when strong EWGs are present.




**Scheme 2. 5.** Synthesis of 1,5-disubstituted-1,2,3-triazoles by using EDG-substituted alkynes.

On the other hand, several alkynes with electron-withdrawing substituents have been reported to provide increased reaction rates and preferred 1,4-regioisomers under thermal conditions.[67] In particular, some alkynyl Fisher carbene complexes give single 1,4-regioisomers[68] and propiolic acid derivatives[69,70] also show a similar trend (**Scheme 2. 6**). It is noteworthy that *N*-porpargyl propiolamide reacts with benzylazide in a fully chemoselective way, providing a mixture of 1,4 and 1,5-regioisomers exclusively at the more electrodeficient alkyne position.[71]

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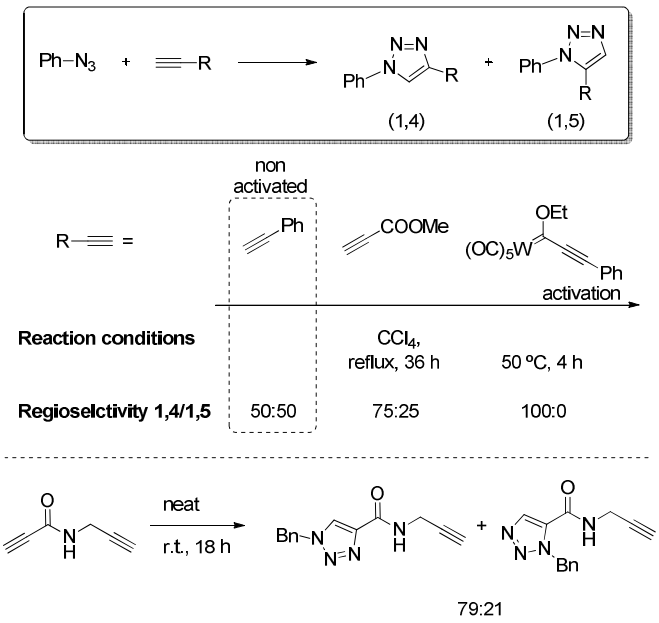
67 Becer, C. R.; Hoogenboom, R.; Schubert, U. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 4900-4908. "Click chemistry beyong metal-catalyzed cycloaddition".

68 Sawoo, S.; Dutta, P.; Chakraborty, A.; Mukhopadhyay, R.; Bouloussa, O.; Sarkar, A. *Chem. Commun.* **2008**, 5957-5959. "A new bio-active surface for protein immobilisation via copper-free 'click' between azido SAM and alkynyl Fischer carbene complex".

69 Molteni, G.; Ponti, A. *Chem. Eur. J.* **2003**, *9*, 2770-2774. "Arylazide cycloaddition to methyl propiolate: DFT-based quantitative prediction of regioselectivity".

70 Li, Z.; Seo, T. S.; Ju, J. *Tetrahedron Lett.* **2004**, *45*, 3143-3146. "1,3-Dipolar cycloaddition of azides with electron-deficient alkynes under mild condition in water".

71 Elamari, H.; Meganem, F.; Herscovici, J.; Girard, C. *Tetrahedron Lett.* **2011**, *52*, 658-660. "Chemoselective preparation of disymmetric bistriazoles from bisalkynes".



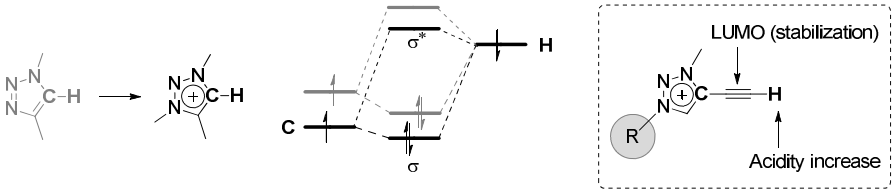

**Scheme 2. 6.** Reaction rate activation and 1,4-regioselectivity enhancement for electrodeficient alkynes under thermal cycloaddition conditions.

In contrast to the reports covering the reactivity of electrodeficient propiolic alkynes with azides under thermal conditions, to our knowledge there are no studies on a parallel reactivity enhancement conducted under CuAAC catalytic conditions. Since the mechanisms of both processes are completely different, it is not obvious to assume a straight translation of the chemical behavior observed for thermal cycloadditions with electrodeficient alkynes to CuAAC reactions.

## 2.2 Hypothesis

It is well known that the acidity of CH proton increases significantly in 1,2,3-triazolium salts with respect to the parent triazoles. As the C-H bond polarization is enhanced, the σ*(C-H) orbital is lowering in energy. We anticipated that a similar electronic trend would occur at 4-ethynyl-triazolium cations (**Scheme 2. 7**). As far as we are aware, the use of metal-free alkynes directly linked to a cationic heterocycle to assist dipolar cycloadditions has been almost completely neglected, with the exception of a few

ethynylpyridinium salts.[72] Since 4-ethynyl-triazolium salts can easily incorporate structurally complex substituents through "click" chemistry, we decided to study such novel family of compounds as metal-free *cationic* alkynes to promote fast and selective azide-alkyne cycloadditions under both thermal and CuAAC conditions.




**Scheme 2. 7.** Molecular orbital energy change caused to the C-H bond by the replacement of a 1,2,3-triazole ring (grey) by a 3-methyl-1,2,3-triazolium (black). Expected electronic effects for a triazolium cationic alkyne.

There are two reasons to consider cationic triazolium alkynes as privileged electrodeficient dipolarophiles for cycloadditions with azide dipoles: a) Many structurally different 3-alkyl-4-ethynyl-1,2,3-triazolium salts can be easily obtained from the corresponding "click" 4-ethynyl-1,2,3-triazoles by simple *N*3-alkylation under smooth conditions (e.g. *N*-methylation with MeI, MeOTf or $Me_3OBF_4$); b) Upon *N*-methylation, a simultaneous electronic stabilization of the alkyne LUMO orbital and an acidity-increase of the terminal alkyne proton can be achieved. These combined effects should increase their reactivity towards azides under thermal conditions and also under CuAAC conditions.

Regarding thermally activated azide-alkyne cycloadditions, and in agreement with the FMO model, cationic 3-methyl-1,2,3-triazolium alkynes would constitute exceptionally strong EWG dipolarophiles appropriate to accelerate the reaction and favour simultaneously the formation of 1,4-isomers by lowering both the LUMO energy level and narrowing the HOMO-LUMO gap (**Figure 2. 4**).

[72] Glasnov, T. N.; Kappe, C. O. *QSAR Comb. Sci.* **2007**, *26*, 1261-1265. "Microwave-assisted click chemistry for the preparation of 3- and 4-triazolyl-2(1*H*)-quinolones as potential fluorescent probes".

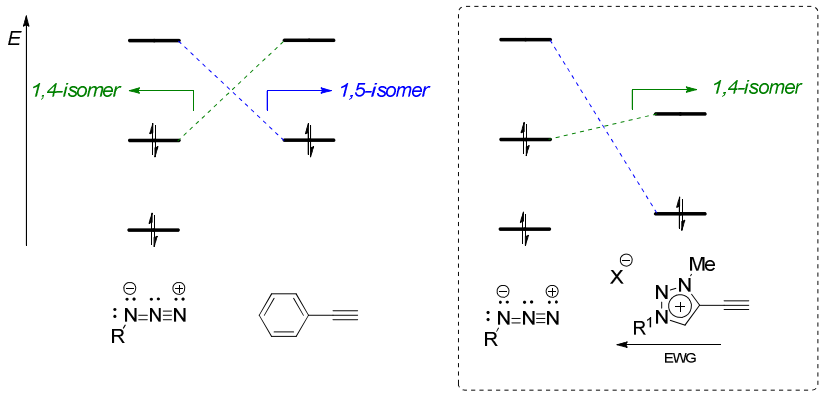
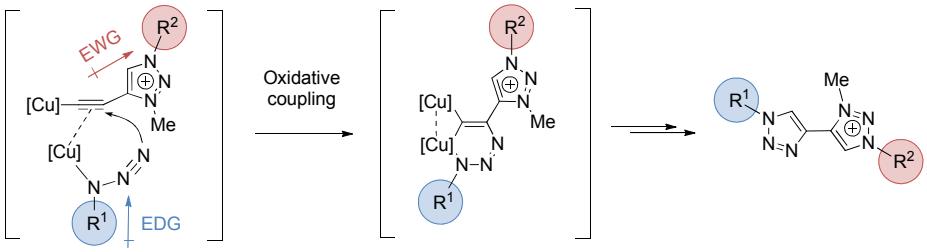



**Figure 2. 4.** Schematic representation of FMO interactions between azide and alkyne (left: phenylacetylene and right: cationic 3-methyl-4-ethynyl-1,2,3-triazolium salt).

On the other hand, it is also conceivable that CuAAC reactions could be accelerated using 4-ethynyl-3-methyl-1,2,3-triazolium cations as alkyne components. According to the mechanism proposal of CuAAC (**Scheme 2. 3**), the rate-limiting step of the catalytic cycle to form triazoles is the oxidative coupling of a di-copper(I)-alkyne-azide complex to form a nitrogen carbon bond between the terminal nitrogen of the azide and the internal carbon of the alkyne to give a di-copper-metalacycle (**step D**). We hypothesized that a strongly electron-withdrawing triazolium cation group attached to the alkyne moiety should facilitate considerably such process increasing the rate of the whole reaction. Furthermore, the increased acidity of the terminal alkyne group should cooperate to provide the key copper acetylide intermediates under milder conditions (**Scheme 2. 8**). Conversely, electron-rich azides should accelerate the reaction by facilitating the Cu(I) π coordination at the substituted nitrogen atom of the azide, which would increase the electron density on the metal center, facilitating the subsequent oxidative coupling.

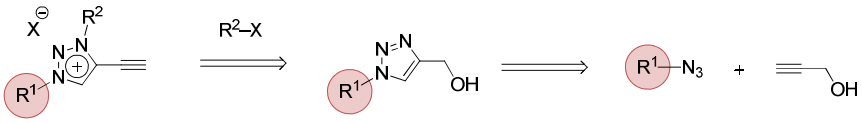



**Scheme 2. 8.** Expected acceleration of the rate-limiting CuAAC reaction step assisted by 1,2,3-triazolium cationic alkynes.

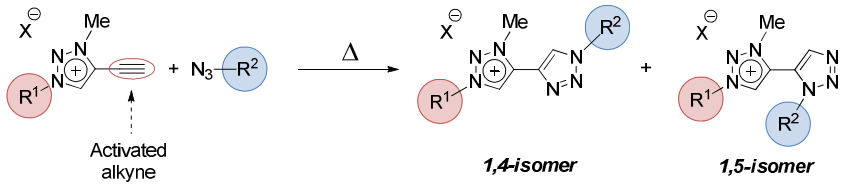
## 2.3 Objectives

According to the hypotheses described above, we selected the following partial objectives for the first part of this doctoral thesis work:

1. To design and synthesize a novel class of cationic alkynes, comprising the 3-alkyl-4-ethynyl-1,2,3-triazolium moiety, from 4-hydroxyethyl-1,2,3-triazoles.

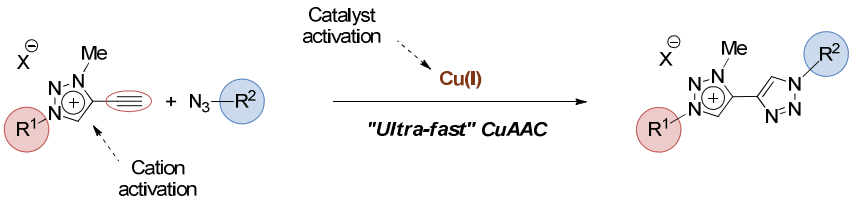



2. To conduct a kinetic study of the reaction of 4-ethynyl-3-methyl-1,2,3-triazolium salts with azides to give bicyclic 3-methyl-4-(1,2,3-triazolyl)-1,2,3-triazolium salts under thermal activation conditions. Variable temperature NMR techniques will be used to determine the main thermodynamic and kinetic parameters ($k_i$, *Ea*, $\Delta G^{\ddagger}$, $\Delta\Delta G^{\ddagger}$, etc.) involved in the transformation of cationic alkynes and azides into the 1,4- and 1,5-regioisomeric bis-triazole products.




Computational DFT calculations will be also conducted to assess the experimental results and to establish a general model to predict the activation degree and regioisomer ratios formed in this kind of Huisgen reactions. This methodology will be extended to 3-methyl-4-(propyn-1-yl)-1,2,3-triazolium salts.

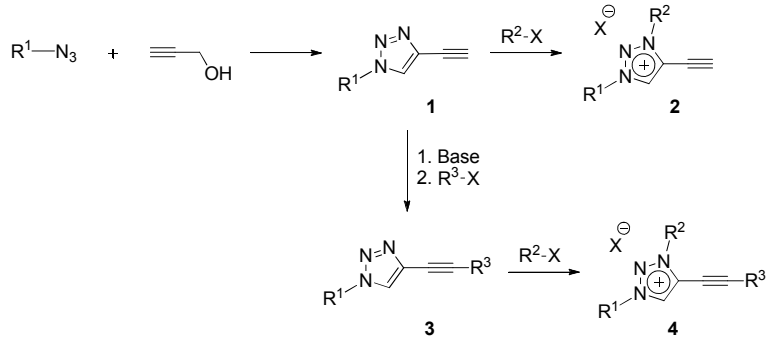
3. To develop a doubly activated azide-alkyne “click” reaction, taking advantage of the simultaneous reaction rate-acceleration provided by the use of triazolium cationic alkynes and Cu(I)-catalysts. This could be an “ultra-fast” CuAAC reaction.



## 2.4 Results and discussion

### 2.4.1 Synthesis of *N*-alkyl-1,2,3-triazolium alkynes

As stablished in the first objective of our working plan, we aimed to develop a methodology to synthesize novel cationic 3-alkyl-4-alkynyl-1,2,3-triazolium salts **2** from the corresponding 4-alkynyl-1,2,3-triazoles **1** (**Scheme 2. 9**). Seeking to conduct mechanistic studies (see below), we also considered the preparation of a few 4-alkynyl triazolium salts with internal alkyne substituents **4**.



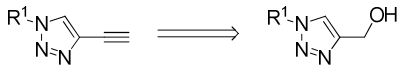

**Scheme 2. 9.** Synthesis of *N*3-alkyl-4-alkynyl-1,2,3-triazolium salts.

In the next sections of this chapter we will disclose the preparation of the parent 4-ethynyl triazoles applying a methodology previously stablished in our group, followed by a study of the *N*-alkylation of 4-alkynyl-triazoles using different alkylating reagents.

#### 2.4.1.1 Synthesis of 4-alkynyl-1,2,3-triazoles

The synthesis of 4-ethynyl-1,2,3-triazoles **1** was setted up by Dr. Itxaso Azcune and Dr. Maialen Sagartzazu-Aizpurua in our laboratory along their PhD thesis work. They used 4-hydroxymethyl-1,2,3-triazoles **5** as the key intermediate to synthesize nonsymmetrically substituted 4,4'-bis(1,2,3-triazoles) by applying a "double-click" disconnection.[42] They prepared 4-ethynyl-1,2,3-triazoles **1** following a two-step process consisting of a Swern

oxidation[73,74] followed by a Bestmann-Ohira alkynylation of the intermediate 4-formyl-1,2,3-triazoles **5** (**Scheme 2. 10**).




**1** **5**

**Scheme 2. 10.** Retrosynthesis of 4-ethynyl-1,2,3-triazoles **1**: stepwise Swern oxidation/Bestmann-Ohira alkynylation.

Following this method, we prepared the triazoles **5**, comprising a good electron-donating group (Bn) and a moderately electron-withdrawing aromatic group (NC-$C_6H_4$) (**Table 2. 1**). The Cu(I)-catalyzed click reactions of propargyl alcohol with different azides proceeded in 74-87 % yields. 4-Hydroxymethyl triazoles **5** were submitted to Swern oxidation in a very clean and almost quantitative reaction in all instances. Then, the freshly prepared aldehydes were treated directly with the Bestmann-Ohira reagent **8** and the homologated alkyne products were monitored by $^1$H NMR. The triazoles **1** were easily identified by the terminal alkyne proton signal around 3.20-3.30 ppm. As a representative example, in **Figure 2. 5** the $^1$H NMR spectra of compounds derived from 1-benzyl-4-hydroxymethyl-1,2,3-triazole **5a** are shown. In all cases, the alkynyl-triazoles **1** were prepared in good overall yields (**Table 2. 1**).

---

[73] Takizawa, K.; Nulwala, H.; Thibault, R. J.; Lowenheilm, P.; Yoshinaga, K.; Wooley, K. L.; Hawker, C. J. *J. Polym. Sci. Part A* **2008**, 2897-2912. "Facile Synthesis of 4-vinyl-1,2,3-triazole monomers by click azide/acetylene coupling".

[74] Swern oxidation mechanism:

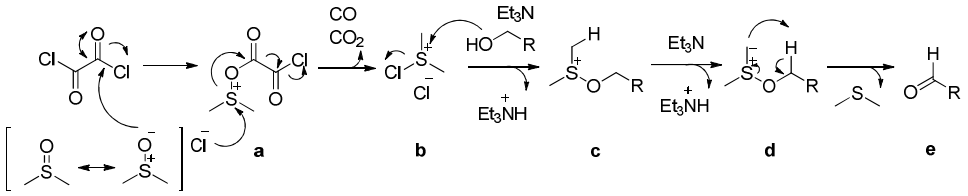
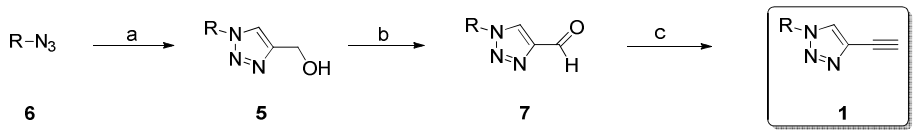


**Table 2. 1.** Homologative synthesis of 4-ethynyl-1,2,3-triazoles **1**.




Reagents and conditions: (a) $HC{\equiv}CCH_2OH$, $CuSO_4{\cdot}5H_2O$, sodium ascorbate, *t*BuOH:THF:$H_2O$, r.t., 16 h; (b) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, from -55 ºC to r.t., 75 min; (c) $MeCOCN_2PO(OMe)_2$ **8**, $K_2CO_3$, MeOH, from 0 ºC to r.t., 3 h.

| Entry | R | Azide | Alkyne | Yield[a] (%) |
|---|---|---|---|---|
| 1 | Bn- | **6b** | **1a** | 75 |
| 2 | Ph- | **6a** | **1b** | 83 |
| 3 | 4-NC-$C_6H_4$– | **6c** | **1c** | 80 |

[a]Overall yields for the transformation of alcohols **5** into alkynes **1**.

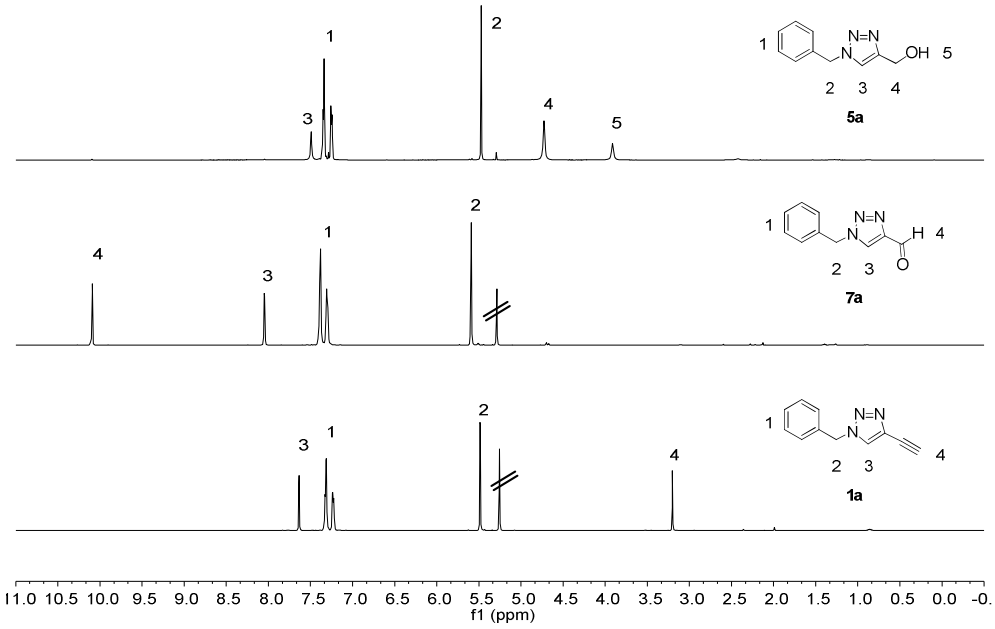
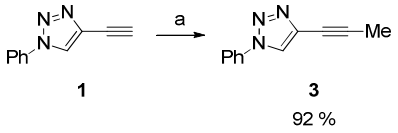



**Figure 2. 5.** $^1H$ NMR (500 MHz, $CDCl_3$) spectra of compounds **5a**, **7a** and **1a**.

The 4-(prop-1-ynyl)-1,2,3-triazole **3** was also prepared following a standard alkyne alkylation procedure.[75] Thus, the 4-ethynyl-1,2,3-triazole **1** was deprotonated with BuLi in THF at -78 ºC to form the corresponding acetylide, which was quenched with an excess MeI to provide the internal alkyne product in excellent yields (**Scheme 2. 11**).




**Scheme 2. 11.** Synthesis of the internal alkyne **3**. Reagents and conditions: (a) BuLi, THF, -78 ºC, then MeI, r.t., 5 h.

With the 4-alkynyl-1,2,3-triazoles **1** and **3** in hand, we undertook the preparation of the corresponding *N*3-alkyl-4-alkynyl-1,2,3-triazolium salts **2** and **4**.

### 2.4.1.2 Synthesis of *N*-alkyl-1*H*-1,2,3-triazolium alkynes

In an early experiment we applied the standard *N*-methylation conditions used for alkyl- or aryl-substituted triazoles.[76] Thus, the 1-benzyl-4-ethynyltriazole **1a** was treated with an excess MeI in refluxing acetonitrile for several hours. Unfortunately, this reaction resulted in a very low conversion to the expected *N*-methyl-triazolium iodide and the formation of large amounts of degradation products. Changing the iodomethane equivalents, the solvent or the reaction temperature led to unsatisfactory results in every case.

It is known that trialkyloxonium tetrafluoroborates (Meerwein salts) are highly reactive towards the *N*3 position of 1,2,3-triazoles giving a regioselective methylation or ethylation reaction of nitrogenated heterocycles, including 4,4´-bistriazoles and 4,4´-bistriazoles bridged by aromatic or aliphatic groups.[77]

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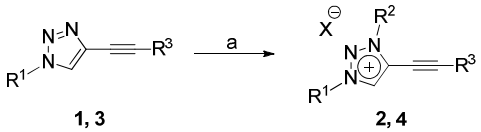
[75] Cao, C., Li, Y.; Shi, Y.; Odom, A. L. *Chem. Commun*. **2004**, 2002-2003. "α,β-Unsaturated imines from titanium hydroamination and functionalization by rhodium C–H activation".

[76] Yacob, Z.; Liebscher, J. "Chemistry of 1,2,3-triazolium salts" in Chemistry of 1,2,3-triazoles, *Topics in Heterocyclic Chemistry*, **2014**, *40*, 167-210. Eds. Dehaen, W.; Bakulev, V.A.; Springer-Verlag; Heidelberg.

[77] Schulze, B.; Friebe, C.; Hager, M. D.; Günther, W.; Köhn, U.; Jahn, B. O.; Görls, H.; Schubert, U. S. *Org. Lett.* **2010**, *12*, 2710-2713. "Anion complexation by triazolium "ligands": mono- and bis-tridentate complexes of sulfate".

**Table 2. 2.** Synthesis of *N*3-alkyl-4-ethynyl-1,2,3-triazolium salts **2** and **4**.




Reagents and conditions: (a) Alkylating reagent ($R^2$-X), $CH_2Cl_2$, r.t., 5 h.

| Entry | $R^1$ | $R^2$ | $R^3$ | $R^2$-X | Reaction Conditions | Product | Yield[a] (%) |
|---|---|---|---|---|---|---|---|
| 1 | Bn | Me | H | $Me_3OBF_4$ | $CH_2Cl_2$, r.t., 5 h | **2a** | 84 |
| 2 | Bn | Et | H | $Et_3OBF_4$ | $CH_2Cl_2$, r.t., 5 h | **2b** | 72 |
| 3 | 4-$NCC_6H_4$- | Me | H | $Me_3OBF_4$ | $CH_2Cl_2$, r.t., 5 h | **2c** | 70 |
| 4 | 4-$NCC_6H_4$- | Et | H | $Et_3OBF_4$ | $CH_2Cl_2$, r.t., 5 h | **2d** | 78 |
| 5 | Ph | Me | H | $Me_3OBF_4$ | $CH_2Cl_2$, r.t., 5 h | **2e** | 83 |
| 6 | Ph | Me | Me | MeOTf | $CH_2Cl_2$, r.t., 5 h | **4** | >99 |

[a]Yield of isolated pure product.

Accordingly, we prepared 3-alkyl-4-ethynyl-1,2,3-triazolioum tetrafluoroborates **2** (**Table 2. 2**) by treating the 4-ethynyl-1,2,3-triazoles **1** with the corresponding Meerwein salt in dichloromethane at room temperature for 5 hours. The reaction products were obtained in good yields after a single washing with $Et_2O$. A similar smooth *N*-alkylation reaction led to the 4-propynyl-triazolium compound **4** using methyl triflate instead of Meerwein salts (see entry 6 in **Table 2. 2**)

The *N*-methylation reaction was monitored by $^1$H NMR (**Figure 2. 6**) and, as expected, a substantial deshielding was observed for the terminal alkyne proton H1 and the triazole proton H2 signals of the 4-ethynyl-1,2,3-triazole **1b** after their conversion to the *N*-alkyl-triazolium salts 2. In particular, $H_1$ showed a 1 ppm downfield shift with respect to the parent triazole. This effect could be considered an evidence of the striking polarization change of the alkyne moiety caused by the *N*-methylation of the triazole ring and the subsequent formation of a conjugated cation-alkyne electronic system.

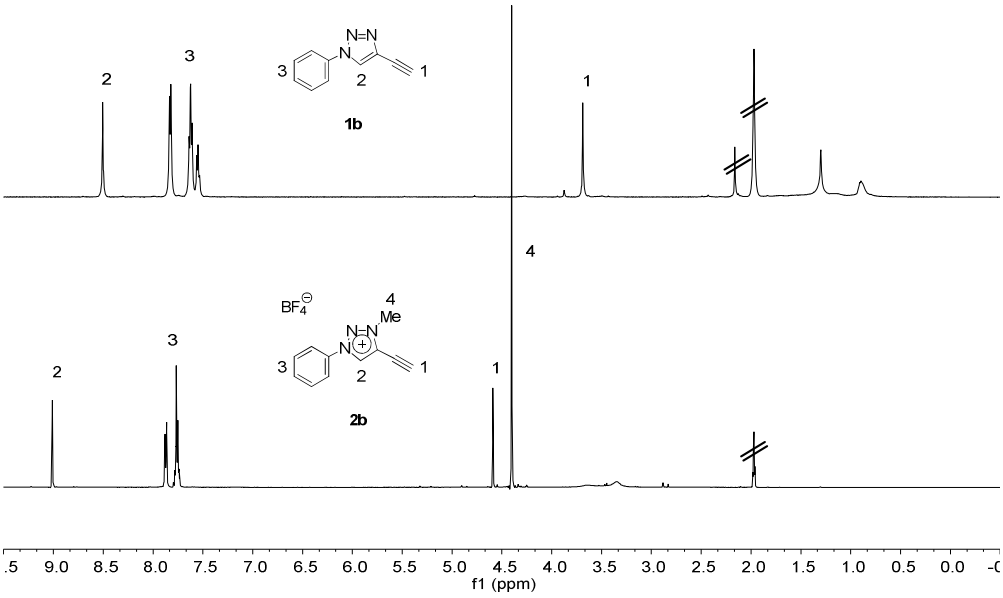
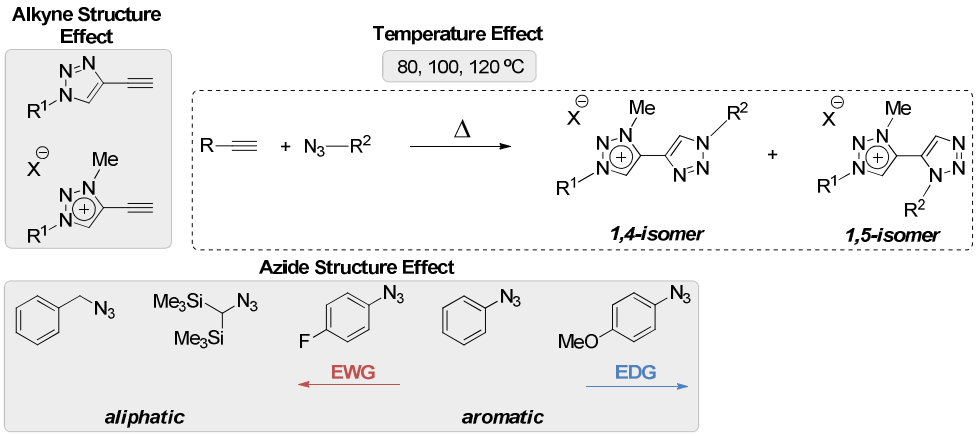



**Figure 2. 6.** $^{1}$H NMR (500 MHz, $CD_3CN$-$d_3$) spectra of 4-ethynyl-1,2,3-triazole **1b** and 4-ethynyl-3-methyl-1,2,3-triazolium tetrafluoroborate **2b**.

### 2.4.2 Kinetic study of the thermal cycloaddition reaction of cationic triazolium alkynes with azides

The next objective of our work was to conduct a study to determine the main thermodynamic and kinetic parameters ($k_i$, *Ea*, $\Delta G^{\neq}$, $\Delta\Delta G^{\neq}$, etc.) of the reaction of cationic triazolium alkynes and azides to give 1,4- and 1,5-regioisomeric bistriazole products (**Scheme 2. 12.**). We chose variable temperature NMR techniques to record the conversion-time diagrams because the conversion can be monitored in an NMR tube using deuterated solvents covering a convenient temperature range.

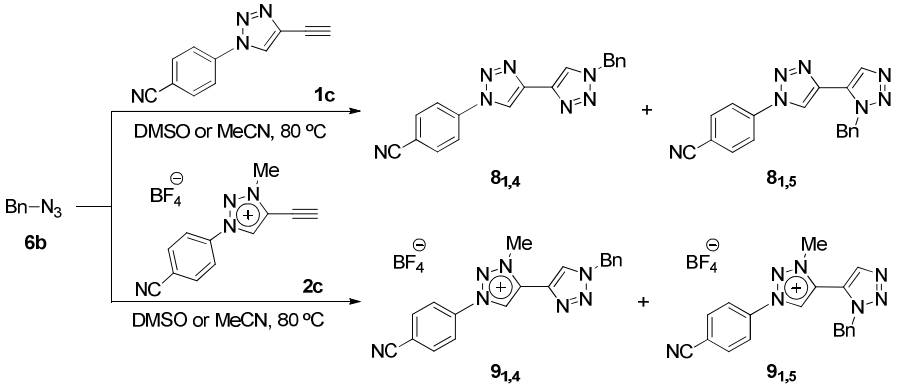



**Scheme 2. 12.** Kinetic study of the thermal cycloaddition reaction of cationic triazolium alkynes with azides.

Seeking to disclose the contribution of the dipolarophile and dipole reagents to the reaction rate and regioselectivity, we conducted three separate test sets covering the following effects: a) the structure of the cationic alkyne, b) the structure of the azide and c) the reaction temperature.

### 2.4.2.1 Alkyne structure effect

In order to determine the activation effect directly assignable to the inductive effect caused by the triazolium moiety on the alkyne reactivity, we chose to compare the kinetic




**Scheme 2. 13.** Thermal cycloaddition reaction of benzylazide with the triazole alkyne **1c** and the cationic triazolium alkyne **2c**.

behaviour of the analogous triazolium/triazole alkynes **1c** and **2c**, differing only in the methyl group attached to the triazole ring. Each reaction shown in **Scheme 2. 13** was monitored for 120 hours in two different solvents (MeCN-$d_3$ and DMSO-$d_6$) at 80 ºC following the intensity changes of the $^1$H NMR signals assigned to the triazole and triazolium protons of the reactants and products.

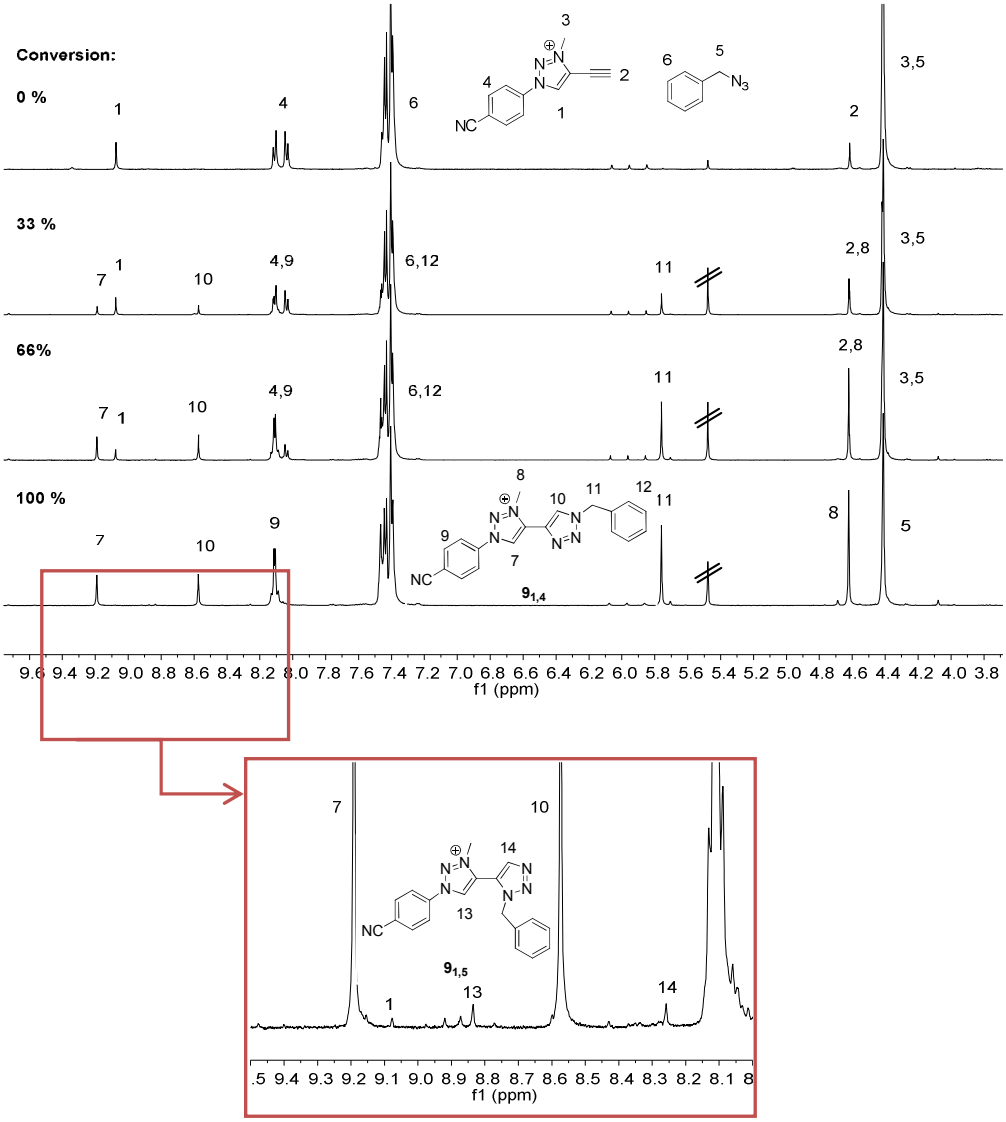



**Figure 2. 7.** $^1$H NMR (500 MHz, MeCN-$d_3$) spectra of the cycloaddition reaction of cationic triazolium alkyne **2c** with benzylazide **6b**. Bottom: expansion of the triazole proton region showing the signals of the minor 1,5-regioisomer.

For instance, **Figure 2. 7** shows a set of $^{1}$H NMR spectra recorded at different conversion for the cycloaddition of benzylazide **6b** with the triazolium alkyne **2c** to form the bis-triazoles **9**. Among the two isomeric product, the major 1,4-regioisomer was largely prevalent, but the minor 1,5-regioisomer could be detected upon expansion of the triazole C5-H region.

Conversions of 15-33 % (in MeCN-$d_3$ and DMSO-$d_6$, respectively) were recorded after the monitored time frame for alkyne **1c** (**Figure 2. 8**). Under identical conditions, a full conversion was observed for **2c** in MeCN-$d_3$ and DMSO-$d_6$. In addition, no solvent effect was observed when the cationic alkyne **2c** was used as substrate, whereas the neutral akyne **1c** showed a higher reaction rate in the polar DMSO-$d_6$ solvent than in MeCN-$d_3$.

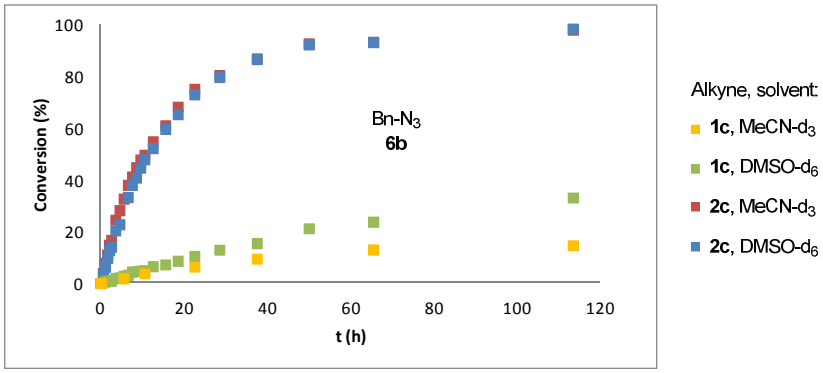



**Figure 2. 8.** Conversion-time plots for the cycloaddition reactions of benzylazide **6b** with the triazole alkyne **1c** and the cationic triazolium alkyne **2c** at 80 ºC.

Regioselectivities were also measured by $^{1}$H NMR (**Table 2. 3**). Thus, quasi-total regioselectivity in favour of 1,4-isomer (> 94 %) was observed for **2c** in MeCN-$d_3$ and DMSO-$d_6$ upon complete conversion. However, this effect was not observed when alkyne **1c** was used as the dipolarophile, and only modest regisoselectivities in favour of the 1,4-isomer (54-68%, MeCN-$d_3$ and DMSO-$d_6$, respectively) were obtained.

**Table 2. 3.** Regioselectivity of the cycloaddition of benzylazide with triazole alkynes (see **Scheme 2. 13**).

| Entry[a] | Alkyne | Product | Time (h) | Conversion (%) | 1,4-Isomer (%) | 1,5-Isomer (%) |
|---|---|---|---|---|---|---|
| 1 | **1c** | **8** | 113 | 15 (33) | 54 (68) | 46 (32) |
| 2 | **2c** | **9** | 113 | 99 (100) | 95 (94) | 5 (6) |

[a]Reactions conducted in MeCN-$d_3$ at 80 ºC. Values in parentheses correspond to equivalent reactions conducted in DMSO-$d_6$.

In **Figure 2. 9** are compared the evolutions of the concentrations of reagents and products along the reaction time, showing a dramatic increase of the reaction rate when the cationic triazolium alkyne **2c** was reacted with benzylazide in acetonitrile solution at 80 ºC. In both cases, the application of a standard kinetic simulation algorithm confirmed a concentration variation matching an ideal second order kinetic, with first order for each reagent.

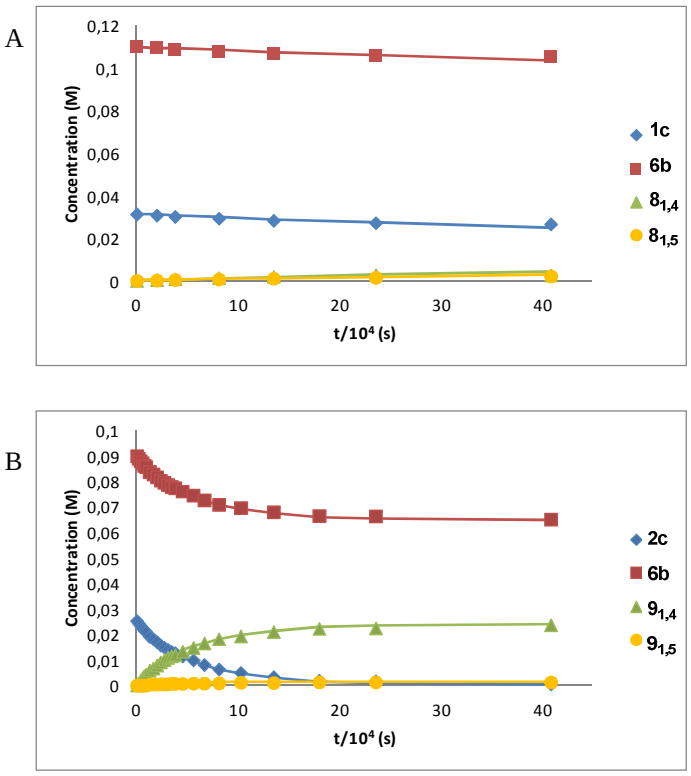
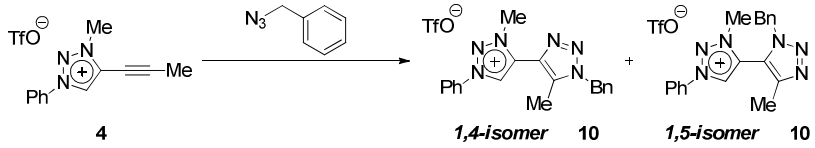



**Figure 2. 9.** Conversion evolution for the cycloaddition of benzylazide **6b** with the triazole alkyne **1c** (plot A) and the cationic triazolium alkyne **2c** (plot B) conducted in MeCN-$d_3$. Experiments conducted using 3 equivalents of benzylazide per mol of alkyne.

From these experiments, it was evident that cationic 3-alkyl-1,2,3-triazolium alkynes show a substantially higher thermal reactivity towards azides than neutral triazole alkynes. Furthermore, in good agreement with our hypothesis, an alkyne *LUMO-controlled* cycloaddition leading preferably to 1,4-regioisomers should prevail in the FMO interaction of cationic 3-alkyl-1,2,3-triazolium alkynes to form bis-triazole products. Since the structures of **1c** and **2c** only differ in the methyl group attached to the triazole *N*3 atom, these activation

and regiocontrol effects could be mostly attributed to the inductive effect exerted by the triazolium cation on the alkyne.

Finally, we ran an additional cycloaddition reaction with benzylazide to check whether the triazolium cation activation observed for the terminal alkyne **2c** could be extended to the analogous internal cation alkyne **4** (**Scheme 2. 14**).




| Solvent, T (ºC), t (h) | Overall yield (%) | 1,4/1,5 Ratio |
|---|---|---|
| MeCN-$d_3$, 80 ºC, 200 h | < 5 % | n.d. |
| Toluene, 130 ºC, 18 h | 62 % | 89:11 |

**Scheme 2. 14**. Cycloaddition reaction of benzylazide with the cationic triazolium internal alkyne **4**.

In a preliminary trial conducted in MeCN-$d_3$ at 80 ºC, only a small conversion to the bis-triazoles **10** was evidenced by $^1$H NMR after 200 h, but it was no possible to quantify the formation of the minor 1,5-regioisomer and, therefore, the 1,4/1,5 ratio. The standard procedure to carry out Huisgen cycloadditions with internal alkynes[78] often involves the heating of the reactants in boiling toluene. We adopted such methodology and heated a mixture of the internal alkyne **4** and benzylazide **6b** at 130 ºC in a sealed tube for 18 h. Under such conditions, we achieved a 62 % conversion and a remarkable[79] 1,4/1,5 isomer ratio of 89:11. This result is among the highest selectivities reported for such kind of transformations.

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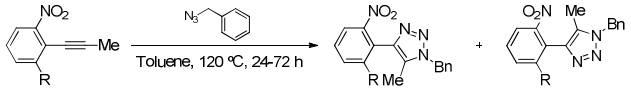
[78] McIntosh, M. L.; Johnston, R. C.; Pattawong, O.; Ashburn, B. O.; Naffziger, M. R.; Cheong, P. H.-Y.; Carter, R. G. *J. Org. Chem.* **2012**, *77*, 1101-1112. "Synthesis and computational analysis of densely functionalized triazoles using *o*-nitrophenylalkynes".

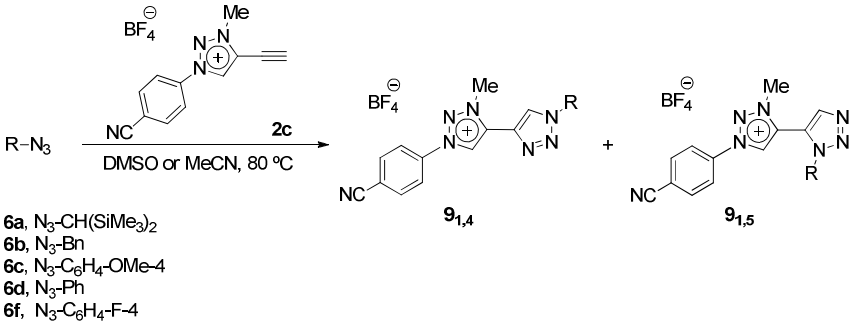



| R | t (h) | Overall yield (%) | 1,4/1,5 Ratio |
|---|---|---|---|
| Me | 72 | 43 | 50:50 |
| Cl | 24 | 65 | 67:33 |

[79] The configuration of triazole ring was confirmed by selective NOESY experiment.

### 2.4.2.2 Azide structure effect

Next, we studied the activation/stereodirection effect exerted on the cycloaddition reaction by azides of different electron charge density (**Scheme 2. 15**). In this case, according to FMO theory, azides with EDG should increase the reaction rate improving the 1,4-regioselectivity at the same time. To evaluate the implementation of this hypothesis to cationic alkynes, we studied the reaction of the triazolium dipolarophile **2c** with the azide dipoles **6a-f**, which bear different substituents representing a wide array of electronic and steric patterns.




**Scheme 2. 15.** 1,3-Dipolar cycloaddition of the cationic triazolium alkyne **2c** with different azides **6**.

The reactions shown in **Scheme 2. 15** were monitored for 113 hours in two different solvents (DMSO-$d_6$ and MeCN-$d_3$) at 80 ºC by following the intensity changes of the $^1$H NMR signals assigned to the triazole and triazolium protons of the alkyne **2c** and products **9**. Conversions higher than 90 % (MeCN-$d_3$ and DMSO-$d_6$, respectively) were attained after the monitored time frame for the alkyne (**Figure 2. 10**). Surprisingly, a strong activation was observed for bis(trimethylsilyl)methyl azide dipole, and conversion was complete after 14 hours at 80 ºC. As in previous trials, no solvent effect was observed for the cycloaddition of any of the azides tested with the cationic alkyne **2c**.

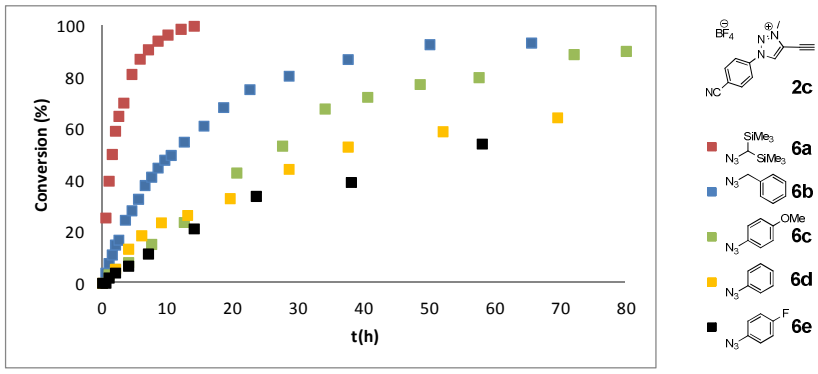
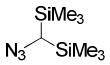
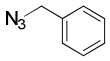
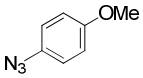
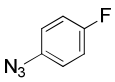



**Figure 2. 10.** Conversion-time plot for the cycloaddition reaction of the cationic alkyne **2c** (**Scheme 2. 15**) with azides (**6a-f**) in MeCN-$d_3$ (for an equivalent conversion-time plot in DMSO-$d_6$ see **Appendix 2**).

As can be seen from the conversion times listed in **Table 2. 4**, azides with aliphatic substituents (entries 1, 2) are more reactive than aromatic ones (entries 3-5). Among aromatic azides, electron-rich azides (entry 3) gave a slightly faster conversions than electron-poor aromatic azides (entry 5). Briefly, the studied azides can be ordered as follows according to their reactivity: **6e** < **6d** < **6c** < **6b** < **6a**.

**Table 2. 4.** Cycloaddition reaction outcome of the cationic triazolium alkyne **2c** with different azides.

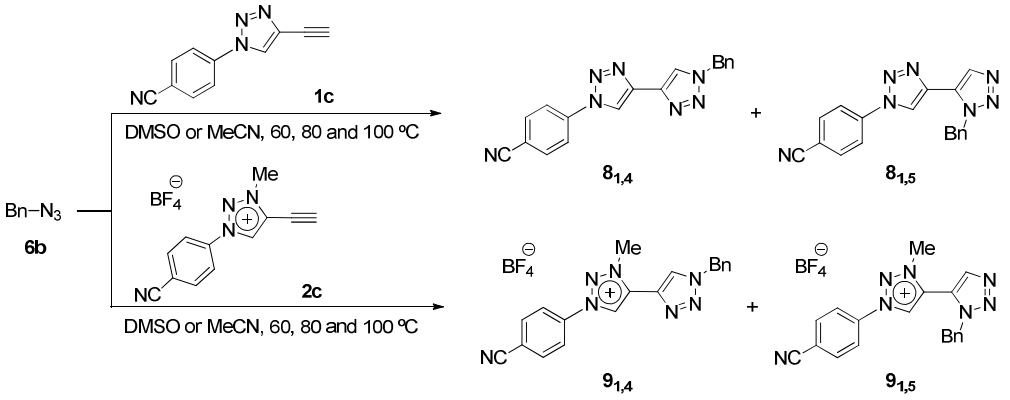
| Entry[a] | Azide | | Time (h) | Conversion (%) | 1,4-Isomer (%) | 1,5-Isomer (%) |
|---|---|---|---|---|---|---|
| 1 |  | **6a** | 14 | 100 | 99 | 1 |
| 2 |  | **6b** | 60 | 99 | 95 | 5 |
| 3 |  | **6c** | 80 | 95 | 95 | 5 |
| 4 |  | **6d** | 113 | 92 | 96 | 4 |
| 5 |  | **6e** | 113 | 90 | 94 | 6 |

[a]Reactions conducted in MeCN-$d_3$ at 80 ºC.

Finally, the very high regioselectivity (> 94 %) attained in every instance is worth mentioning. Specially, because it is only marginally affected when the azide is substituted with sterically demanding or electron-withdrawing/donating groups. This fact suggests that energy perturbations on the azide HOMO orbital caused by usual substituents makes a relatively modest contribution to the HOMO-LUMO interactions governing the reaction regioselectivity.

### 2.4.2.3 Temperature effect

Although the reaction rate enhancement of alkyne-azide cycloadditions by increasing the temperature can be confidently anticipated, the precise effect of the temperature on the regioselectivity is not obvious. In order to establish such effect, we studied the reaction of benzylazide **6b** with triazole alkynes **1c** and **2c** at different temperatures. Experiments were conducted in a sealed NMR tube in MeCN-$d_3$ and DMSO-$d_6$ at 60, 80 and 100 ºC.




**Scheme 2. 16.** Thermal cycloaddition of benzylazide with the triazole alkyne **1c** and the cationic triazolium alkyne **2c** at different temperatures.

Again, the reaction conversions were easily calculated from the intensity changes of the $^1$H NMR signals assigned to the triazole and triazolium protons of the reactants and products. As shown in **Figure 2. 11**, temperature rapidly increased the reaction rate when the cationic alkyne **2c** was used as a dipolarophile with benzylazide. For instance, after a 13 h reaction time, the conversion raised from 20 % at 60 ºC, 52 % at 80 ºC to 90 % at 100 ºC.

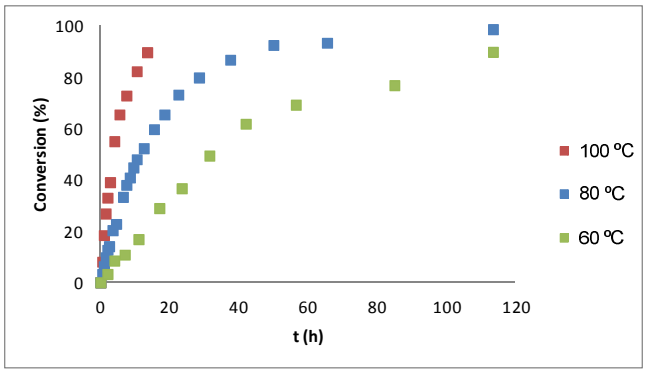



**Figure 2. 11.** Conversion-time plot for the cycloaddition reaction of cationic triazolium alkyne **2c** with benzylazide at 60, 80 and 100 ºC in MeCN-$d_3$ (for an equivalent conversion-time plot in DMSO-$d_6$ see **Appendix 2**).

**Table 2. 5.** Conversion of triazole alkyne **1c** and cationic triazolium alkyne **2c** into bis-triazole products **8** and **9** (see **Scheme 2. 16**) at different temperatures.

| Entry[a] | Alkyne | Product[b] | Temperature (ºC) | Time (h) | Conversion (%) | 1,4-Isomer (%) | 1,5-Isomer (%) |
|---|---|---|---|---|---|---|---|
| 1 | | | 60 | 113 | 10 (14) | 65 (69) | 35 (31) |
| 2 | **1c** | **8** | 80 | 113 | 23 (37) | 54 (68) | 46 (32) |
| 3 | | | 100 | 13 | 16 (38) | 62 (66) | 38 (34) |
| 4 | | | 60 | 113 | 90 (93) | 85 (88) | 15 (12) |
| 5 | **2c** | **9** | 80 | 113 | 99 (100) | 95 (94) | 5 (6) |
| 6 | | | 100 | 13 | 92 (100) | 97 (95) | 3 (5) |

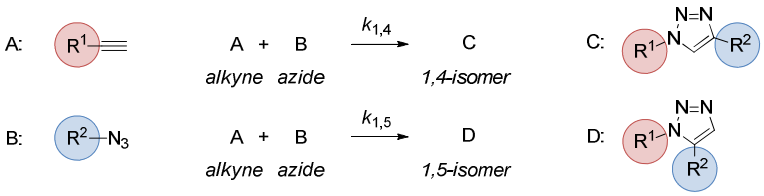
[a]Reactions conducted in MeCN-$d_3$. Values in parentheses correspond to equivalent conversions in DMSO-$d_6$. [b]Combined mixtures of 1,4- and 1,5- isomers.

The reaction rates and conversions increase by raising the temperature. In addition, 1,4-regioselectivity was also slightly improved with the temperature when the cationic alkyne **2c** was used as dipolarophile. However, this effect was not observed for the neutral alkyne **1c** which gave very similar regioselectivities at the three different temperatures.

After the accomplishment of our preliminary reactivity investigation of the cycloaddition reaction of cationic triazolium alkynes with azides, we conducted a more accurate quantitative study to determine the kinetic parameters governing these reactions.

#### 2.4.2.4 Determination of the reaction rate constants by NMR spectroscopy

From a kinetic point of view, the thermal cycloaddition of an alkyne (**A**) and an azide (**B**) to give a mixture of 1,4-triazole (**C**) and 1,5-triazole (**D**) is actually the combination of two different competitive bimolecular reactions, each of them is 1st order with respect to **A** and **B**.[80] Therefore, two independent rate constants ($k_1$ and $k_2$) have to be determined at a given temperature to establish the conversion of the system at any time.




The kinetic constants were calculated by solving the set of differential equations by a standard fourth order Rounge-Kutta method along with the minimization of an objective function using the last square approach.[81]

In a constant-volume isothermal ideal system, ignoring the backward reaction for a large excess of one reactant, excluding side reactions and neglecting the activity coefficients of the compounds in the mixture, the reaction rate of the alkyne (**A**) is calculated as follows:

$$-\mathrm{r_A} = \frac{\partial[A]}{\partial t} = \frac{\partial[B]}{\partial t} = k_{1,4}[A][B] + k_{1,5}[A][B] = (k_{1,4} + k_{1,5})[A][B] \qquad \textbf{eq. 2. 1}$$

**Eq. 2.1** may be writen in terms of alkyne mole fraction, $X_A$:

$$-\mathrm{r_A} = [A]_0 \frac{\partial X_A}{\partial t} = (k_{1,4} + k_{1,5})([A]_0 - [A]_0 X_A)([B]_0 - [A]_0 X_A) \qquad \textbf{eq. 2. 2}$$

if $M = \frac{[B]_0}{[A]_0}$ is the initial mole ratio of reactants **A** and **B**,

[80] *Ingeniería de las Reacciones Químicas*, Octave Levenspiel, Ed. Reverté, S. A., **1986**, Barcelona.
[81] H. S. Fogler. Elements of chemical reaction engineering. Ed. Prentice Hall. 3a ed. New Jersey, 1999

$$-\mathrm{r_A} = (k_{1,4} + k_{1,5})[A]_0^2(1 - X_A)(M - X_A) \qquad \textbf{eq. 2. 3}$$

this differential equation can be integrated as follows:

$$\int_0^{X_A} \frac{dX_A}{(1 - X_A)(M - X_A)} = [A]_0 k \int_0^t dt \qquad \textbf{eq. 2. 4}$$

and solved to give:

$$\boxed{ln\frac{[B]}{M[A]} = ([B]_0 - [A]_0)(k_{1,4} + k_{1,5})t = ([B]_0 - [A]_0)m_1 t} \qquad \textbf{eq. 2. 5}$$

wherein $(k_{1,4} + k_{1,5}) = m_1$

On the other hand, taking into account the formation rates of the products **C** and **D**:

$$r_C = \frac{\partial[C]}{\partial t} = k_{1,4}[A][B] \qquad \textbf{eq. 2. 6}$$

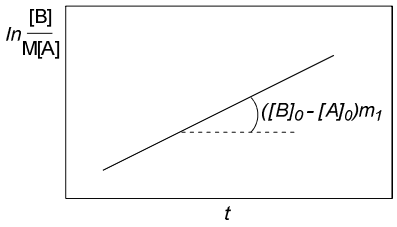
$$r_D = \frac{\partial[D]}{\partial t} = k_{1,5}[A][B] \qquad \textbf{eq. 2. 7}$$

the following rate constant ratio can be established dividing **eq. 2.6** by **eq. 2.7**:

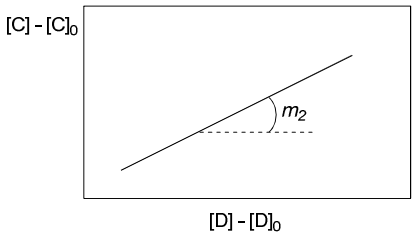
$$\boxed{\frac{r_C}{r_D} = \frac{k_{1,4}}{k_{1,5}} = \frac{[C] - [C]_0}{[D] - [D]_0} = m_2} \qquad \textbf{eq. 2. 8}$$

$m_1$ and $m_2$ can be calculated from the slope of **eq. 2.5** and **eq. 2.8**:

From **eq. 2.5**:




From **eq. 2.8**:




Finally, the rate constants $k_{1,4}$ and $k_{1,5}$ can be calculated from $m_1$ and $m_2$,

$$\left.\begin{array}{l} k_{1,4} + k_{1,5} = m_1 \\ \dfrac{k_{1,4}}{k_{1,5}} = m_2 \end{array}\right\} \rightarrow \begin{array}{l} k_{1,4} = m_1 - k_{1,5} \\ k_{1,5} = \dfrac{m_1}{1 + m_2} \end{array} \qquad \textbf{eq. 2. 9}$$

The second order kinetics plots used to calculate $k_{1,4}$ and $k_{1,5}$ constants for the reaction of benzylazide **6b** with alkynes **1c** and **2c** in MeCN-$d_3$ at different temperatures are shown in **Figure 2. 12** and **Figure 2. 13**. In each case, the rate constant $k_{1,4}$ leading to the 1,4-regioisomers was calculated ploting *ln([B]/M[A])* vs *time*, and the $k_{1,5}$ constant leading to the 1,5-regioisomers was calculated plotting $[C]-[C]_0$ vs $[D]-[D]_0$. The calculated $k_{1,4}$ and $k_{1,5}$ values are gathered in **Table 2. 6** and **Table 2. 7** for alkynes **1c** and **2c** respectively.

B

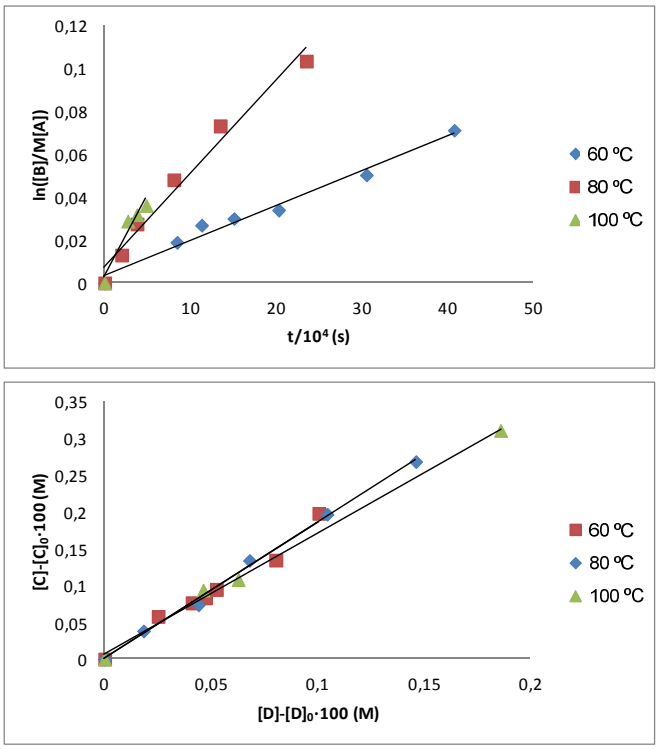
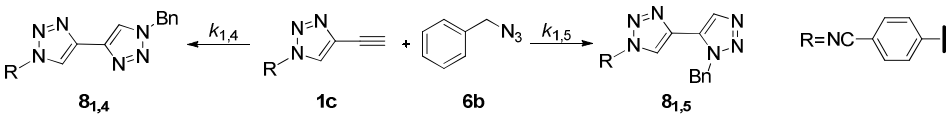



**Figure 2. 12.** Second order reaction rate plots for the cycloaddition of benzylazide **6b** with triazole alkyne **1c**. A: reactants conversion **eq. 2.5**; B: products formation **eq. 2.8**.

**Table 2. 6.** Rate constants measured at different temperatures for the reaction of benzylazide **6b** with the triazole alkyne **1c**.




| Entry | Solvent | T (°C) | $k_{1,4}$ (L·mol$^{-1}$·s$^{-1}$) | $k_{1,5}$ (L·mol$^{-1}$·s$^{-1}$) |
|---|---|---|---|---|
| 1 | | 60 | $1.60\cdot10^{-6}$ | $8.68\cdot10^{-7}$ |
| 2 | MeCN-$d_3$ | 80 | $3.29\cdot10^{-6}$ | $1.78\cdot10^{-6}$ |
| 3 | | 100 | $1.83\cdot10^{-5}$ | $1.10\cdot10^{-5}$ |
| 4 | | 60 | $1.61\cdot10^{-6}$ | $7.32\cdot10^{-7}$ |
| 5 | DMSO-$d_6$ | 80 | $5.55\cdot10^{-6}$ | $2.68\cdot10^{-6}$ |
| 6 | | 100 | $1.78\cdot10^{-5}$ | $9.69\cdot10^{-6}$ |

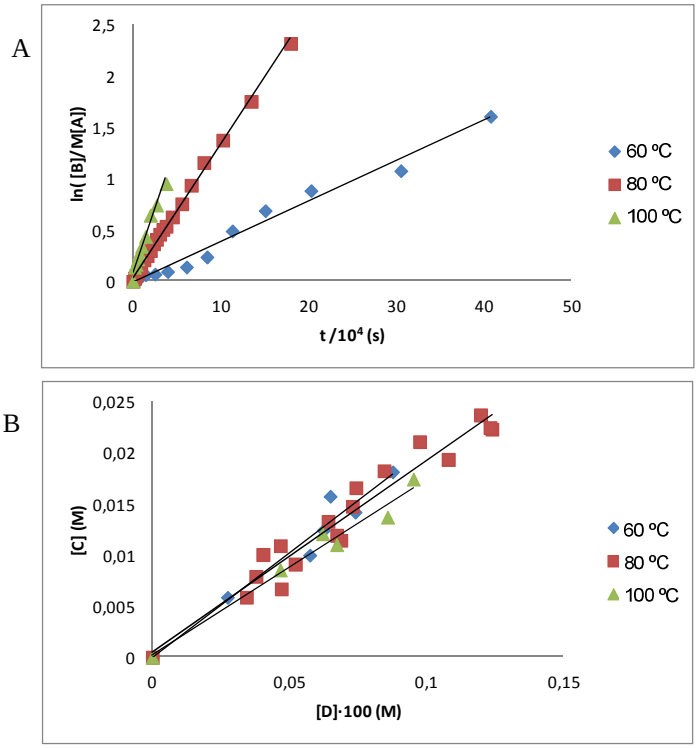
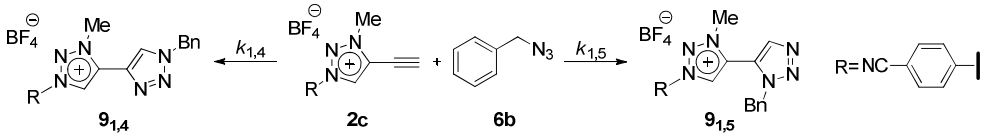



**Figure 2. 13.** Second order reaction rate plots for the cycloaddition of benzylazide **6b** with triazole alkyne **2c**. A: reactants conversion **eq. 2.5**; B: products formation **eq. 2.8**.

**Table 2. 7.** Rate constants measured at different temperatures for the reaction of benzylazide **6b** with the cationic triazolium alkyne **2c**.




**9$_{1,4}$** **2c** **6b** **9$_{1,5}$**

| Entry | Solvent | T (ºC) | $k_{1,4}$ (L·mol$^{-1}$·s$^{-1}$) | $k_{1,5}$ (L·mol$^{-1}$·s$^{-1}$) |
|---|---|---|---|---|
| 7 | | 60 | $7.09\cdot10^{-5}$ | $3.48\cdot10^{-6}$ |
| 8 | MeCN-$d_3$ | 80 | $1.46\cdot10^{-4}$ | $7.84\cdot10^{-6}$ |
| 9 | | 100 | $2.75\cdot10^{-4}$ | $1.60\cdot10^{-5}$ |
| 10 | | 60 | $6.67\cdot10^{-5}$ | $3.20\cdot10^{-6}$ |
| 11 | DMSO-$d_6$ | 80 | $1.11\cdot10^{-4}$ | $6.74\cdot10^{-6}$ |
| 12 | | 100 | $4.43\cdot10^{-4}$ | $2.34\cdot10^{-5}$ |

From the data collected in the tables, we draw the following conclusions:

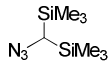
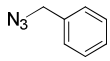
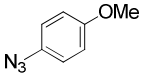
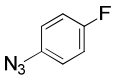
a. Rising the temperature from 60 ºC to 100 ºC caused the increase of both $k_{1,4}$ and $k_{1,5}$ either for the neutral alkyne **1c** or the cationic alkyne **2c**, but the rate-increase was about 11-13 times larger for the former, and only 4-7 times for the later. Thus, the reactivity of cationic alkynes towards azides seems to be less sensitive to temperature changes than neutral alkynes.

b. At comparable temperatures, the cationic alkyne **2c** reacted with benzylazide about 40-44 times faster than the neutral alkyne **1c** to afford the major 1,4-regioisomers. However, this rate increase was only 2-4 times for the minor 1,5-regioisomers. This observation is in agreement with a preferred *HOMO controlled dipole* orbital interaction (see **Figure 2. 1** in **section 2.1.1**) for cationic triazolium alkynes with respect to the neutral triazole counterparts.

c. In all instances, the solvent effect on the reaction rate constants was found to be negligible, since all the values were essentially identical in acetonitrile and DMSO.

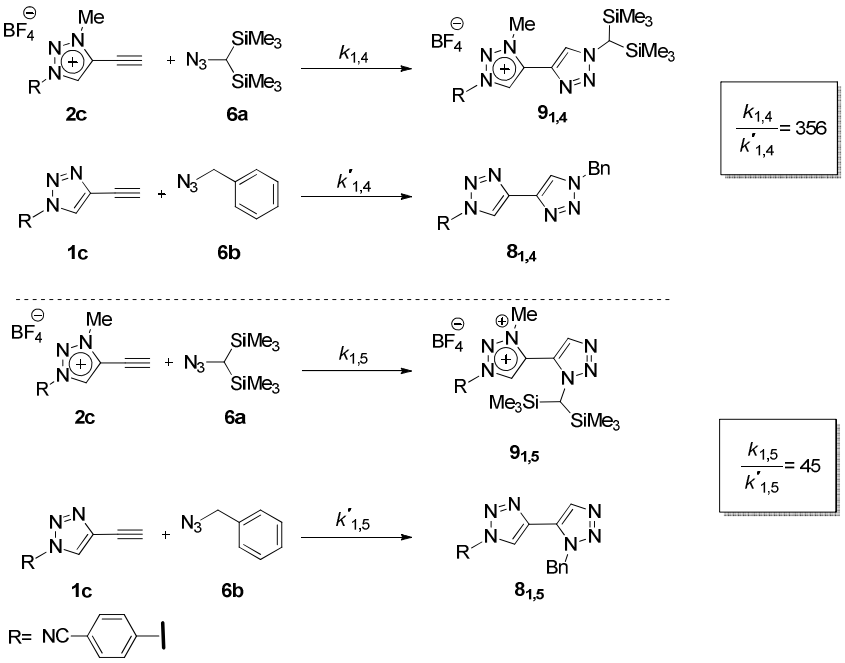
Following the same procedure described above, we calculated the rate constants for the cycloaddition of the cationic triazolium alkyne **2c** with different azides at 80 ºC in MeCN-$d_3$ and DMSO-$d_6$, respectively. The calculated $k_{1,4}$ and $k_{1,5}$ constants leading to the 1,4- and 1,5-regioisomers are listed in **Table 2. 8**.

**Table 2. 8.** Rate constants for the reaction of different azides with the cationic triazolium alkyne **2c** measured at 80 ºC in MeCN-$d_3$ and DMSO-$d_6$.

| Entry[a] | Azide | $k_{1,4}$ (L·mol$^{-1}$·s$^{-1}$) | $k_{1,5}$ (L·mol$^{-1}$·s$^{-1}$) |
|---|---|---|---|
| 1 |  **6a** | $1.17\cdot10^{-3}$ ($0.70\cdot10^{-3}$) | $8.15\cdot10^{-5}$ ($9.96\cdot10^{-5}$) |
| 2 |  **6b** | $1.46\cdot10^{-4}$ ($1.11\cdot10^{-4}$) | $7.94\cdot10^{-6}$ ($6.89\cdot10^{-6}$) |
| 3 |  **6c** | $7.84\cdot10^{-5}$ ($7.98\cdot10^{-5}$) | $4.45\cdot10^{-6}$ ($3.10\cdot10^{-6}$) |
| 4 |  **6d** | $2.33\cdot10^{-5}$ ($3.63\cdot10^{-5}$) | $1.90\cdot10^{-6}$ ($1.06\cdot10^{-6}$) |
| 5 |  **6e** | $3.56\cdot10^{-5}$ ($3.58\cdot10^{-5}$) | $2.09\cdot10^{-6}$ ($2.00\cdot10^{-6}$) |

[a]Values in parentheses correspond to DMSO-$d_6$.

Again, it is apparet from the data collected in the table that strongly electron donating azides (entry 1) react with the cationic alkyne **2c** up to 33 times faster than aromatic azides with electron-withdrawing groups (entry 5). Moreover, the combination of such electron rich azides and cationic triazolium alkyne provides an even greater reaction rate increase when compared with the non activated alkynes and azides (**Scheme 2. 17**). This rate increase is much more significant for the cycloaddition leading to 1,4-regioisomers than to the 1,5-regioisomers. For example, the cycloaddition of bis(trimethylsilyl)methyl azide **6a** with the cationic alkyne **2c** is 356 times faster than the cycloaddition of benzylazide with the uncharged triazole alkyne **1c**. But, the formation of the corresponding 1,5-regioisomers from the same substrates is only 45 times faster.




**Scheme 2. 17.** Rate constant comparison for azide-alkyne cycloaddition reactions leading to 1,4- and 1,5-regioisomers.

### 2.4.2.5 Determination of thermodynamic parameters

#### 2.4.2.5.1 Activation energy

The activation energy ($E_a$) of a chemical reaction can be easily calculated from the reaction rate constants ($k$) using the Arrhenius´s law (see **eq. 2.10**):

$$k = k_0 e^{-E_a/RT} \qquad \textbf{eq. 2. 10}$$

For practical purposes, a linear relationship between the rate constant and the temperature can be achieved using **eq. 2.11**:

$$lnk = lnk_0 - \frac{E_a}{RT} \qquad \textbf{eq. 2. 11}$$

A plot of *ln k* vs *1/T* gives a straight line with slope $-E_a/R$ which intercepts the ordinate axis at $k_o$ (frequency factor) as shown in figure **Figure 2. 14** for the reaction of benzylazide with triazole alkyne **1c** (plot A) and triazolium alkyne **2c** (plot B) in MeCN-$d_3$

(for plots in DMSO-$d_6$ see **Appendix 2**). In each diagram separate straights represent the reaction rate variation leading to 1,4-isomers ($k_{1,4}$) and 1,5-isomers ($k_{1,5}$).

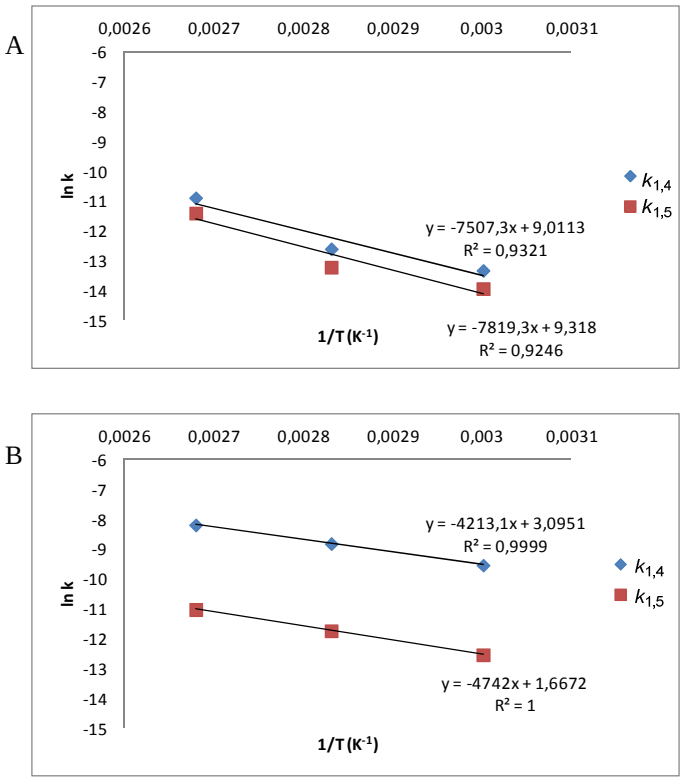



**Figure 2. 14.** Plots of *ln k* vs *1/T*, for the reaction of benzylazide **6b** with the triazole alkyne **1c** (plot A) and the triazolium alkyne **2c** (plot B) measured between 60 ºC and 100 ºC in MeCN-$d_3$.

Values of the activation energies calculated from the plots of **Figure 2. 14** are given in **Table 2. 9**.

**Table 2. 9.** Activation energies, ($E_a^{\neq}$) for the cycloaddition of benzylazide with triazole alkynes **1c** and **2c** in MeCN-$d_3$.

| Entry[a] | Alkyne | $E_a^{\neq}{}_{1,4}$ (kcal·mol$^{-1}$) | $E_a^{\neq}{}_{1,5}$ (kcal·mol$^{-1}$) |
|---|---|---|---|
| 1 | **1c** | 14.92 (14.83) | 15.54 (15.94) |
| 2 | **2c** | 8.37 (11.58) | 9.42 (12.21) |

[a]Values in parentheses correspond to activation energies measured in DMSO-$d_6$.

From the data collected in the **Table 2. 9**, we can conclude that the activation of the cycloaddition reaction of the triazole alkyne **1c** is disfavoured with respect to cationic alkyne **2c** by about 6 kcal·mol$^{-1}$ for the formation of both 1,4- and 1,5-regioisomers. Moreover, the activation energy difference leading to each regioisomer was slightly higher for the cationic alkyne **2c** (1 kcal·mol$^{-1}$) than for the neutral alkyne **1c** (0.6 kcal·mol$^{-1}$). Finally, slightly lower values of activation energies (2.8-3.2 kcal·mol$^{-1}$) were found in DMSO-$d_6$, than in MeCN-$d_3$ only for the cationic alkyne **2c**. This fact is in good agreement with the known tendency of the 1,3-dipolar cycloaddition to occur preferably in non-coordinating solvents.

Although the activation energy provides a useful *macroscopic* indication for a reaction to occur, a *microscopic* approach describing the thermodynamic paramethers governing the formation of the transition state can be more accurately established with the activation Gibbs energy.

#### 2.4.2.5.2 Activation Gibbs energy

The activation Gibbs energy ($\Delta G^{\neq}$) of a reaction is defined by the following relationship between the activation enthalpy ($\Delta H^{\neq}$) and activation entropy ($\Delta S^{\neq}$):

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \qquad \textbf{eq. 2. 12}$$

The activation enthalpy and entropy represent, respectively, the energetic and structural components of the activation Gibbs energy required to attain the reaction transition state from the reagents, and can be calculated from the Eyring equation (occasionally also known as Eyring-Polanyi equation) which describes the variation of the rate of a chemical reaction with temperature:

$$k = \frac{k_B T}{h} e^{-\Delta G^{\ddagger}/RT} \qquad \textbf{eq. 2. 13}$$

wherein $k_B$ is the Boltzmann's constant and $h$ is the Planck's constant. **eq. 2.13** may be written as:

$$k = \left(\frac{k_B T}{h}\right) e^{-\Delta H^{\ddagger}/RT} \cdot \mathrm{e}^{\Delta S^{\ddagger}/\mathrm{R}} \qquad \textbf{eq. 2. 14}$$

To find the linear form of the Eyring-Polanyi equation:

$$ln\frac{k}{T} = -\frac{\Delta H^{\ddagger}}{R}\frac{1}{T} + ln\frac{k_B}{h}\frac{\Delta S^{\ddagger}}{R} \qquad \textbf{eq. 2. 15}$$

Plotting of $ln\,(k/T)$ vs $1/T$ gives a straight line of slope $-\Delta H^{\ddagger}/R$ from which the activation enthalpy can be calculated. This straight intercepts the coordinate axis at $ln(k_B/h) + \Delta S^{\ddagger}/R$ providing the activation entropy value. Plots corresponding to the triazole alkyne **1c** (plot A) and the cationic triazolium alkyne **2c** (plot B) are shown in **Figure 2. 15** (see **Appendix** 2 for equivalent plots in DMSO-$d_6$). In each case, the activation paramethers $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were independently calculated for the reactions leading to 1,4-regioisomers ($k_{1,4}$) and to 1,5-regioisomers ($k_{1,5}$). The calculated paramethers together with the activation Gibbs energy $\Delta G^{\neq}$ are collected in **Table 2. 10**.

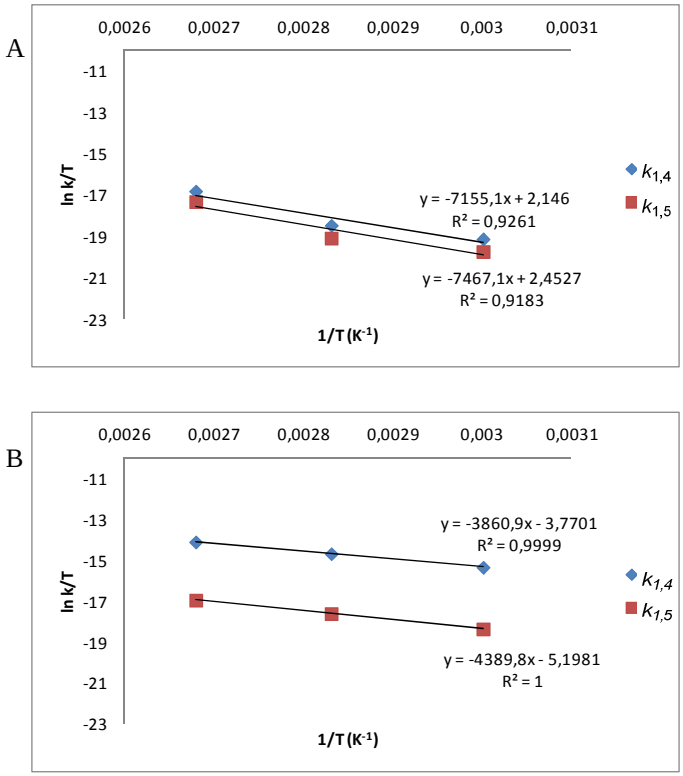



**Figure 2. 15.** Eyring-Polanyi equation plots for the cycloaddition of benzylazide with the triazole alkyne **1c** (plot A) and the triazolium alkyne **2c** (plot B) in MeCN-$d_3$.

**Table 2. 10.** Main kinetic activation parameters measured for the cycloaddition of benzylazide **6b** with the triazole alkyne **1c** and the cationic triazolium alkyne **2c**.

| Entry[a] | Alkyne | $\Delta H^{\neq}_{1,4}$ | $\Delta H^{\neq}_{1,5}$ | $\Delta S^{\neq}_{1,4}$ | $\Delta S^{\neq}_{1,5}$ | $\Delta G^{\neq}_{1,4}$ | $\Delta G^{\neq}_{1,5}$ | $\Delta\Delta G^{\neq}_{1,4\rightarrow 1,5}$[b] |
|---|---|---|---|---|---|---|---|---|
| | | kcal·mol$^{-1}$ | | cal·mol$^{-1}$·K$^{-1}$ | | kcal·mol$^{-1}$ | | |
| 1 | **1c** | 14.22 | 14.84 | - 43 | - 42 | 29.38 | 29.79 | 0.41 |
| | | (14.13) | (15.24) | (- 43) | (- 41) | (29.27) | (29.76) | (0.49) |
| 2 | **2c** | 7.67 | 8.72 | - 55 | - 58 | 26.99 | 29.04 | 2.05 |
| | | (10.89) | (11.52) | (- 46) | (- 50) | (26.95) | (29.00) | (2.05) |

[a]Masured in MeCN-$d_3$. Values in parentheses correspond to reactions conducted in DMSO-$d_6$. [b]$\Delta\Delta G^{\neq} = \Delta G^{\neq}_{1,5} - \Delta G^{\neq}_{1,4}$.

An inspection of the activation parameters of the **Table 2. 10** revealed that both enthalpy ($\Delta H^{\neq} > 0$) and entropy ($\Delta S^{\neq} < 0$) activation parameters were moderately unfavorable for an spontaneous transformation. A more detailed comparison of entries 1 and 2 showed, however, that the enthalpy factor was about 6 kcal·mol$^{-1}$ lower for the cationic alkyne **2c**, whereas the entropy component was 12-16 cal·mol$^{-1}$·K$^{-1}$ lower for the neutral alkyne **1c**. This observation was consistent with a mechanistic interpretation of the cycloaddition reaction with benzylazide **6b** involving a stronger electronic activation for the cationic alkyne **2c** and a less sterically hindered interaction for alkyne **1c** to form the corresponding triazole products.

Regarding the reaction regioselectivity, a comparison of the activation Gibbs energy columns 5, 6 and 7, reveals that both alkynes **1c** and **2c** have higher $\Delta G^{\neq}_{1,5}$ activation energies than $\Delta G^{\neq}_{1,4}$. Nevertheless, the activation energy difference ($\Delta\Delta G^{\neq}$) is significantly larger (2.1 kcal·mol$^{-1}$) for the cationic alkyne **2c** than for the neutral alkyne **1c** (0.4 kcal·mol$^{-1}$). This results were in good agreement with the experimental observation that isomer ratio 1,4/1,5 was larger for the cationic alkyne **2c** than for the neutral akyne **1c**. Finally, an excellent correlation of the measured $\Delta\Delta G^{\neq}$ values and the experimental 1,4/1,5 isomer ratio was found in each case (see bellow, **Table 2. 11**).

### 2.4.3 Computational study of the thermal cycloaddition reaction of benzylazide with triazole and triazolium alkynes

In parallel to the experimental work, a collaboration with Dr. José Ignacio Miranda (SGIker, UPV-EHU) enabled us to conduct a computational exploration of the [3+2] dipolar cycloaddition of benzylazide **6b** and the triazole alkynes **1c**, **2c** and **4** shown in **Figure 2. 16**.

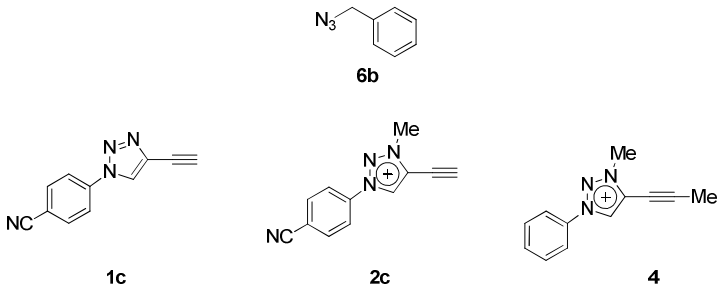



**Figure 2. 16.** Structures of the triazole alkynes studied for cycloaddition with benzylazide. Anionic components were excluded from computation.

Computational calculations were conducted B3LYP/6-31++G** level of theory, as implemented in the Gaussian09 suite of programs.[82] Stationary points had only one negative frequency and thermodynamic corrections were derived by calculating the Hessian matrix analytically at such level of theory. Single-point calculations with the self-consistent reaction field (SCRF) based on the IEF-PCM8 solvation model (MeCN, ε = 36.64; Toluene, ε = 2.37) were carried out on the previously optimized most relevant structures at 80ºC and 130ºC, respectively. The standard state for all thermodynamic data was 298.15 K and 1 atm. Two transition states and reaction products were computed for each benzylazide/alkyne pair leading, respectively to the 1,4- and 1,5-regioisomers, as shown in **Figure 2. 17**.

[82] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.

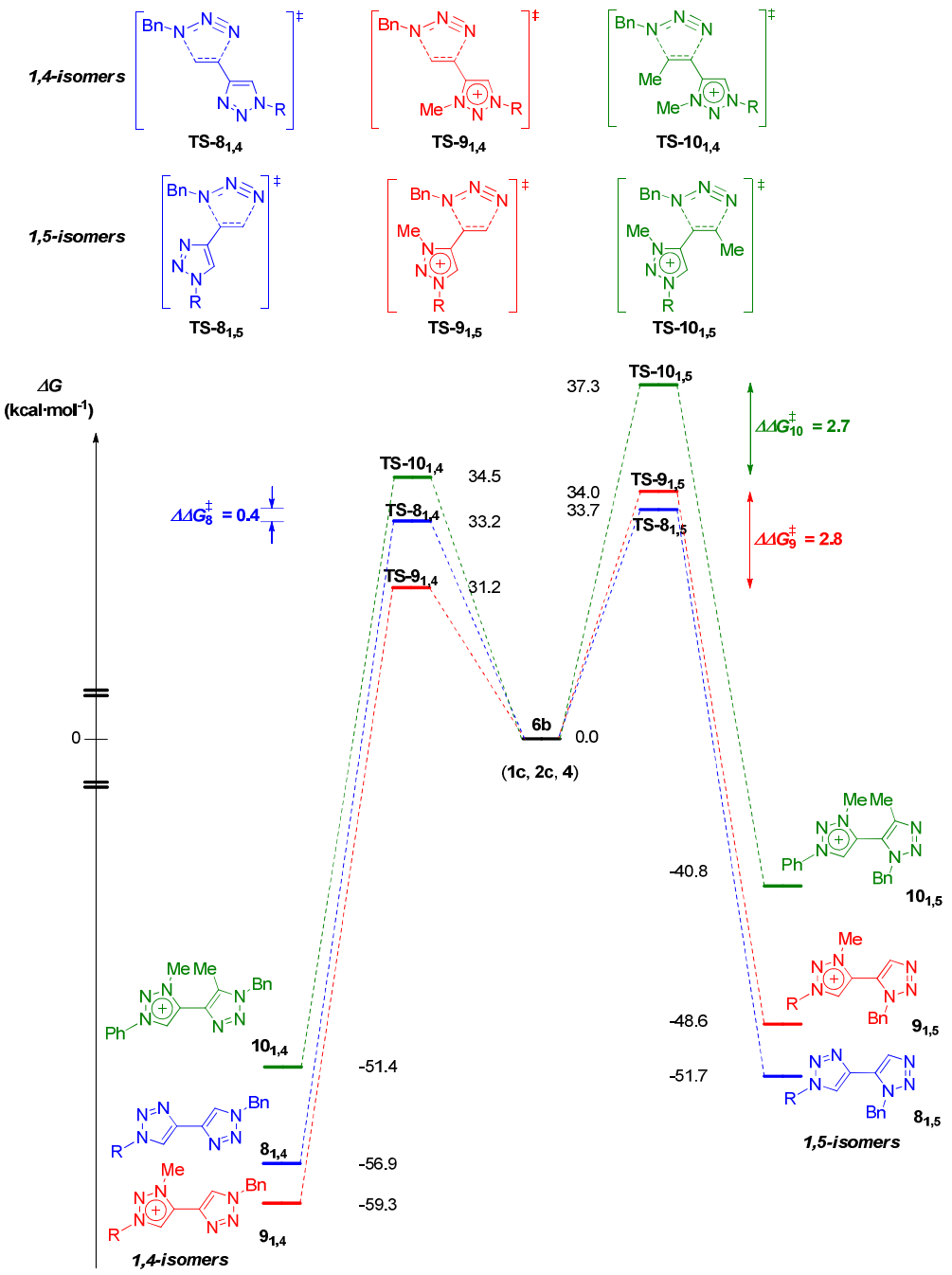


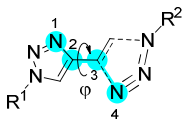

**Figure 2. 17.** Transition states and reaction products computed at B3LYP/6-31++G** level of theory for the cycloaddition reaction of benzylazide **6b** and triazole alkynes **1c**, **2c** and **4**. Relative $\Delta G^{\neq}$ energies in kcal·mol$^{-1}$ calculated at 80 ºC in MeCN (for **1c** and **2c**) and 130 ºC in toluene (for **4**).

A comparison of the activation Gibbs energies computed for the 6 transition states showed that the lower activation barriers corresponded in all instances to the 1,4-regioisomers. Such pathways were always of lower activation free energy than the equivalent transition states leading to 1,5-regioisomers. The activation barrier difference $\Delta\Delta G^{\neq}$ between each pair of 1,4-/1,5- isomers was about 2.7 kcal·mol$^{-1}$ for the cationic alkynes **2c** and **4**, but for the neutral alkyne **1c**, was only 0.4 kcal·mol$^{-1}$. Calculated activation Gibbs energies and regioselectivities collected in **Table 2. 11** were in excellent agreement with the experimental values measured (see **Table 2. 10**).

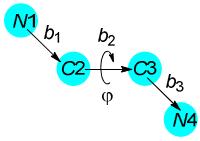
The selective stabilizing trend predicted by the calculations for charged alkynes **2c** and **4** with respect to uncharged alkyne **1c**, could also be extended to the reaction products. Indeed, each 4-(triazolyl)triazolium salt $\mathbf{9_{1,4}}$ or $\mathbf{10_{1,4}}$ was about 10-11 kcal·mol$^{-1}$ more stable than the equivalent $\mathbf{9_{1,5}}$ and $\mathbf{10_{1,5}}$ regioisomers. However, the neutral 4,4-bis-triazole $\mathbf{8_{1,4}}$ was only 5 kcal·mol$^{-1}$ more stable than the regioisomer product $\mathbf{8_{1,4}}$.

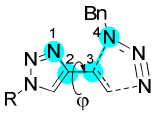
The origin of the higher cycloaddition regioselectivity observed for the cationic alkynes **2c** and **4** with respect to the neutral alkyne **1c** was assumed to be related to geometry differences in the transition states (**Table 2. 11**). After a carefull inspection, we noticed that the dihedral angle (φ), comprising the *N*1-*C*2 atoms of the parent triazole and the *C*3-*N*4 atoms of the newly formed triazole, was substantially different for the $TS_{1,4}$ and $TS_{1,5}$ transition states of the charged alkynes **2c** and **4** and the uncharged alkyne **1c**. For the later, both $TS_{1,4}$ and $TS_{1,5}$ displayed two quasi coplanar triazole rings forming 177 º and 29 º torsion angles, respectively. In contrast, the two triazole rings of the $TS_{1,4}$ and $TS_{1,5}$ transition states of the cationic alkyne **2c** were coplanar only for $TS_{1,4}$ (φ= 178 º), but orthogonal for $TS_{1,5}$ (φ= -90 º). This fact should allow a stabilizing conjugated electron-withdrawing effect of the triazolium ring *only for the coplanar* $TS_{1,4}$ of the charged alkyne **2c**, but not for $TS_{1,5}$. This should account for the experimentally measured activation free energy difference $\Delta\Delta G^{\neq}$ of about 2-3 kcal·mol$^{-1}$ between $TS_{1,4}$ and $TS_{1,5}$ transition states. A similar pattern applies for the internal cationic alkyne **4**.

**Table 2. 11.** B3LYP/6-31++G** transition state structures and Gibbs energies for the 1,3-dipolar cycloaddition of benzylazide and triazole alkynes **1c**, **2c** and **4**. Relative free energies are in kcal·mol$^{-1}$.

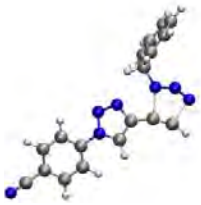



1,4-isomer




1,5-isomer

| Entry[a] | $\Delta G^{\neq}$ $TS_{1,4}$ | $\Delta G^{\neq}$ $TS_{1,5}$ | $\Delta\Delta G^{\neq}_{1,4/1,5}$ | 1,4/1,5 Ratio |
|---|---|---|---|---|
| 1 |  **TS-8$_{1,4}$** $\Delta G^{\neq}_{1,4}$= 33.3[b] (29.4) φ= 177 º |  **TS-8$_{1,5}$** $\Delta G^{\neq}_{1,5}$= 33.7[b] (29.8) φ= 29 º | 0.4[b] (0.4) | 65:35[b] (54:46) |
| 2 |  **TS-9$_{1,4}$** $\Delta G^{\neq}_{1,4}$= 31.2[b] (27.0) φ= 178 º |  **TS-9$_{1,5}$** $\Delta G^{\neq}_{1,5}$= 34.0[b] (29.0) φ= -90 º | 2.8[b] (2.0) | 98:2[b] (95:5) |
| 3 |  **TS-10$_{1,4}$** $\Delta G^{\neq}_{1,4}$= 34.5[c] φ= 179 º |  **TS-10$_{1,5}$** $\Delta G^{\neq}_{1,5}$= 37.3[c] φ= -84 º | 2.8[c] | 95:5[c] (89:11) |

[a]All values are in kcal·mol$^{-1}$. Values in parentheses represent experimental results. [b]Calculated in MeCN at 80 ºC. [c]Calculated in toluene at 130 ºC.

From the computational data recorded above and the previously measured kinetic activation values, it was possible to draw some general conclusions on the particular reactivity shown by triazolium cationic alkynes towards azides in [2+3] thermal cycloadditions:

a. Azides react with cationic triazolium alkynes to form 1,4-disubstituted triazoles at a significantly higher rate than the equivalent uncharged alkynes.

b. Relative energy barriers of the $TS_{1,4}$ transitions states for cationic triazolium alkynes are about 2-3 kcal·mol$^{-1}$ lower than the $TS_{1,5}$ ones for a given azide. Therefore, the resulting regioisomeric bis-triazole products usually show 1,4-/1,5- ratios above 90%.

c. The selective triazolium activating effect for 1,4-regioisomers occurs not only in terminal triazolium alkynes, but also in internal alkynes directly attached to the triazolium cation.

### 2.4.4 Doubly activated CuAAC reactions

As demostrated above, cationic triazolium alkynes show an enhanced thermal reactivity with azides. A qualitative activation range of up to two orders of magnitude with respect to equivalent neutral alkynes could be stablished (**Figure 2. 18**, **A**). Following our work plan, we addressed the third objective of this chapter, the study of the reactivity of cationic triazolium alkynes with azides under CuAAC conditions. We surmised that a double inductive and catalytic activation would occur allowing an "ultra-fast" conversion to the corresponding 1,4-disubstituted-triazole products (**Figure 2. 18**, **B**).

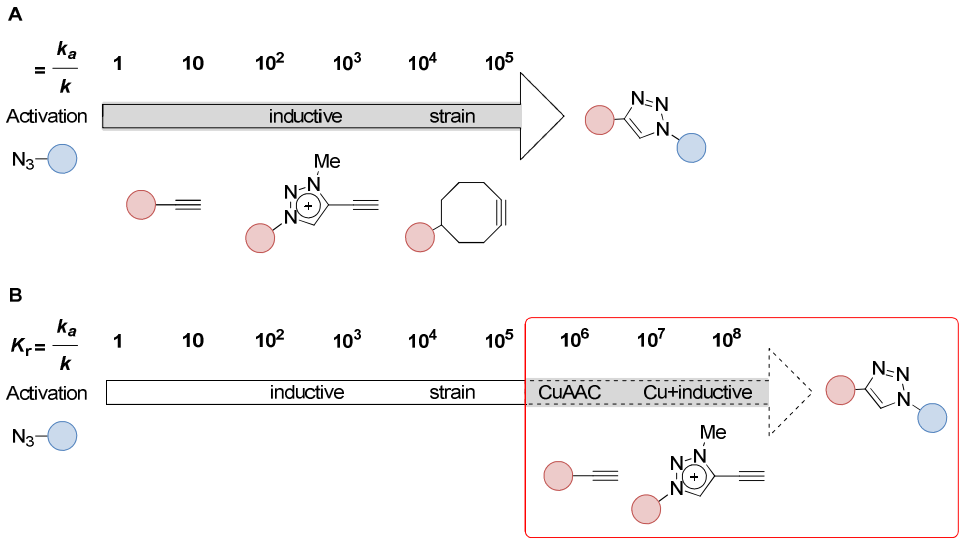
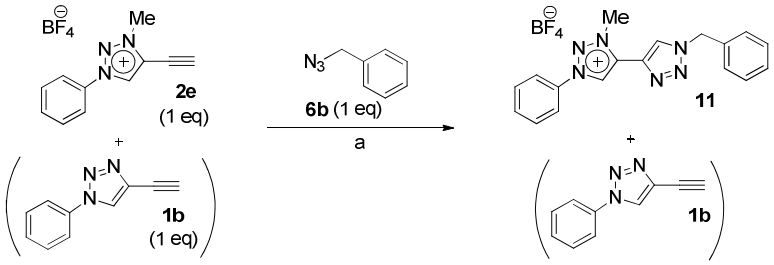



**Figure 2. 18.** Relative reaction rate acceleration: A) Thermal cycloadditions; B) Copper(I) catalyzed cyclizations.

To put into evidence the reaction rate acceleration promoted by the triazolium ring, we carried out some competition experiments submitting an equimolar mixture of the cationic triazolium alkyne **2e** and the neutral akyne **1b** to cyclization reaction with an equivalent of benzylazide **6b** in the presence of a copper(I) catalysts. To monitor the reaction conversion we chose to conduct it in a NMR sample tube recording the data as in previous experiments ran with thermally activated cycloaddition reactions. Looking for fully homogeneous reactions conditions, we found that all reactants (32 mM) and a catalytic system formed by CuOAc/NaOAc was completely soluble in a 10:1 mixture of MeCN-$d_3$ and $D_2O$ at room temperature (27 ºC) (**Scheme 2. 18**).




**Scheme 2. 18.** Competitive CuAAC reation of the cationic triazolium alkyne **2e** with benzylazide **6b** in the presence of triazole alkyne **1b**. Reagents and conditions: (a) CuOAc, NaOAc, MeCN-$d_3$:$D_2O$ 1:0.1, 27 ºC, up to 25 min.

As shown in **Figure 2. 19** a fully chemoselective transformation of the cationic triazolium alkyne **2e** took place in the presence of a 40 mol% catalyst load (> 99 % conversion after 20 min). Importantly, no conversion was observed for the neutral triazole **1b** during the monitored time frame.

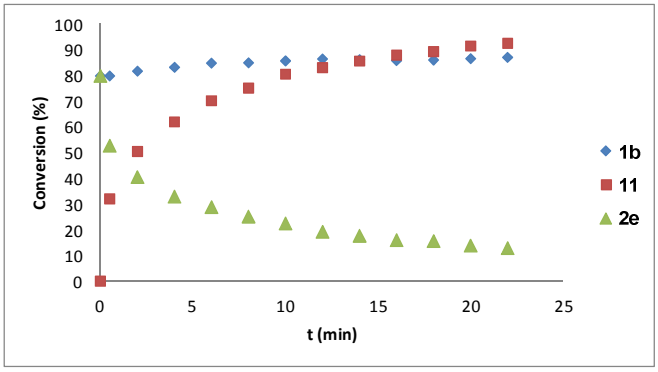



**Figure 2. 19.** Conversion-time plot of the competitive cyclization reaction of a mixture of alkynes **1b** and **2e** with benzylazide **6b** catalyzed by CuOAc/NaOAc (40 mol%).

As illustrated in **Figure 2. 20**, the reaction conversion of benzylazide to the bistriazole **11** could be easily determined from the $^{1}$H NMR spectra recorded at different reaction times. The $^{1}$H NMR signals of alkynes were easily identified by the triazole and triazolium protons signals around 8.5 ppm and 9.0 ppm, respectively.

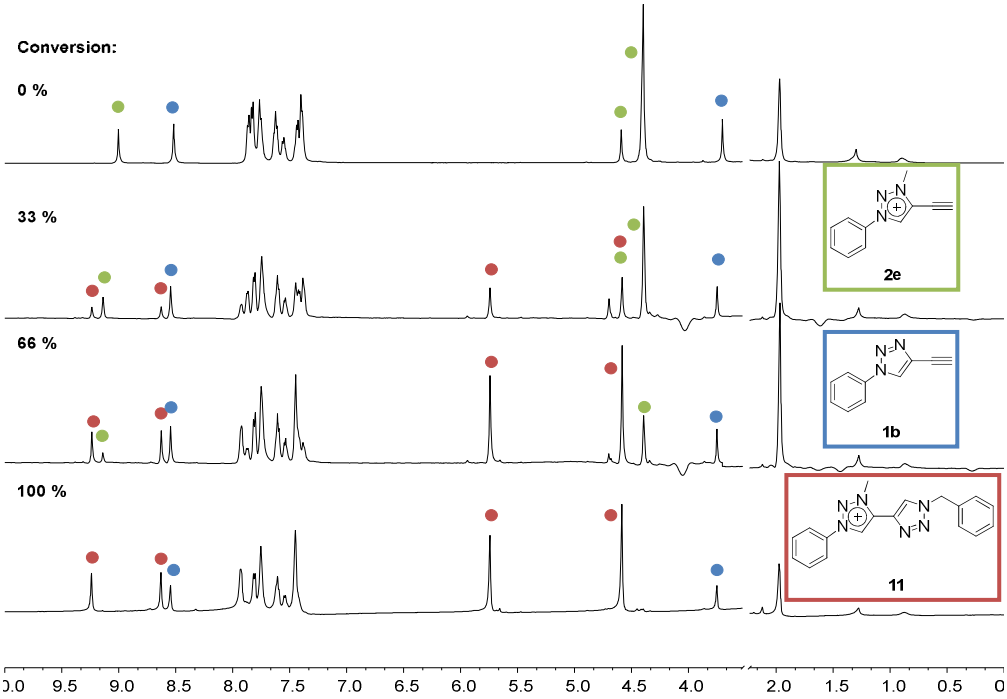



**Figure 2. 20.** $^{1}$H NMR (500 MHz, MeCN-$d_3$:$D_2O$ 1:0.1) spectra for the competitive reaction of benzylazide with the cationic triazolium alkyne **2e** in the presence of the neutral alkyne **1b**.

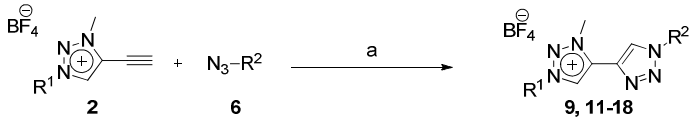
A totally chemoselective reaction of benzylazide with the cationic triazolium alkyne **2e** was achieved under the studied conditions, and the neutral triazole alkyne **1b** could be recovered unchanged, showing that the reactivity of **2e** was significantly higher than **1b**.

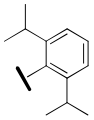
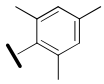
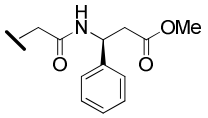
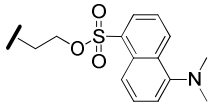
These results were interesting not only from a mechanistic point of view, but were applicable to preparative reactions conducted under “ultra-fast” conditions.

### 2.4.5 Cu(I)-catalyzed "ultra-fast" synthesis of 3-methyl-4-triazolyl-1,2,3-triazolium salts

Taking advantage of the fast transformation disclosed in the previous section, we decided to extend such methodology to different azides at a preparative scale. As shown in **Table 2. 12** total conversions and high isolated yields were achieved in less than 5 minutes for all instances.

**Table 2. 12.** "Ultra-fast" CuAAC reactions of cationic triazolium alkynes with azides promoted by Cu(I) sources. Reagents and conditions: (a) Cu(I)-catalyst, solvent, r.t., 5 min.



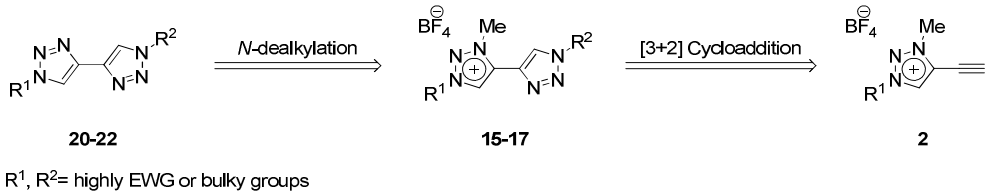

| Entry | $R^1$ | $R^2$ | Product | Catalysts | Solvent | Yield[a](%) |
|---|---|---|---|---|---|---|
| 1 | 4-NC-$C_4H_6$ | Bn | **9** | $CuSO_4$/Asc. Na | THF/*t*BuOH/$H_2O$ | 73 |
| 2 | Ph | Bn | **11** | CuOAc/NaOAc | MeCN/$H_2O$ | 89 |
| 3 | Bn | Ph | **12** | $CuSO_4$/Asc. Na | THF/*t*BuOH/$H_2O$ | 83 |
| 4 | Ph | 4-$NO_2C_6H_4$ | **13** | CuOAc/NaOAc | MeCN/$H_2O$ | 78 |
| 5 | Ph | 4-$MeOC_6H_4$ | **14** | CuOAc/NaOAc | MeCN/$H_2O$ | 84 |
| 6 | Ph | 4-$FC_6H_4$ | **15** | $CuSO_4$/Asc. Na | THF/*t*BuOH/$H_2O$ | 63 |
| 7 | Ph |  | **16** | $CuSO_4$/Asc. Na | THF/*t*BuOH/$H_2O$ | 66 |
| 8 | Ph |  | **17** | $CuSO_4$/Asc. Na | THF/*t*BuOH/$H_2O$ | 64 |
| 9 | Ph |  | **18** | $CuSO_4$/Asc. Na | THF/*t*BuOH/$H_2O$ | 70 |
| 10 | Ph |  | **19** | CuOAc/NaOAc | MeCN/$H_2O$ | 82 |

[a]Yield of isolated pure product.

The click reactions were very efficient using a 20 mol% load of Cu(I) salts, including the previously mentioned CuOAc/NaOAc system and also the Sharpless´ $CuSO_4$/sodium ascorbate system (compare entries 1 and 3).

The scope of the reaction included standard aliphatic azides (entries 1 and 3) and also poorly reactive aromatic azides with electron-withdrawing groups (see entries 4 and 6). The reaction also worked efficiently for strongly hindered aromatic azides (see entries 7 and 8) and was tolerant with functionalized aliphatic azides (entries 9 and 10).

As previously noted by different autors,[83] electron-rich alkynes often fail to react with electron-deficient or strongly hindered aromatic azides under CuAAC conditions. In particular, our group reported[84] that 4-ethynyl-triazoles give very sluggish cyclization to 4,4´-bistriazoles with such kind of azides. To overcome this drawback, we considered the *N*-demethylation of 4-triazolyl-1,2,3-triazolium salts as an alternative to prepare 4,4'-bis(1,2,3-triazoles) reluctant to form under standard CuAAC conditions (**Scheme 2. 19**).




**Scheme 2. 19.** Retrosynthesis of non-symmetrically substituted 4,4'-bis(1*H*-1,2,3-triazoles) from 3-methyl-triazolium salts.

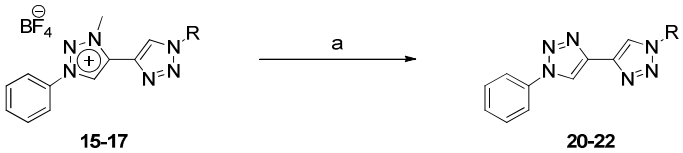
After extensive experimentation, we found that treating the electron defficient or strongly hindered bis-triazolium salts **15-17** with thiophenol in the presence of $K_2CO_3$ in MeCN at 50 ºC for 18 hours, the desired *N*-demethylated bistriazoles **20-22** were obtained in good yields (68-88 %) (**Table 2. 13**).

---

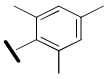
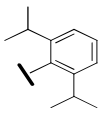
83 a) Wamhoff, H. 1,2,3-Triazoles and their benzo derivatives, In comprehensive heterocyclic chemistry, Vol. 5, Katritzky, A. R.; Rees, C. W.; Pott, K. T. Eds. Pergamon Press: Oxford, **1984**, 669. b) Schubert, U. S.; Hoogenboom, R.; Hager, M. D.; Winter, A.; Friebe, C.; Happ, B. *Chem. Asian J.* **2009**, *4*, 154.

84 a) Aizpurua, J. M.; Sagartzazu-Aizpurua, M.; Azcune, I.; Miranda, J. I.; Monasterio, Z.; García-Lecina, E.; Fratila, R. M. *Synthesis* **2011**, 2737-2742. ""Click" synthesis of nonsymmetrical 4,4´-bis(1,2,3-triazolium) salts". b) Aizpurua, J. M.; Azcune, I.; Fratila, R. M.; Balentova, E.; Sagartzazu-Aizpurua, M.; Miranda, J. I. *Org. Lett.* **2010**, *12*, 1584-1587. ""Click" synthesis of nonsymmetrical 4,4´-bis(1,2,3-triazolium) salts".

**Table 2. 13.** Synthesis of nonsymmetrically substituted 4,4'-bis(1,2,3-triazoles) by *N*-demethylation of triazolium salts.




Reagents and conditions: (a) Thiophenol, $K_2CO_3$, MeCN, 50 ºC, 18 h.

| Entry | R | Substrate | Product | Yield (%)[a] |
|---|---|---|---|---|
| 1 | 4-F-$C_6H_4$ | **15** | **20** | 73% |
| 2 |  | **16** | **21** | 68% |
| 3 |  | **17** | **22** | 88% |

[a]Yield of isolated pure product.

## 2.5 Conclusions

3-Alkyl-4-alkynyl-1,2,3-triazolium salts can be prepared in good yields from "click" 4-alkynyl-1*H*-1,2,3-triazoles by *N*3-alkylation with Merweein's salts ($Me_3OBF_4$, $Et_3OBF_4$) or methyl trifluoromethanesulfonate.

It has been found that these novel cationic triazolium alkynes react with alkyl- and aryl azides under thermal activation conditions (60 – 100 ºC) to give mixtures of bicyclic 4-(1,2,3-triazolyl)-3-methyl-1,2,3-triazolium salts with 1,4- and 1,5-substitution at the newly created triazole ring. These reactions occur about 40-350 times faster than the equivalent cycloadditions with neutral 4-alkynyl-1*H*-1,2,3-triazoles, demonstrating the strong electron withdrawing effect exerted by the triazolium ring on the reaction outcome.

Cationic triazolium alkynes react with azides to give higher 1,4-/1,5- regioisomer selectivities (typically > 95%) than their neutral triazole equivalent alkynes. According to kinetic measurements conducted using variable temperature $^1$H NMR techniques, the $\Delta G^{\neq}$ activation energy barriers for the TS-1,4 transition states of cationic triazolium alkynes are 2-

3 kcal·mol$^{-1}$ lower than TS-1,5 transition states. In contrast, this difference is only 0.4 kcal·mol$^{-1}$ for similar neutral triazole alkynes.

Computational DFT calculations suggest that cationic triazolium alkynes act as strong LUMO-lowering dipolarophiles, narrowing the HOMO–LUMO energy gap of the azide–alkyne interaction, and favoring the reaction with nucleophilic azides. The same calculations indicate that the high 1,4/1,5- regioselectivity observed arises from the different approaches of the azide to the cationic triazolium alkyne in the transition states TS-1,4 and TS-1,5. The former has a coplanar geometry around the newly created triazole ring, whereas the second adopts a more hindered and energetically costly orthogonal geometry.

Finally, it has been demonstrated that cationic triazolium alkynes react with azides under “ultra-fast” CuAAC conditions (< 5 min) to give bicyclic 4-(1,2,3-triazolyl)-3-methyl-1,2,3-triazolium salts in good yields. Competitive reactions have shown that this reactions can be conducted in the presence of neutral alkynes with complete chemoselectivity. In some instances, the bis-triazolium salts can be demethylated to 4,4’-bis(1,2,3-triazoles) with thiophenol in a basic medium.

# 3

*Triazolium salts with latent “click” reactivity by N3-alkylation of 1,2,3-triazoles*

# 3 Triazolium salts with latent "click" reactivity by *N*3-alkylation of 1,2,3-triazoles

## 3.1 Introduction

To address the second general objective of this PhD thesis, consisting in the introduction of alkyl substituents with functional groups in 1,2,3-triazoles by *N*3-alkylation (**section 1.2.1**, page 20), we first surveyed the main contributions to the topic.

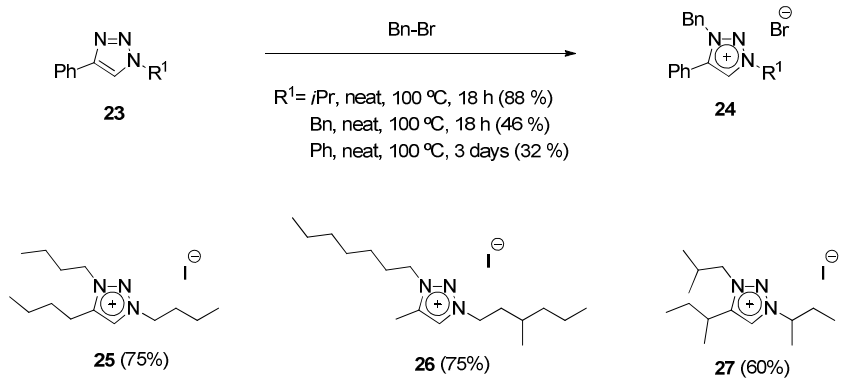
As previously discussed in the general introduction (**section 1.1**), 1,2,3-triazolium salts are prepared in a *N*3-regioselective manner from 1,4-disubstituted-1*H*-1,2,3-triazoles by using soft alkylating reagents, as for example alkyl iodides and bromides (RX), alkyl triflates (ROTf) and Meerwein´s salts ($R_3OBF_4$). Occasionally, other less common alkylating reagents such as alkyl tosylates (ROTs)[85], trimethyl phosphate ($Me_3PO_4$) and methyl sulfate ($Me_2SO_4$)[86] have been used. Triazoles are considerably more difficult to alkylate than basic aromatic heterocycles (e.g. pyridines). The reaction is strongly dependent on the steric hindrance of the alkylating group and is limited to primary alkyl groups. Small groups (methyl, ethyl) or activated groups (allyl, benzyl) give generally good yields albeit a large excess of the alkylating reagent is often required. On the other hand, the reaction is also sensitive to the *N*1-substituent of the heterocycle. For example, Huynh[87] carried out the alkylation reaction of 1,2,3-triazoles with benzyl bromide and observed a dramatic yield drop as the donor inductive effect of the *N*1 substituent decreases changing from aliphatic to aromatic (**Scheme 3. 1**).

---

85 Begtrup, M. *Acta Chem. Scand.* **1971**, *25*, 249-259. "Reactions between azolium salts and nucleophilic reagents.2. Bromo-1,2,3-triazolium salts and sodium hydroxide".

86 a) Begtrup, M. *Acta Chem. Scand.* **1971**, *25*, 3500-3508. "Reactions between azolium salts and nucleophilic reagents.7. The preparation of properties of 1,3-disubstituted 4-methylthio-1,2,3-triazolium salts". b) Khan, S. S.; Hanelt, S.; Liebscher, J. *ARKIVOC* **2009**, *xii*, 193-208. "Versatile synthesis of 1,2,3-triazolium-based ionic liquids".

87 Yuan, D.; Huynh, V. *Organometallics* **2012**, *31*, 405-4012. "1,2,3-Triazolin-5-ylidenes: synthesis of hetero-bis(carbene) Pd(II) complexes, determination of donor strengths, and catalysis".




**Scheme 3. 1**. *N*3-alkylation reaction of 1*H*-1,2,3-triazoles with alkyl halides.

For 1,4-dialkyl-substituted triazoles, the scope of the *N*3-alkylation reaction has been extended to medium length and β-branched alkyl groups. For example, triazolium salts **25-27** were obtained in good yields by treating the corresponding triazoles with alkyl iodides in refluxing MeCN overnight.[88]

The functional group tolerance for the *N*3-alkylation reaction of 1,4-disubstituted triazoles with small or activated alkylating halides has been screened by several authors (**Figure 3. 1**). Accordingly, it is possible to prepare triazolium salts from 1,2,3-triazoles bearing ethers, amides,[89] carbamates[90] and even sulfide functionalities[91] in their *N*1 and *C*4 substituents.

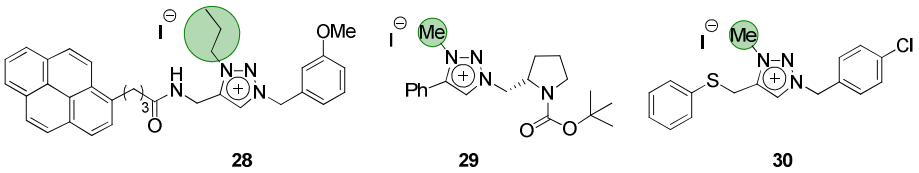



**Figure 3. 1.** Functional group tolerance for the *N*-alkylation of 1,2,3-triazoles.

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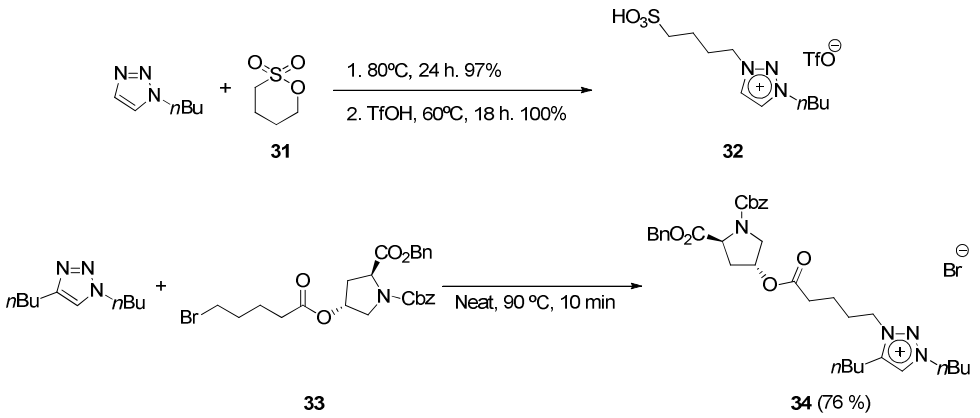
88 Yan, F.; Lartey, M.; Jariwala, K.; Bowser, S.; Damodaran, K.; Albenze, E.; Luebke, D. R.; Nulwala, H. B.; Smit, B.; Haranczyl, M. *J. Phys. Chem. B* **2014**, *118*, 13609-13620. "Toward a materials genome approach for ionic liquids: synthesis guided by *ab initio* property maps".

89 Hanelt, S.; Liebscher, J. *Synlett* **2008**, 1058-1060. "A novel versatile access to task-specific ionic liquids based on 1,2,3-triazolium salts".

90 Karthikeyan, T.; Sankararaman, S. *Tetrahedron Lett.* **2009**, *50*, 5834-5837. "Palladium complexes with abnormal *N*-heterocyclic carbene ligands derived from 1,2,3-triazolium ions and their application in Suzuki coupling".

91 Mendoza-Espinosa, D.; González-Olvera, R.; Osornio, C.; Negrón-Silva, G. E.; Santillan, R. *New. J. Chem.* **2015**, *39*, 1587-1591. "Versatile *O*- and *S*-functionalized 1,2,3-triazoliums: ionic liquids for the Baylis-Hillman reaction and ligand precursor for stable MIC-transition metal complexes".

As far as we are aware, there are only two examples of *N*3-alkylation of 1,2,3-triazoles with functionalized alkylating agents. The first one is the ω-sulfonylbutylation of a monosubstituted triazole with the cyclic sulfonate **31** to give the triazolium salts **32** with a terminal sulphonic acid group. This compound was used as a recyclable Brønsted acidic ionic liquid and proved to be an effective promoter for the cycloisomerization of alkenyl alcohols (**Scheme 3. 2**).[92]




**Scheme 3. 2**. Examples of 1,2,3-triazolium salts obtained by *N*3-alkylation reaction with functionalized alkylating reagents.

The second example was reported by Liebscher[93] and described the synthesis of the triazolium salt **34** by alkylating the 1,4-dibutyl-1,2,3-triazole with the elaborated alkyl bromide **33**.

## 3.2 Hypothesis

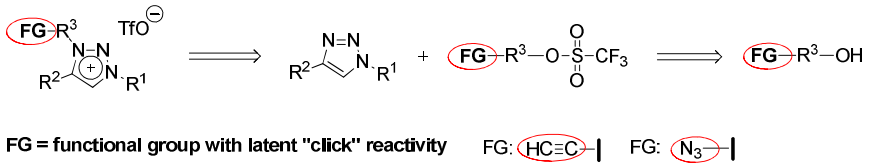
There is little information accounting for the mechanistic details governing the *N*-alkylation reaction of triazoles with alkylating agents.[94] Nevertheless, we assumed that the nature of the living group of the alkylating reagent plays a critical role to get a successful *N*3-

[92] Jeong, Y.; Kim, D.-Y.; Choi, Y.; Ryu, J.-S. *Org. Biomol. Chem.* **2011**, *9*, 374-378. "Intramolecular hydroalkoxylation in Brønsted acidic ionic liquids and its application to the synthesis of (±)-centrolobine".

[93] Shah, J.; Khan, S. S.; Blumenthal, H.; Liebscher, J. *Synthesis* **2009**, 3975-3982. "1,2,3-Triazolium-tagged prolines and their application in asymmetric aldol and Michael reactions".

[94] Obadia, M. M.; Mudraboyina, B. P.; Serghei, A.; Montarnal, D.; Drockenmuller, E. *J. Am. Chem. Soc.* **2015** (DOI: 10.1021/jacs.5b02653) "Reprocessing and recycling of highly cross-linked ion-conducting networks through transalylation exchanges of C-N bonds".

alkylation of 1,2,3-triazoles with relatively complex and/or functionalized alkyl groups. On the basis of the previous experience of our research group, we observed that alkyl triflates were more efficient alkylating agents than similar alkyl iodides, bromides or Merweein's salts (see, for example **Table 2.2** in section **2.4.1.2**). Since alkyl triflates are easily available from alcohols by treatment with trifluoromethanesulfonic anhydride, we considered such compounds as ideal precursors to prepare functionalized alkylating agents for 1,2,3-triazoles (**Scheme 3. 3**).




**Scheme 3. 3.** General strategy to incorporate latent reactivity into 1*H*-1,2,3-triazoles from functionalized alcohols.

To endorse the desired latent "click" reactivity to the triazolium salts, we selected starting alcohols incorporating terminal azide or alkyne groups in their structure, assuming the chemical compatibility of the azide and alkyne groups with the strongly electrophilic alkyltriflate moiety.

In addition to the incorporation of reactive functional groups, we hypothesized that *N*3-alkylation could also be a useful reaction to introduce labelling groups into triazole mimetics of bioactive molecules.[95] In a recent contribution from our research group,[96] Dr. Sagartzazu-Aizpurua described the novel iodinated Arg-Gly-Asp (RGD) mimetic **35** (**Scheme 3. 4**), which showed high affinity for $\alpha_V\beta_3$ tumor integrins and acted as a tissue-selective contrast agent for X-ray computed tomography (CT) scanning (see also **section 3.4.2**). We surmised that *N*-alkylation reaction of monoiodinated triazole peptidomimetics like **35** with alkyl triflates labeled with a densely iodinated group, could be a practical route to transform them into tetraiodinated triazolium derivatives with improved radiological

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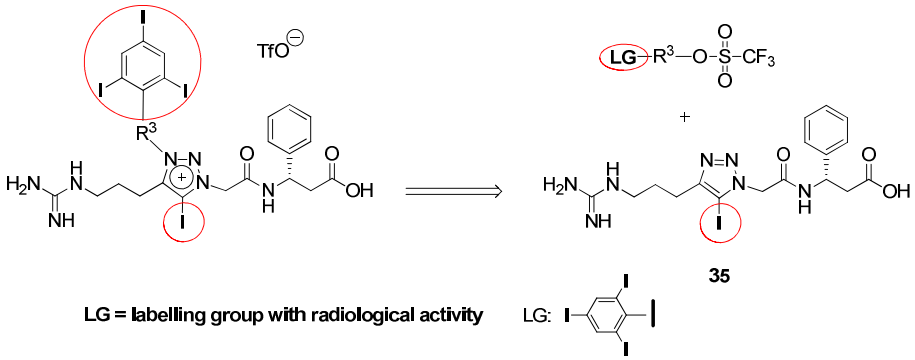
95 Carvalho da Silva, F.; Carmo-Cardoso, M. F.; Garcia-Ferreira, P.; Ferreira, V. F. "Biological properties of 1*H*-1,2,3-triazoles and 2*H*-1,2,3-triazoles" in Chemistry of 1,2,3-triazoles, *Topics in Heterocyclic Chemistry*, **2014**, *40*, 117-166. Eds. Dehaen, W.; Bakulev, V.A.; Springer-Verlag; Heidelberg.

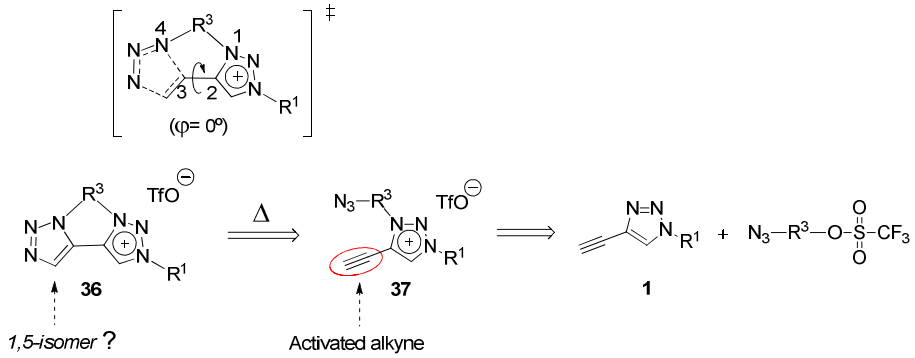
96 Sagartzazu-Aizpurua, M. *PhD Thesis UPV-EHU*. **2015**"1,2,3-Triazoles 1,3,4- y 1,4,5-trisustituidos: síntesis y aplicaciones a la preparación de contrastes radiológicos, peptidomiméticos osteogénicos y carbenes mesoiónicos quirales".

activity. This approach, though, involves important structural and electronic changes that could affect the affinity of the labeled salt with the biological receptor.




**Scheme 3. 4.** General strategy to incorporate labelling groups into bioactive 1,2,3-triazoles using a *N*3-alkylation reaction.

Finally, we conceived that *N*-alkylation of suitable 1,2,3-triazoles could be used to trigger unusual reactivity. In particular, we hypothesized that *N*3-alkylation of 4-ethynyl-1,2,3-triazoles **1** with ω-azidoalkyl triflates should provide the cationic triazolium alkynes **37** incorporating simultaneously an azide group (**Scheme 3. 5**). Since the cycloaddition torsion angle φ is close to zero, we believed that a reaction pathway leading to unprecedented tricyclic 1,5-/1,4-bis-triazole cycloadducts **36** would be strongly favoured.

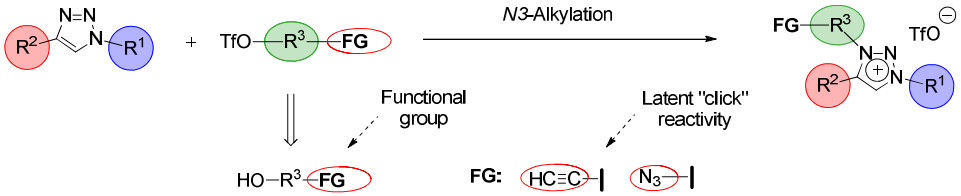



**Scheme 3. 5.** Likely synthetic route to tricyclic 1,5/1,4-bis-triazoles from cationic triazolium alkynes using a *N*3-alkylation reaction.

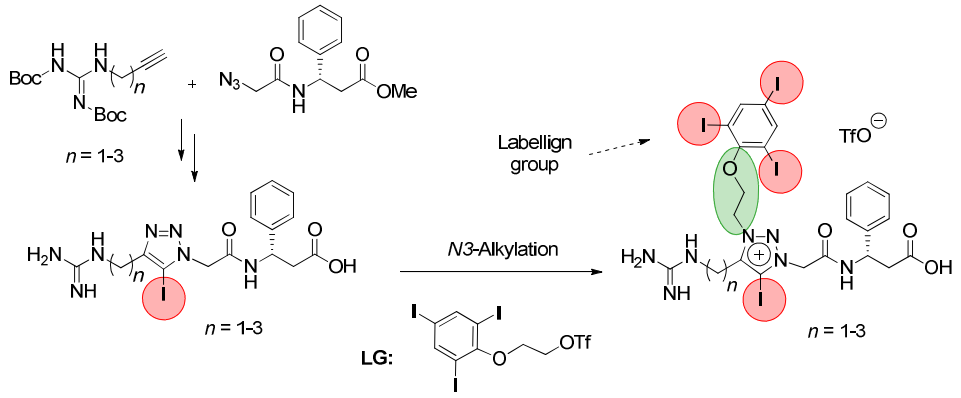
## 3.3 Objectives

According to the hypothesis discussed above, we selected the following partial objectives for the second part of this doctoral thesis work:

1. To synthesize novel 3-*N*-alkyl-1,2,3-triazolium salts incorporating *N*3-substituents with functional groups. More particularly, we focused on triazolium salts with terminal azide and alkyne groups with latent “click” reactivity. To conduct the N-alkylation reactions, we planned to use primary alkyl triflates obtained from ω-azidoalcohols and terminal alkynols.

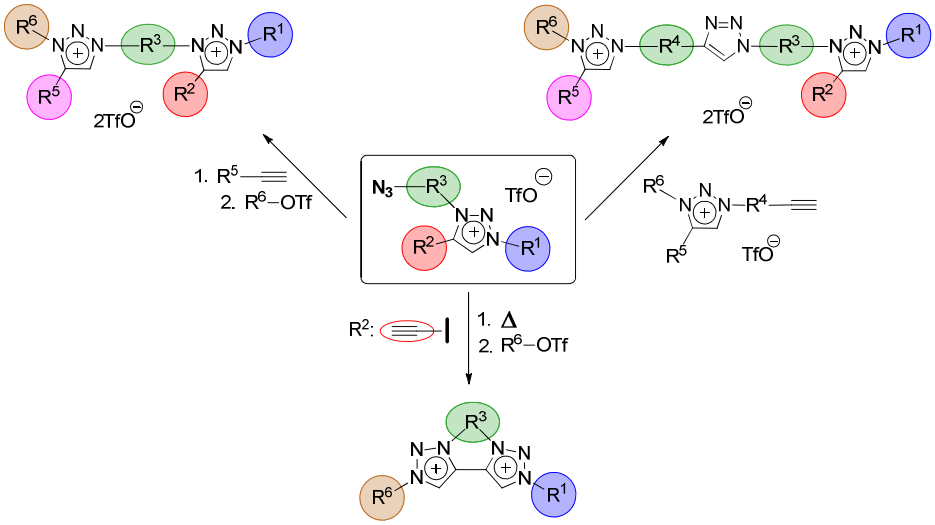



2. The synthesis of a series of densely iodinated Arg-Gly-Asp (RGD) peptidomimetics for radiological CT scanning following the *N*3-alkylation with alkyl triflates. To accomplish this task, we intended to prepare the requisite triazole precursors using the Cu(I)-catalyzed alkyne-azide cycloaddition reaction approach. In order to check potential affinity improvements with the tumor integrin receptors, we designed three RGD mimetics with *C*4 substituents of variable length.




3. To demonstrate the actual reactivity of the *N*3 substituents of 1,2,3-triazolium salts by performing azide-alkyne cycloadditions, both under CuAAC and under thermal activation conditions. These transformations should allow the first synthesis of novel

bis-triazolium heterocyclic systems with complete positional control for all the substituents.



## 3.4 Results and discussion

### 3.4.1 Synthesis of 1,2,3-triazolium salts with functionalized *N*3-substituents

To address the first objective, we divided our working plan into three tasks. First, to develop an improved method to prepare alkyl triflates from primary alcohols functionalized with azide groups or terminal alkyne groups. Then, to use the resulting functionalized alkyl triflates to alkylate 1,4-disubstituted 1,2,3-triazoles, and finally to extend such procedure to the preparation of a densely iodinated contrast agents designed to enhance the radiological opacity of soft tissues under anatomic X-ray computed tomography (CT) scanning.

Alkyl triflates are excellent alkylating reagents, but their preparation as pure isolated compounds is not obvious. They are often prepared from alcohols by reaction with triflic anhydride in the presence of organic bases, like pyridine[97] or poly(vinylpyridine).[98] However, the mild basic aqueous washing required to separate reaction byproducts often causes a considerable hydrolysis of alkyl triflates rendering their purification unpractical.

Hanack and Collins took advantage of using heterogeneous reaction conditions to prepare enol triflates from ketones.[99] Following this approach, we found that treating an alcohol with equimolar amounts of triflic anhydride and anhydrous $KHCO_3$ in $CH_2Cl_2$ (**Table 3. 1**) resulted in quantitative conversion to the desired alkyl triflates. After a simple filtration of the heterogeneous reaction mixture under anhydrous conditions, a solution of a practically pure alkyl triflate was obtained ready for use in *N*-alkylation reactions. Some of the alkyl triflates **38** prepared using our heterogeneous water-free conditions are shown in **Table 3. 1**.

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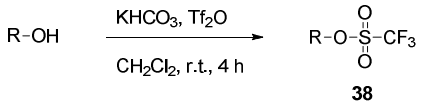
97 Kramer, J. R.; Deming, T. J. *Biomacromolecules* **2012**, *13*, 1719-1723. “Preparation of multifunctional and multireactive polypeptides via methonine alkylation”.

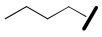
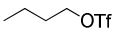
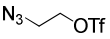
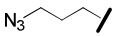
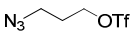
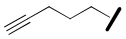
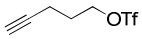
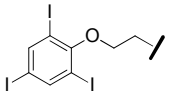
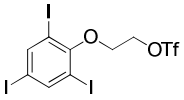
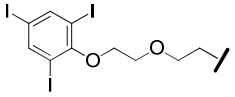
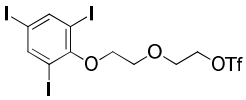
98 Ross, S. A.; Pitíe, M.; Meunier, B. *J. Chem. Soc., Perking Trans. 1* **2000**, 571-574. “A straightforward preparation of primary alkyl triflates and their utility in the synthesis of derivatives of ethidium”.

99 Hanack, M.; Fuchs, K.-A.; Collins, C. J. *J. Am. Chem. Soc.* **1983**, *105*, 4008-4017. “Vinyl cations. 40. π- and σ-Routes to vinyl cations. Solvolysed of 2-methylcyclohexenyl, cyclopentylideneethyl, hex-5-yn-1-yl, and related triflates”.

**Table 3. 1.** Synthesis of alkyl triflates from alcohols.




**38**

| Entry | R | Product | | Yield (%) |
|---|---|---|---|---|
| 1 |  |  | **38a** | >95[a] |
| 2[100] |  |  | **38b** | >95[a] |
| 3[101] |  |  | **38c** | >95[a] |
| 4 |  |  | **38d** | >95[a] |
| 5[102] |  |  | **38e** | 94[b] |
| 6[102] |  |  | **38f** | 98[b] |

[a]Not isolated. Conversion determined by $^1$H NMR. [b]Isolated yield.

The method was useful to prepare not only simple alkyl triflates (entry 1), but also functionalized ones (entries 2 and 3), including the alkyl triflate **38d** which incorporates the acid-sensitive alkynyl group (entry 4). Some bulky aromatic alkyl triflates could be isolated. For example, the 2,4,6-triiodophenol derivatives **38e-f** (entries 5 and 6) were stable and could be stored at -20 ºC for months without appreciable decomposition.

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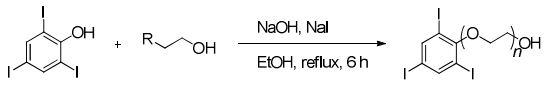
100 Dowlut, M.; Hall, D. G.; Hindsgaul, O. *J. Org. Chem.* **2005**, *70*, 9809-9813. "Investigation of non-specific effects of different dyes in the screening of labeled carbohydrates against inmobilized proteins".

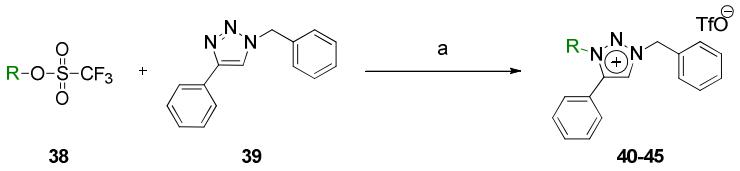
101 Aucagne, V., Hänni, K. D.; Leigh, D. A.; Lusby, P. J.; Walker D. B. *J. Am. Chem. Soc.* **2006**, *128*, 2186-2187. "Catalytic "Click" rotaxanes: a substoichiometric metal-template pathway to mechanically interlocked architectures".

102 Radek, O.; Nemecek, O. Czech Patent **1966**, CS 118450. "Basic 2,4,6-triiodophenol ethers".




**1** R= Br, *n*= 1, quantitative
**2** R= $OCH_2CH_2Cl$, *n*= 2, 48%

Next, we used the freshly prepared dichloromethane solutions of alkyl triflates **38** to study the *N*3-alkylation of the model 1,4-disubstituted triazole **39** (**Scheme 3. 6**). In a first trial, we checked by $^{1}$H NMR the aliquots of an equimolar mixture of the triazole and the triflate **38e** in deuterated chloroform. Disappointingly, after 10 hours at ambient temperature, only minor amounts (<20 %) of the desired triazolium salt **40** were detected. Heating the mixture or prolonging the reaction time did not led to a significant conversion improvement. Several experiments to screen different solvents and reaction conditions failed to provide a clean *N*-alkylation reaction. Finally, we tried the reaction of a neat mixture of the triflate and the triazole obtained by the slow evaporation of an equimolar solution of both reactants in dichloromethane under a nitrogen stream. To our delight, the expected triflate triazolium salt **39** formed at room temperature after 18 hours and was isolated in 98 % yield.




**Scheme 3. 6.** Synthesis of *N*3-substituted 1,2,3-triazolium triflates **40**-**45**. Reagents and conditions: (a) Neat, 30 ºC, 18 h.

When the solvent-free reaction conditions were extended to other alkyl triflates, the corresponding triazolium salts were obtained in moderate to excellent isolated yields after a flash chromatographic purification (**Figure 3. 2**). Importantly, latent functional groups like azide or alkyne were tolerated.

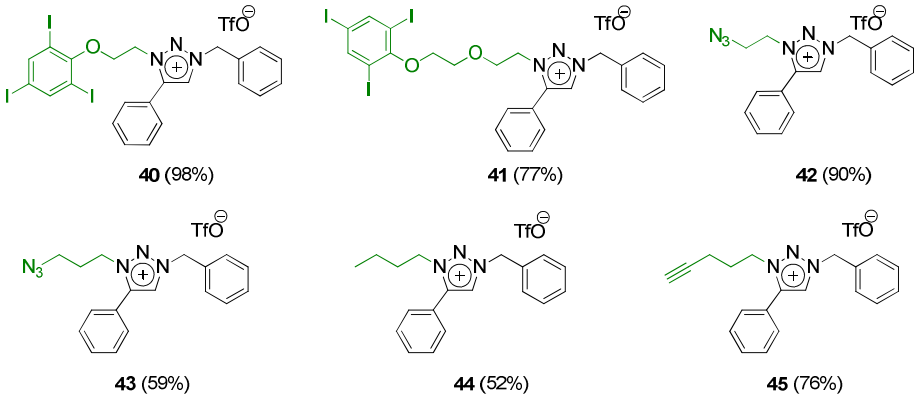



**Figure 3. 2.** 1,2,3-Triazolium salts prepared by *N*3-alkylation of **39** with alkyl triflates. Yield of isolated pure product in parentheses.

In **Figure 3. 3** are compared the $^{1}$H NMR spectra of the alkyl triflate **38e**, the triazole **39** and the triazolium salt **40**. As expected, upon *N*-alkylation, the triazole proton (4) shifted downfield from 7.6 ppm to 9.0 ppm in the final triazolium triflate. A similar behavoiur, albeit less pronounced, was observed for the benzylic protons (5).

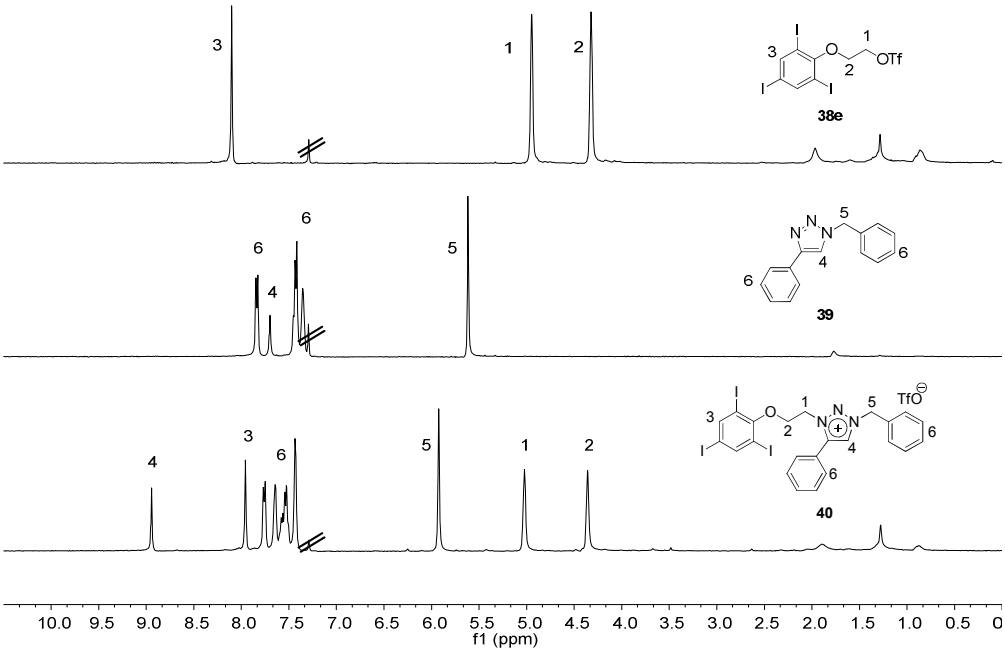



**Figure 3. 3.** $^{1}$H NMR Spectra (400 MHz, $CDCl_3$) of reactants **38e**, **39** and product **40**.

Finally, a functional group tolerance test was conducted with triflate **38e** and different 1,4-disubstituted triazoles bearing moderately basic functional groups (**Figure 3. 4**). Good to excellent yields of *N*-alkylated triazoles were obtained in the presence of a wide array of electron rich functional groups, comprising alkynes (**46**), esters (**47**) or carbamates (**49**). The monoalkylated bis-triazole (**50**) was worth mentioning. This alkylation reaction occurred in a clean stepwise manner and no formation of *N*,*N´*-dialkylated product was observed, likely due to the deactivation effect exerted by newly formed triazolium cation on the neighboring triazole *N*3-nitrogen.

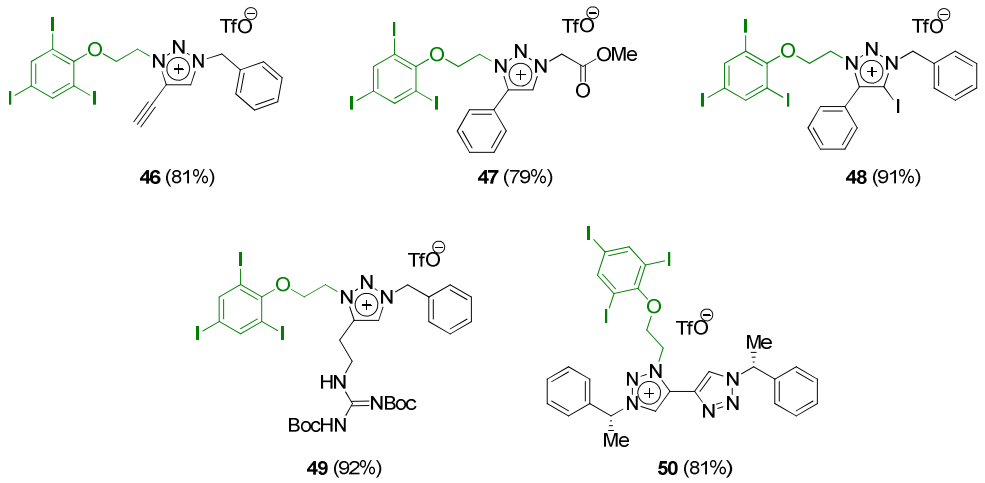
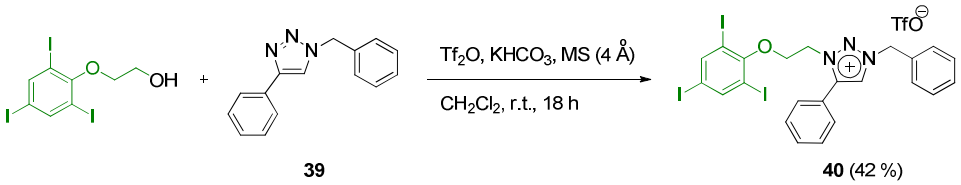



**Figure 3. 4.** Functional group tolerance test for the *N*3-alkylation of triazoles with the model alkyl triflate **38e**.Yield of isolated pure product.

In an attempt to make the *N*-alkylation reaction amenable to a “one-pot” procedure by generating the alkyl triflates *in situ* from alcohols and triflic anhydride in the presence of triazoles, we explored the test reaction shown in **Scheme 3. 7**. A maximum 42 % conversion to the desired triazolium triflate **40** was recorded by NMR analysis when the reaction was carried out overnight at room temperature in the presence of molecular sieves. Despite many trials carried out to improve this result, no complete conversion of the starting triazole could be achieved.




**Scheme 3. 7.** Direct “one-pot” synthesis of triazolium triflate **40** from triazoles and alcohols.

After proving the wide scope and functional group tolerance of the triazole alkylation method, we addressed the second objective of this chapter, consisting in the obtention of densely iodinated *N*-alkyl-triazolium salts derived from the angiogenic tripeptide Arg-Gly-Asp (RGD), and their evaluation as contrast agents for X-ray computed tomography scanning.

### 3.4.2 Iodinated RGD triazolium salts for X-ray computed tomography (CT) scanning

#### 3.4.2.1 Background and previous work

X-Ray computed tomography scanning is one of the most useful and popular anatomic imaging radiographic techniques in medical pratice. Usually, iodinated contrast agents are used to diffract X-ray beams and get proper CT images. Among these radiological opacity promoters, iodixanol **51** (Visipaque®) is used worldwide in routine tumor diagnosis, although it shows no selective affinity for tumor tissues (**Figure 3. 5**). Therefore, densely iodinated organic molecules with high affinity for tumor tissues are highly desirable for tumor-targeted CT scanning diagnosis. Unfortunately, they are not available at present.

As mentioned above (see **section 3.2**), our group has designed and synthesized the novel iodinated triazole RGD mimetic **35** (**Figure 3. 5**). This compound displayed a high affinity for $\alpha_V\beta_3$ integrins, which are overexpressed in many tumor tissues.

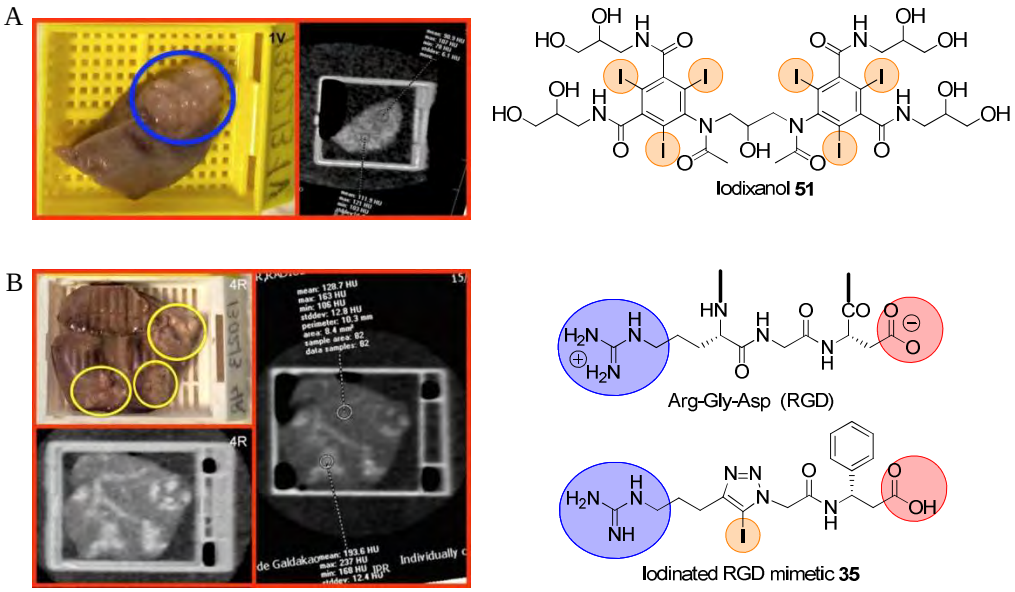
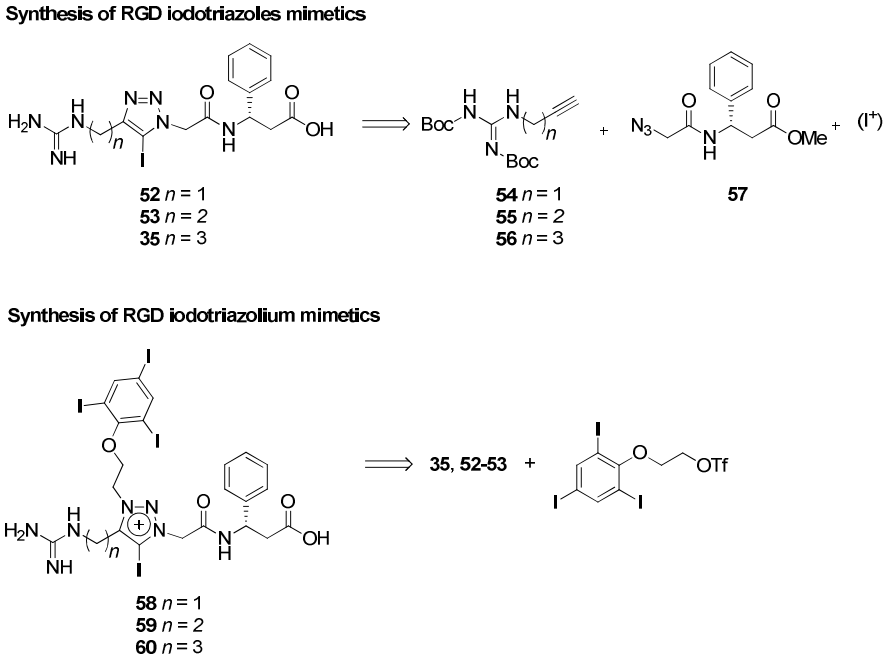



**Figure 3. 5.** X-Ray computed tomography (CT) scanning images of two samples of CC531 human colocarcinoma cells inoculated in the liver of Waj/Rij male rats, after the intraarterial injection of iodixanol **51** (A) and the iodinated RGD contrast agent **35** (B). Bright white spots show tumor nuclei and small metastasis.

**Figure 3. 5** shows CT images of two samples of CC531 human colocarcinoma cells inoculated in the liver of Waj/Rij male rats, after the intraarterial injection of iodixanol (sample A) and the iodinated RGD contrast agent **35** (sample B). As expected, no image brightness difference between the liver tissue and the tumor tissue could be appreciated for the iodixanol-treated sample (A). In contrast, the iodinated RGD mimetic **35** was selectively accumulated in the tumor tissue allowing for the record of very small bright metastatic tumors of less than 2 mm diameter (B).

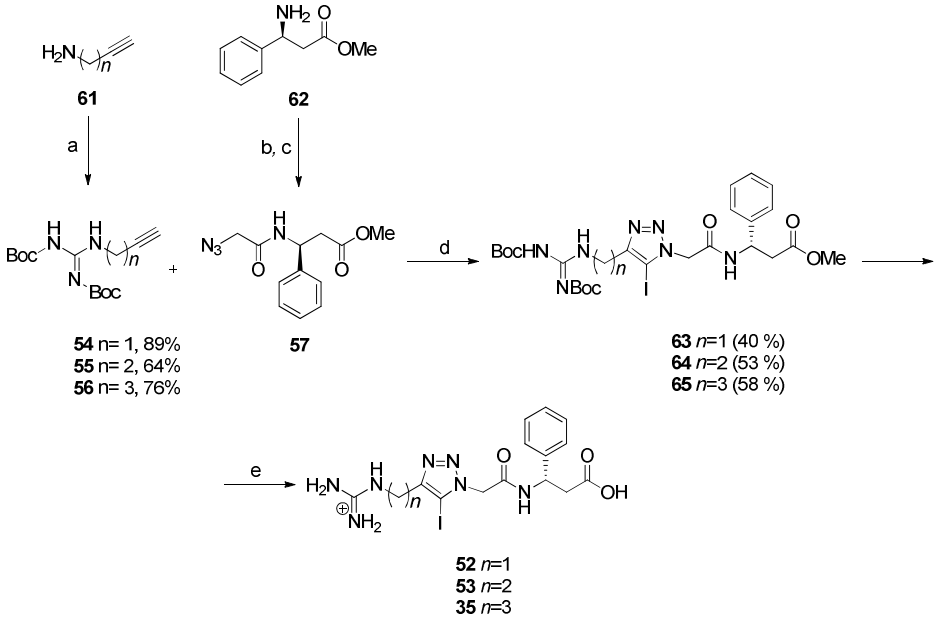
### 3.4.2.2 Synthesis of iodinated RGD triazolium salts

Our working plan to prepare the densely iodinated triazolium salts **58-60** was divided into two parts (**Scheme 3. 8**). First, we synthesized the 5-iodotriazoles **35**, **52** and **53** with C4 substituents of different length in order to study their affinity for $\alpha_v\beta_3$ tumor integrins. This transformation was planned using CuAAC reactions conducted in the presence of a iodonium ion source. Then, after selecting the more active RGD triazoles, we intended to apply the *N*-alkylation method developed above (**section 3.4.1**) to get the desired tetraiodinated triazolium salts **58-60**.




**Scheme 3. 8.** Retrosynthetic analysis of tetraiodinated RGD triazolium salts **58-60**.

Our synthesis started with the preparation of alkynes **54-56** and the azide **57**, using a methodology adapted from the approach of Calorini and Guarna.[103] Alkynes **54-56** were prepared in 64-89 % yield from the commercially available ω-alkynylamines **61** upon treatment with 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea and a catalytic amount of *N*,*N*-dimethylaminopyridine (DMPA). In turn, azide **57** was prepared in two reaction steps. First, the β-aminoester[104] **62** was acylated with bromoacetyl chloride and triethylamine to give an intermediate bromoacetamide (87 %), which was immediately treated with sodium azide in DMF at 80 ºC to provide the azidopeptide **57** in 83 % yield.




**Scheme 3. 9.** Reagents and conditions: (a) (n=1, n=2) BocHN-C(SMe)=NBoc, DMAP (cat.), $CH_2Cl_2$, 35 ºC, 3 days then, 40ºC, 18 h; (n=3) BocHN-C(SMe)=NBoc, DMAP (cat.), $CH_2Cl_2$, 60 ºC, 24 h; (b) TEA, $BrCH_2COCl$, $CH_2Cl_2$, -10 ºC, 15 min, then r.t., 30 min; (c) $NaN_3$, DMF, 80 ºC, 16 h; (d) CuI, NBS, DIPEA, MeCN, r.t., 4 h; (e) HCl 4M, 1,4-dioxane:$H_2O$ 1:1, r.t., 16h.

[103] Trabocchi, A.; Menchi, G.; Cini, N.; Bianchini, F.; Raspanti, S.; Bottoncetti, A.; Pupi, A.; Calorini, L.; Guarna, A. *J. Med. Chem.* **2010**, *53*, 7119-7128. "Click-chemistry-derived triazole ligands of arginine-glycine-aspartate (RGD) integrins with a broad capacity to inhibit adhesion of melanoma cells and both in vitro and in vivo angiogenesis".

[104] Liu, Y.; Zhou, E.; Yu, K.; Zhu, J.; Zhang, Y.; Xie, X.; Li, J.; Jiang, H. *Molecules* **2008**, *13*, 2426-2441. "Discovery of a novel CCR5 antagonist lead compound through fragment assembly".

With the alkynes and the azide in hand, we followed the method of Zhang[105] to prepare 5-iodo-1,2,3-triazoles conducting the CuAAC reaction in the presence of iodinium ion generated *in situ* from CuI and *N*-bromosuccinimide (NBS). Accordingly, each alkyne **54-56**, the azide **57** and DIPEA were added to a solution of CuI and NBS in anhydrous acetonitrile. After 4 hours, the product was purified by column chromatography to give the corresponding 5-iodo-1,2,3-triazoles **63-65** in fair yields (40-58 %). Finally, the Boc groups and the methyl ester were simultaneously deprotected in acid medium to yield the corresponding iodinated RGD mimetics **35**, **52** and **53**.

In **Figure 3. 6** are compared the fully assigned $^{1}$H NMR spectra of iodinated triazoles **63-65**. As expected, analogous protons show very similar chemical shifts in three spectra, excepting for the signals of the alkyl chain linking the guanidine moiety and the triazole C4 position.

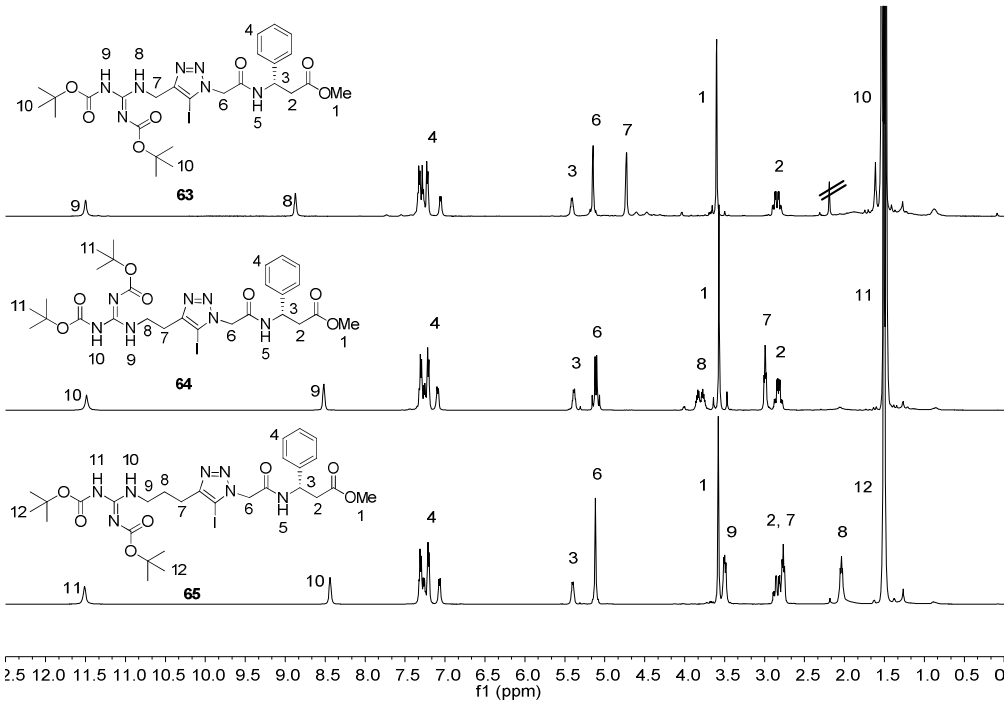
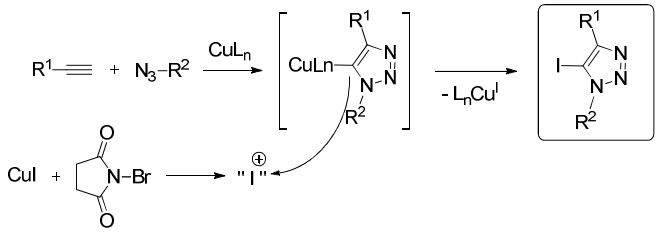



**Figure 3. 6.** $^{1}$H NMR Spectra (500 MHz, $CDCl_3$) of iodinated RGD mimetic precursors **63-65**.

[105] Li, L.; Zhang, G.; Zhu, A.; Zhang, L. *J. Org. Chem.* **2008**, *73*, 3630-3633. "A convenient preparation of 5-iodo-1,4-disubstituted-1,2,3-triazoles: Multicomponent one-pot reaction of azide and alkyne mediated by CuI-NBS".

A mechanistic sketch of the three component CuAAC reaction leading to 5-iodotriazoles is outlined in **Scheme 3. 10**. The copper triazolide intermediate formed in the CuAAC catalytic cycle exchanges the metal for a iodonium "$I^+$" specie generated "*in situ*" from NBS and CuI. This leads to the liberation of the iodinated triazole and the regeneration of an active copper salt to complete the catalytic cycle.




**Scheme 3. 10.** Mechanistic sketch for the triazole iodination step from a copper triazole intermediate and a iodonium species.

All the monoiodinated RGD mimetics **35**, **52** and **53** were submitted to a radiologic study carried out in collaboration with Dr. Ignacio García-Alonso (Departamento de Cirugía y Radiología y Medicina Física at UPV/EHU), Dr. Néstor Etxebarria (Departamento de Química Analítica at UPV/EHU) and Dr. José Javier Echevarría (Servicio de Radiología Hospital Galdakao-Usánsolo).

The iodinated RGD mimetics **35**, **52** and **53** were homogeneized with one molar equivalent of (*L*)-lactic acid and dissolved in a saline solution. Then, each sample was injected intraarterially to Waj/Rij male rats inoculated with human CC531 colocarcinoma cells. One hour after the administration of the corresponding contrast agents, X-ray computed tomographic (CT) images were recorded *in vivo*. Then, the animals were killed and radiologic attenuations were determined separately in the liver and in the tumor for a set of three rats in each experiment. The measured attenuation ranges (in Hounsfield units) are collected in **Table 3. 2**. Finally, the samples from liver and tumor tissue were analyzed by inductively coupled plasma mass spectrometry (ICP-MS) to determine the iodine content.

**Table 3. 2.** Radiologic attenuation in Hounsfield Units (HU) and iodine content in the liver and the tumor after intraarterial administration of iodinated contrast agent to Waj/Rij male rats inoculated with CC531 human colocarcinoma cells.

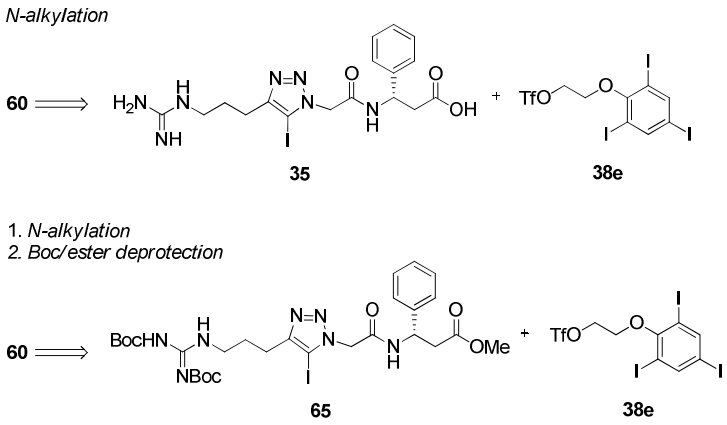
| Entry | Contrast agent | [I][a] (mg) | Liver | | Tumor | |
|---|---|---|---|---|---|---|
| | | | X-Ray CT (HU) | ICP-MS [I][b] (µg/g) | X-Ray CT (HU) | ICP-MS [I][b] (µg/g) |
| 1 | Iodixanol | 30 | 114-120 | 32 | 79-87 | 35 |
| 2 | **35** | 27 | 129-137 | 430 | 188-201 | 2444 |
| 3 | **53** | 17 | 103-133 | —[c] | 96-113 | —[c] |
| 4 | **52** | 24[b] | 123-152 | —[c] | 95-123 | —[c] |

[a]Iodine weight equivalent injected. [b]Iodine content in the tissue determined by inductively coupled plasma mass spectrometry (ICP-MS). [c]Only basal iodine concentrations detected.

From the results collected in **Table 3. 2**, we concluded that only compound **35** displayed a strong a selective radiological attenuation increase in the tumor tissue compared to the liver (entry 2). This observation was also confirmed by the higher accumulation of iodine determined by ICP-MS in the tumor. Unfortunately, the RGD iodotriazoles **53** and **52** with shorter C4 alkyl linkers failed to give a differential radiological attenuation or iodine accumulation in the tumor (entries 3 and 4).

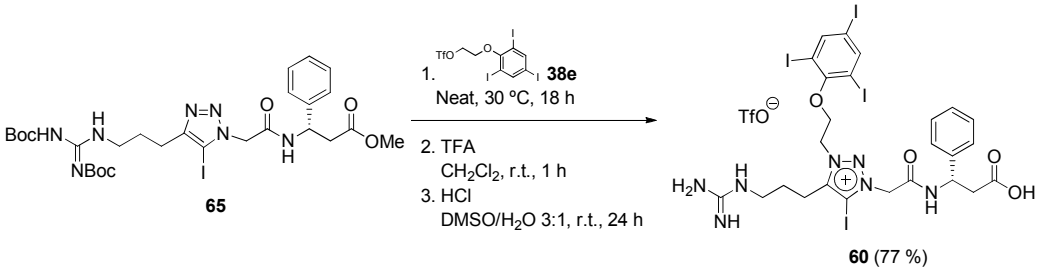
#### 3.4.2.3 Synthesis of iodotriazolium RGD mimetic

Since only iodotriazole **35** gave significant radiological activity, we decided to prepare the *N*-alkylated triazolium salt **60**. To accomplish this task, we tried two approaches (**Scheme 3. 11**).




**Scheme 3. 11.** Synthetic approaches for the preparation of the tetraiodinated triazolium salt **60** by *N*-alkylation of iodotriazoles **35** and **65**.

The most desirable and direct approach was the *N*-alkylation reaction of the RGD mimetic iodotriazole **35** with 2,4,6-triiodophenyl trifate **38e**. Disappointingly, the starting compound **35** was recovered unchanged after several alkylation trials carried out by evaporating a suspension of the iodotriazole and the alkylating agent **38e** in $CH_2Cl_2$ or MeCN. This reaction failure was attributed to the lack of solubility of **35** in noncoordinating organic solvents. To overcome the solubility issues, we tried an alternative stepwise transformation from the fully protected iodotriazole **65**, which was soluble in dichloromethane.



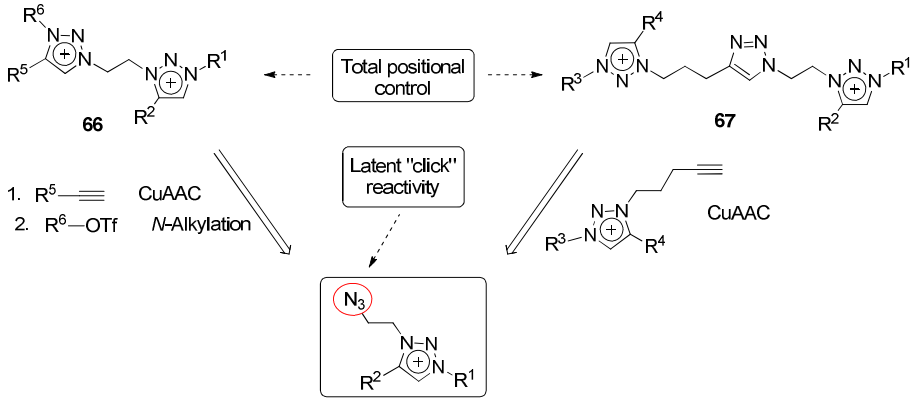

**Scheme 3. 12.** Synthesis of the tetraiodinated triazolium RGD mimetic **60**.

Evaporation of an equimolar mixture of compound **65** and the iodinated triflate **38e** from a dichloromethane solution and warming the residue overnight at 30 ºC provided an intermediate *N*-alkylated triazolium salt in 77 % isolated yield after purification by flash column chromatography. This compound was submitted to the cleavage of the guanidine Boc

groups with trifluoroacetic acid, followed by the quantitative demethylation of the ester group with hydrochloric acid in aqueous DMSO to afford the tetraiodinated RGD mimetic **60** in quantitative yield. This compound is currently under screening as a contrast agent for X-ray CT scanning and the results will be reported in due course.

### 3.4.3 Synthesis of polysubstituted bis(1,2,3-triazolium) systems with total positional control

Following our general working plan, we addressed our next objective, consisting in the demonstration of the "click" reactivity on *N*-alkyltriazolium salts incorporating terminal azide and alkyne functionalities at the *N*3-substituent. In particular, we chose to synthesize a few fully substituted bis(1,2,3-triazolium) systems (**66** and **67**) with unprecedented positional control following a CuAAC approach (**Scheme 3. 13**).




**Scheme 3. 13.** Accessing polysubstituted bis(1,2,3-triazolium) systems with total positional control.

In the literature, there are several reports on symmetrically substituted bis(1,2,3-triazolium) salts prepared by CuAAC cycloaddition reactions of diynes or diazides followed by *N*-alkylation (**Figure 3. 7**). Among them, rigid 4,4´-bis(triazolium) salts,[106] alkylene

[106] Aizpurua, J. M.; Sagartzazu-Aizpurua, M.; Azcune, I.; Miranda, J. I.; Monasterio, Z.; García-Lecina, E.; Fratila, R. M. *Synthesis* **2011**, *17*, 2737-2742. "Click" synthesis of nonsymmetrical 4,4´-bis(1,2,3-triazolium) salts".

bridged bis(triazolium) salts,[107] arylene bridged propylene bis(triazolium) salts[90,108] and spiro bis(1,2,3-triazolium) salts[109] have been described. However, no method exist to prepare nonsymmetrically substituted bis(1,2,3-triazolium) systems with total positional control.[110]

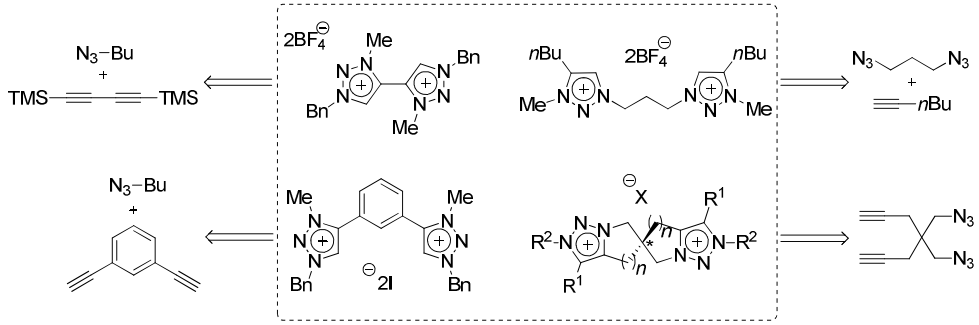


**Figure 3. 7.** Symmetrically substituted bis(1,2,3-triazolium) salts.

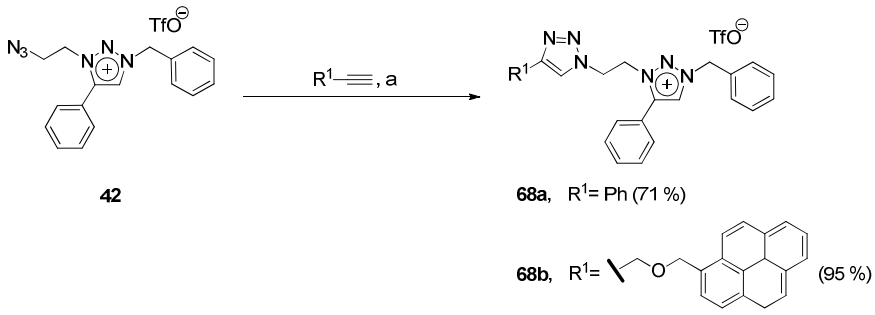
To implement our approach, we chose the azide-functionalized triazolium salt **42** as a model and conducted two CuAAc reactions with phenylacetylene and 1-[(prop-2-yn-1-yloxy)methyl]pyrene, respectively. As expected, a clean and high-yielding transformation to the mixed triazole-triazolium compounds **68a-b** was observed in each case using 20 mol % CuOAc/NaOAc catalyst (**Scheme 3. 14**).

[107] Khan, S. S.; Liebscher, J. *Synthesis* **2010**, 2609-2615. "Synthesis of new dicationic azolium salts and their application as NHC precursors in Suzuki-Miyaura coupling".

[108] Schulze, B.; Friebe, C.; Hager, M. D.; Günther, W.; Köhn, U.; Jahn, B. O.; Görls, H; Schubert, U. S. *Org. Lett.* **2010**, *12*, 2710-2713. "Anion complexation by triazolium "ligands": mono- and bis-tridentate complexes of sulfate".

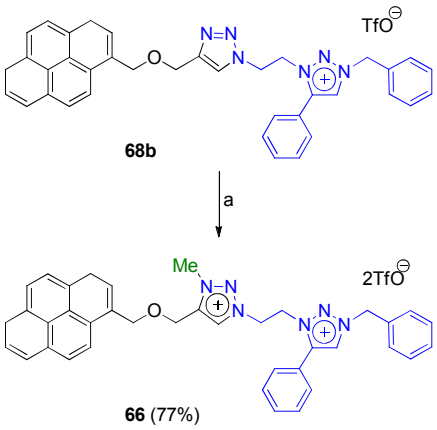
[109] a) Yoshida, Y.; Takizawa, S.; Sasai, H. *Tetrahedron Lett.* **2011**, *52*, 6877-6879. "Synthesis of spiro bis(1,2,3-triazolium) salts as chiral ionic liquids". b) Yoshida, Y.; Takizawa, S.; Sasai, H. *Tetrahedron: Asymmetry* **2012**, *23*, 843-851. "Design and synthesis of spiro bis(1,2,3-triazolium) salts as chiral ionic liquids".

[110] For a comprehensive review on the synthesis of bis(1,2,3-triazole) systems, see: Huo, J.; Wei, X.; Mo, G.; Peng, P.; Zhong, M.; Chen, R.; Wang, Z. *Chin. J. Org. Chem.* **2014**, *39*, 92-106. "Progresses in syntheses and applications of bis-1,2,3-triazoles".




**Scheme 3. 14.** Synthesis of mixed triazole-triazolium compounds **68**. Reagents and conditions: (a) CuOAc, NaOAc, $CH_3CN/^tBuOH/H_2O$ 1:0.4:0.1, r.t., 18 h.

As a proof of principle of the obtention of polysubstituted bis(1,2,3-triazolium) salts **66**, we alkylated the triazole ring of **68b** with methyl triflate to get the expected product in 77 % yield (**Scheme 3. 15**). As far as we know, this dicationic salt constitutes the first example of a completely site-controlled tetrasubstituted bis(1,2,3-triazolium) of this kind.

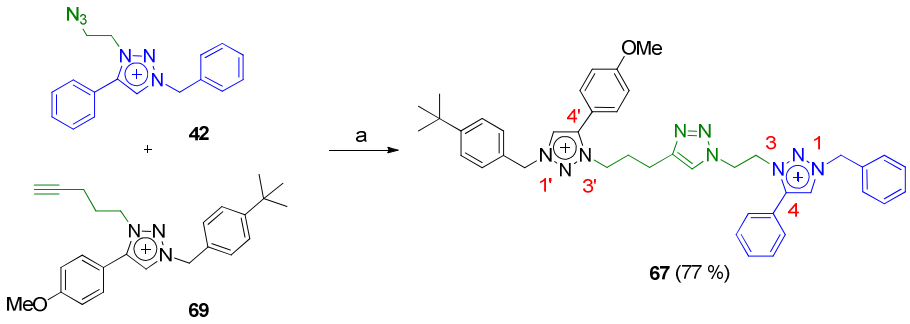



**Scheme 3. 15.** Preparation of a bis(1,2,3-triazolium) salt with total positional control. Reagents and conditions: (a) MeOTf, $CH_2Cl_2$, r.t., 5 h.

Next, we investigated the CuAAC coupling of two triazolium salts through the azide- and alkyne-terminated *N*3,*N*3´-substituents previously introduced by *N*-alkylation (**Scheme 3. 16**). Thus, triazolium alkyne **42** and triazolium alkyne[111] **69** were reacted at room temperature in the presence of 20 mol % of CuOAc/NaOAc catalyst to afford a 77 % yield of

[111] This compound was prepared in 81 % yield by *N*-alkylation of 1-(*tert*-butylbenzyl)-4-(*p*-metoxyphenyl)-1*H*-1,2,3-triazole with 4-pentyn-1-yl triflate under the conditions described in **section 3.4.1**.

the tricyclic bis(1,2,3-triazolium) salt **67**. It is worth mentioning that this approach allows the modular control of up to six structural parameters, including not only the four triazolium *N*1 and C4 substituents, but also the two alkyne spacers linking the triazolium *N*3,*N*3´-positions with the central triazole ring.




**Scheme 3. 16.** Preparation of a hybrid triazole/bis(1,2,3-triazolim) salt with total positional control. Reagents and conditions: (a) CuOAc, NaOAc, $CH_3CN/^tBuOH/H_2O$ 1:1:0.1, r.t., 18 h.

The assigned $^1H$ NMR spectra of the reagents and the polysubstituted bis(1,2,3-triazolium) hybrids **67** are compared in **Figure 3. 8**.

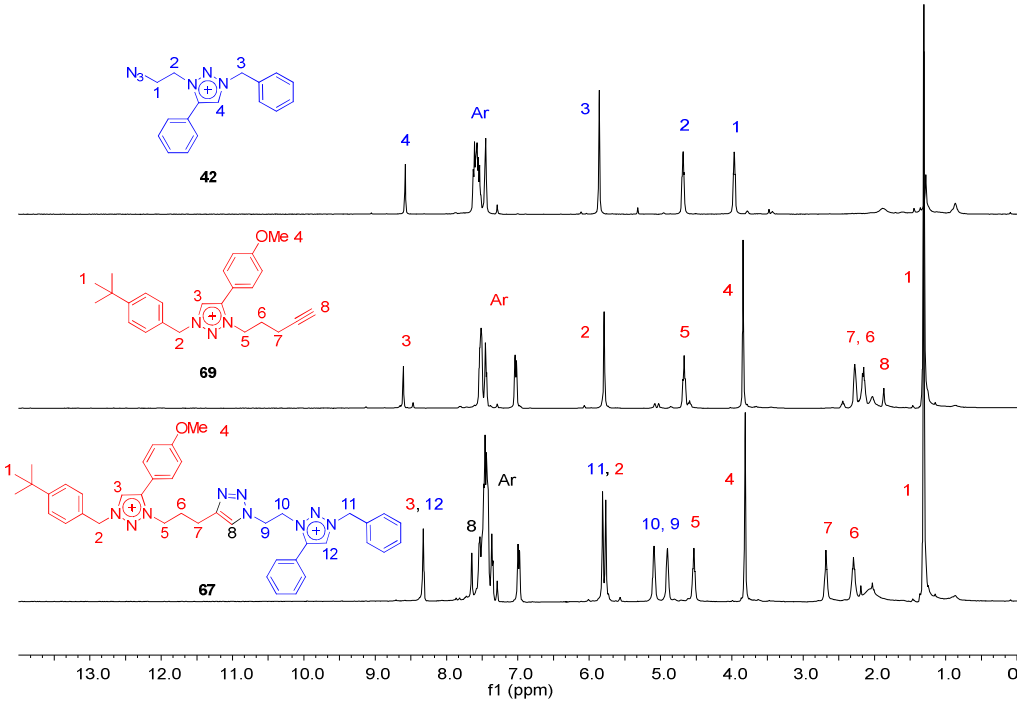
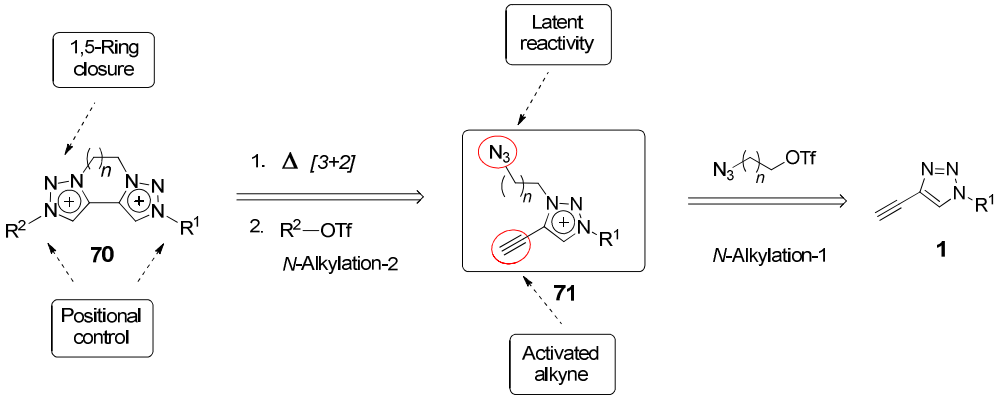



**Figure 3. 8.** $^1H$ NMR spectrum (400 MHz, $CDCl_3$) of triazolium compounds **42**, **69** and **67**.

Again, to the best of our knowledge, compound **67** is the first example of non-symmetrically substituted bis(1,2,3-trizolium)-triazole hybrid salt.

### 3.4.4 Tandem *N*-alkylation/thermal cyclization of 4-alkynyl-triazoles to tricyclic 4,5´-bis(1,2,3-triazolium) salts

From the detailed study disclosed in **section 2.4.2.4** on the thermal [3+2] cycloaddition of azides with cationic triazolium alkynes, we concluded that *N*3-alkylation of 4-alkynyl-1,2,3-triazoles enhances significantly the cycloaddition reaction rate. Now, to complete the last objective of this chapter, we considered an intramolecular version of this reaction using and azide-functionalized alkyl triflate as the reaction promoter (**Scheme 3. 17**).

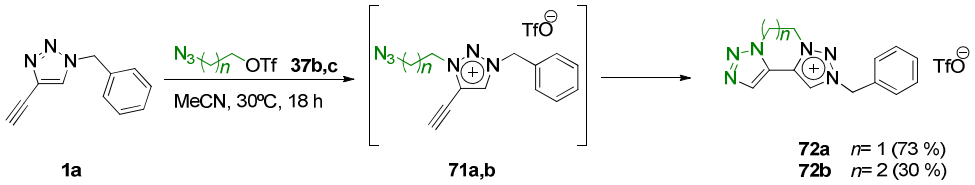



**Scheme 3. 17.** Tandem *N*-alkylation/cycloaddition reaction of 4-ethynyl-1,2,3-triazoles with ω-azidoalkyl triflates.

*N*-alkylation of 4-ethynyl-1,2,3-triazoles **1** with short ω-azidoalkyl triflates (n=1, 2) should provide the intermediate cationic triazolium alkynes **71**, incorporating a latent azide group. Owing to the favorable entropic conditions, such intermediate should likely envolve to a triazole-triazolium tricyclic intermediate through a 1,5- ring closure geometry. Finally, after a second *N*-alkylation with an alkyl triflate of choice, the bridged bis(1,2,3-triazolium) salts **70** should be accessible for the first time.

In a first trial, triazole alkyne **1a** was treated with one equivalent of 2-azidoethyl triflate **38b** following the solvent evaporation protocol described above (**section 3.4.1**). Unfortunately, we only observed the formation of polymer products arising presumably from

intermolecular azide-alkyne cycloaddition reactions. In sharp contrast with this result, when an equimolar solution of both reactants in acetonitrile (concentration ≈ 0.2 M) was warmed at 30 ºC for 18 h, a complete transformation to the tricyclic product **72b** was observed (**Scheme 3. 18**). A similar cyclization reaction took place using 3-azidopropyl triflate **72c**, albeit in significantly lower yield.




**Scheme 3. 18.** Tandem *N*-alkylation/cyclization of triazolyl alkyne **1a** to bridged 1,5-triazole-triazolium compounds **72**.

From a mechanistic point of view, some aspects of this transformation were meaningful: a) the mild thermal conditions required to activate the [3+2] azide-alkyne cycloaddition, b) the easy formation of the triazole 1,5-regioisomer and, c) the strong dependence of the reaction performance with the length of the ω-azidoalkyl triflate.

In the $^{1}$H NMR spectra collected in **Figure 3. 9** are compared the starting ethynyltriazole **1a** and the tricyclic triazole-triazolium adduct **72a**, showing the characteristic downfield chemical shifts of triazole and triazolium protons at 8.2 and 8.7 ppm, respectively.

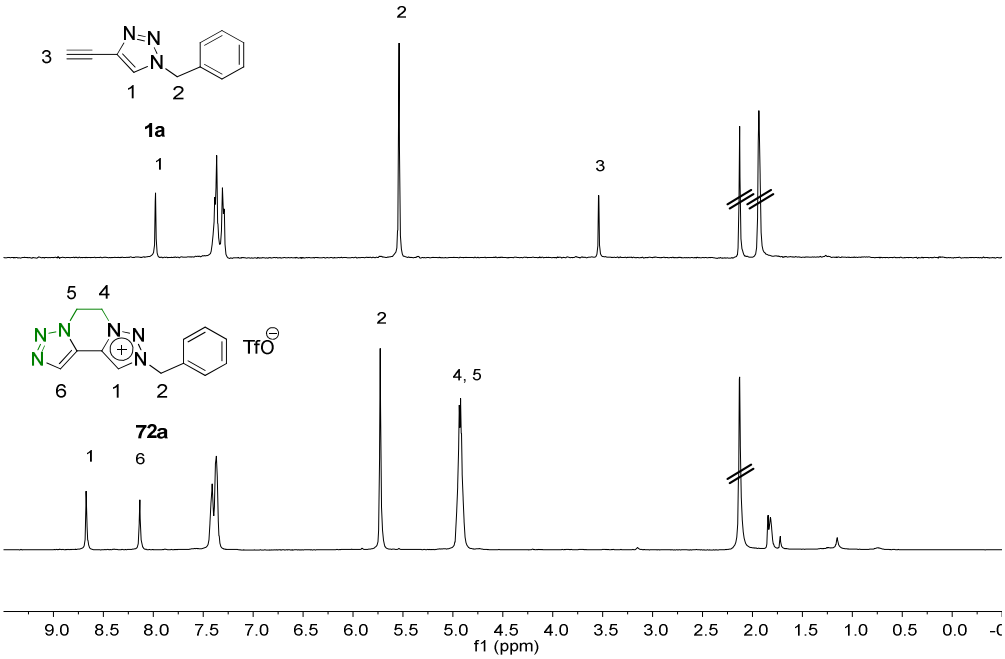



**Figure 3. 9.** $^{1}$H NMR spectra (400 MHz, MeCN-$d_3$) of triazolium compounds **1a** and **72a**.

In both instances, it was possible to observe the transient formation of 4-ethynyl-triazolium intermediates **71** when the reaction was conducted in an NMR sample tube using MeCN-$d_3$ as solvent. Carrying the *N*-alkylation under carefully controlled conditions, the 3-azidopropyl salt **71b** could be isolated and characterized. Its $^{1}$HNMR spectrum is shown in **Figure 3. 9** and the characteristic triazolium and alkyne protons appear at 8.7 and 4.7 ppm, respectively.

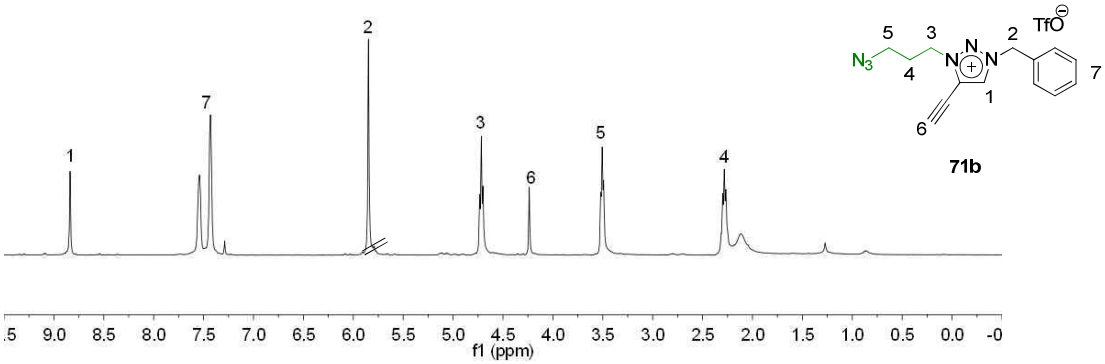
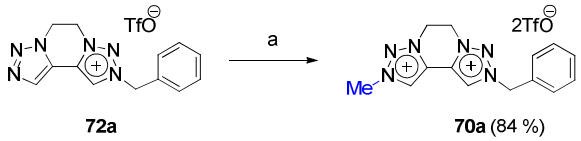



**Figure 3. 10.** $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of the azido alkyne triazolium intermediate **71b**.

To complete our final objective, we submitted the triazole of **72a** to a *N*-alkylation reaction to get the expected bridged bis(1,2,3-triazolium) compound **70a** with nonsymmetrical substituents at *N*1,*N*1' positions. Thus, treating **72a** with one equivalent of methyl triflate afforded the target compound in excellent yield (**Scheme 3. 19**).




**Scheme 3. 19.** Synthesis of nonsymmetrically substituted 4,5´-bis(1,2,3-triazolium) bridged salt **70a**. Reagents and conditions: (a) MeOTf, MeCN, r. t., 5 h.

Again, this was the first synthetic route allowing the preparation of such bridged tricyclic 4,5´-bis(1,2,3-triazolium) salts. Among other potential uses, we anticipate that these novel compounds constitute excellent precursors for mesoionic dicarbenes that could find applications as chelating ligands for transition metal-based catalysts[112] or highly directional ditopic hydrogen donors for supramolecular constructs.

[112] Guisado-Barrios, G.; Bouffard, J.; Donnadieu, B.; Bertrand, G. *Organometallics* **2011**, *30*, 6017-6021. "Bis(1,2,3-triazol-5-ylidenes) (i-bitz) as stable 1,4-bidentate ligands based on mesoionic carbenes(MICs)".

### 3.4.4.1 Computational study of the intramolecular thermal cycloaddition of a triazolium azidoalkynes

To understand the mild thermal conditions (30 ºC) required to activate the intramolecular [3+2] azide-alkyne cycloaddition described above, we established a collaboration with Dr. Miranda (SGIker, UPV-EHU). We chose the triazolium azidoalkyne **73** as a model and, to reduce the computational cost, the *N*1-benzyl group was abbreviated to methyl (**Figure 3. 11**). Calculations were conducted at the B3LYP/631G** level of theory following the same method described in **section 2.4.3**.

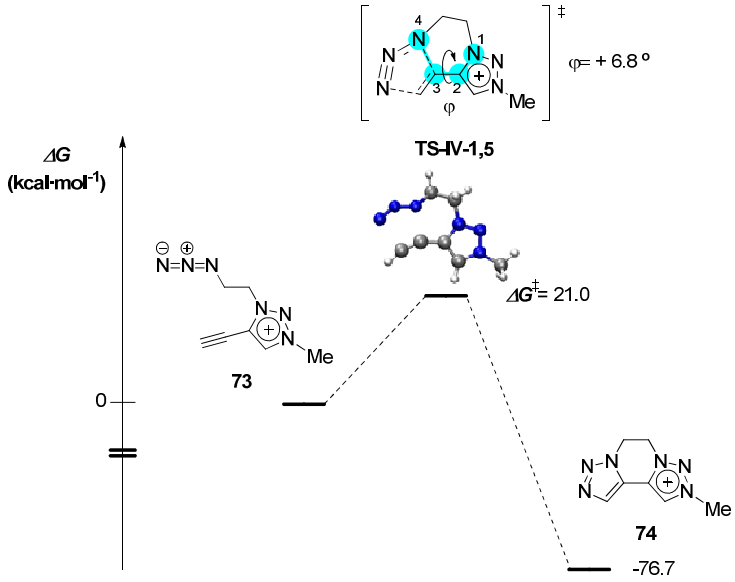



**Figure 3. 11.** Computed activation transition state for the intramolecular thermal cycloaddition of azido-alkyne **73** to the tricyclic triazol-triazolium compound **74**. Relative free energies are in kcal·mol$^{-1}$.

According to the computed results, the activation Gibbs energy for the transition state (**TS-IV-1,5**) leading to 1,5-ring closure was of only 21.0 kcal·mol$^{-1}$. This value was about 10 kcal·mol$^{-1}$ lower than the comparable activation energy for the intermolecular cycloaddition of benzylazide and the cationic triazolium alkyne **2c** described in **chapter 2** (see **Figure 2.18**). Moreover, the small cycloaddition dihedral angle φ= + 6.8 º was also consistent with the low activation energy calculated. All these datas, were in excellent agreement with the experimental observations.

## 3.5 Conclusions

A novel general strategy to introduce an additional labeled or functionalized N3-substituent into readily accessible "click" 1,4-disubtituted-1*H*-1,2,3-triazoles has been developed for the first time.

Alkyl triflates have been shown to be the reagents of choice for such transformation. A two-step protocol consisting in the heterogeneous triflation of alcohols, followed by a solvent-free *N*3-alkylation of 1,2,3-triazoles, provides *N*1,*N*3,C4-trisubstituted-1,2,3-triazolium salts in excellent yields and with great operational simplicity. This methodology has been applied to the preparation of a densely iodinated Arg-Gly-Asp (RGD) mimetic with potential use as imaging contrast agent for X-ray computed tomography scanning.

The latent reactivity of some model *N*3-(ω-azidoalkyl)-1,2,3-triazolium salts has been demonstrated by achieving their CuAAC coupling with alkynes to transform them into multisubstituted bis(1,2,3-triazolium) salts with unprecedented positional control.

Finally, it has been demonstrated that reacting 4-ethynyl-1,2,3-triazoles with short ω-azidoalkyl triflates leads to a novel tandem reaction involving the *N*3-alkylation of the triazole ring, followed by the intramolecular thermal [3+2] azide-alkyne cycloaddition to unique tricyclic bis-triazole-triazolium systems. According to computational calculations, the activation Gibbs energy for the transition state is at least 10 kcal·mol$^{-1}$ lower for this reaction than for standard intermolecular azide-alkyne cycloadditions.

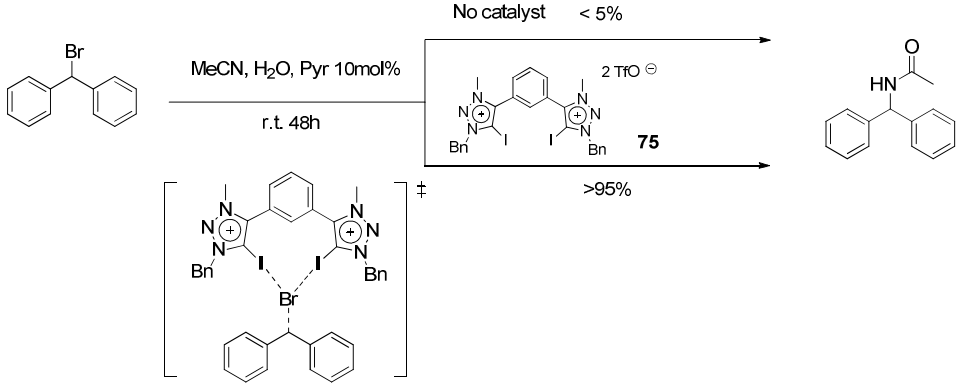
# 4

*Halogenation of 1,2,3-triazolium salts*

# 4 Halogenation of 1,2,3-triazolium salts

## 4.1 Introduction

As mentioned in **section 1.1.4**, halotriazolium salts have been mostly used to assemble supramolecular structures through strong halogen-halogen interactions. This characteristic has also been used to activate some organic reactions taking advantage of the cationic nature of the 1,2,3-triazolium moiety. For example, Huber has recently shown that 5-iodo-1,2,3-triazolium salt **75** can act as an "organic $Ag^+$ equivalent" by facilitating the halide-abstraction step in the nucleophilic substitution reaction of benzhydryl bromide with acetonitrile (**Scheme 4. 1**).[113] This case illustrates the interest to develop novel methods to prepare 5-halo-1,2,3-triazolium salts designed to incorporate proper groups for reaction activation and/or stereocontrol.




**Scheme 4. 1.** Nucleophilic substitution rate enhancement promoted by 5-iodo-1,2,3-triazolium cations.

5-Halo-1,2,3-triazolium salts are usually prepared by *N*3-alkylation of 5-halo-1,2,3-triazoles (**Scheme 4. 2**), which in turn, are prepared by a three component azide-alkyne-halonium CuAAC reaction, using *N*-halosuccinimides as electrophilic halogen sources.[114]

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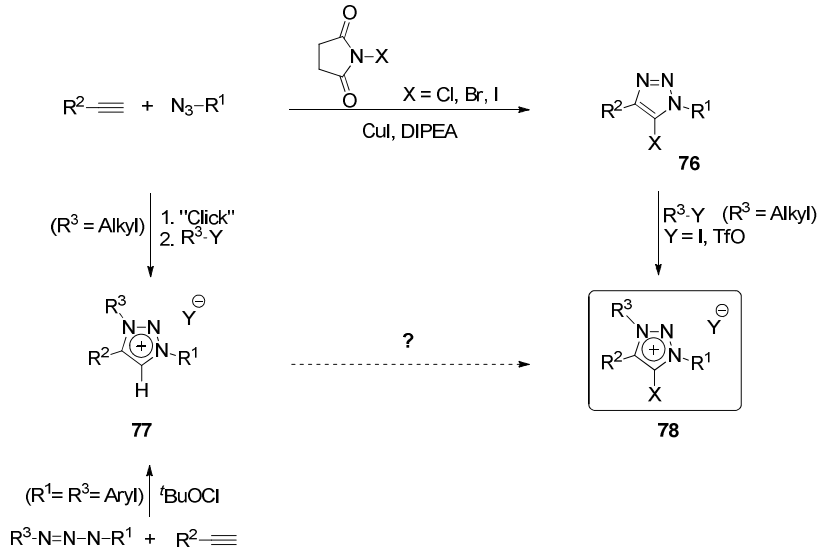
[113] Kniep, F.; Rout, L.; Walter, S. M.; Bensch, H. K. V.; Jungbauer, S. H.; Herdtweck, E.; Huber, S. M. *Chem. Commun.* **2012**, *48*, 9299-9301. "5-Iodo-1,2,3-triazolium-based multidentate halogen-bondo donors as activating reagents".

[114] (a) Brotherton, W. S.; Clark, R. J.; Zhu, L. *J. Org. Chem.* **2012**, *77*, 6443-6455. "Synthesis of 5-iodo-1,4-disubstituted-1,2,3-triazoles mediated by in situ generated copper(I) catalyst and electrophilic triiodide ion". (b) Wang, B.; Zhang, J.; Wang, X.; Liu, N.; Chen, W.; Hu, Y. *J. Org.*

Alternatively, 5-iodotriazoles are also accessible by the direct CuAAC cycloaddition of azides with iodoalkynes.[115] The *N*-alkylation of 5-halotriazoles **76** is considerably more difficult than the *N*-alkylation of nonhalogenated analogs, owing to the electron withdrawing effect of the halogen atom on the triazole ring. In addition, this approach is not compatible with the preparation of 3-aryl-5-halo-1,2,3-triazolium salts **78** ($R^3$= Ar),[2] because the *N*3-arylation of halotriazoles **76** is impracticable. A direct halogenation of triazolium salts **77**, which can be prepared without substitution restrictions, would be an interesting alternative route to prepare 5-halo-1,2,3-triazolium salts overcoming the aforementioned limitations.




**Scheme 4. 2.** Synthetic routes to 5-halo-1,2,3-triazolium salts.

## 4.2 Hypothesis

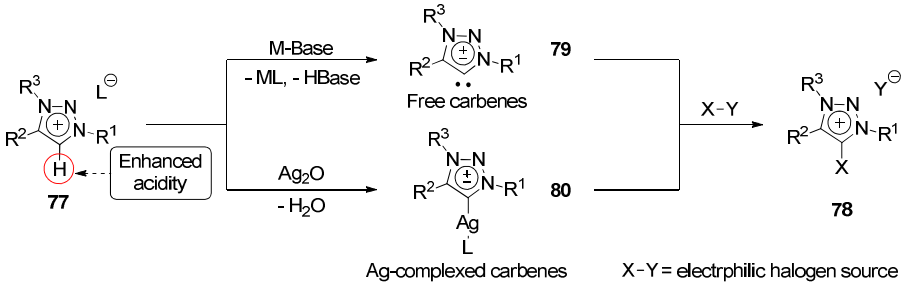
On the basis of the preceding analysis, we considered 1,2,3-triazole mesoionic carbenes[116] as convenient neutral electron-rich species to prepare 5-halotriazolium salts **78**

*Chem*. **2013**, *78*, 10519-10523. "Tandem reaction of 1-copper(I) alkynes for the synthesis of 1,4,5-trisubstituted 5-chloro-1,2,3-triazoles".

[115] Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2009**, *48*, 8018-8021. "Copper(I)-catalyzed cycloaddition of organic azides and 1-iodoalkynes".

[116] (a) Mathew, P.; Neels, A.; Albrecht, M. *J. Am. Chem. Soc*. **2008**, *130*, 13534-13535. "1,2,3-triazolylidenes as versatile abnormal carbene ligands for late transition metals". (b) Guisado-

(**Scheme 4. 3**). Taking advantage of the enhanced C5-H acidity of 1,2,3-triazolium salt **77**, and their easy transformation into free carbenes[116b] **79** or silver carbene complexes[117] **80**, we hypothesized that such activated species would react with suitable electrophilic halogen sources to provide 5-halotriazolium salts **78**.




**Scheme 4. 3.** Direct C5-halogenation of 1,2,3-triazolium salts through 1,2,3-triazole carbene intermediates.

As outlined in **section 1.1.3**, 1,2,3-triazole carbenes have been extensively exploited as strongly σ-donating neutral ligands for a large variety of transition metals.[38] However, the use of 1,2,3-triazole carbenes to form C-C or C-X (X= halogen) bonds through the carbenic lone electron pair remains unexplored.

In a preliminary *ab initio*[118] computational calculation, we estimated the relative electrophilic nature of the iodine atom in several halogenating agents and triazolic species, including *N*-iodosuccinimide or cyanogen iodide[119] (**Figura 1.3**). According to these results, we could anticipate the potential suitability of both reagents as electrophilic halogen sources for triazole carbenes.

Barrios, G.; Bouffard, J.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed*. **2010**, *49*, 4759-4762. "Crystalline 1H-1,2,3-triazol-5-ylidenes: new stable mesoionic carbenes (MICs)".

[117] Lin, I. J. B.; Vasam, C. S. *Coord. Chem. Rev.* **2007**, *251*, 642-670. "Preparation and application of *N*-heterocyclic carbene complexes of Ag(I)".

[118] Computed with the Gaussian 09vB.01 using the basis set 6-311G(d,p) for hydrogen, carbon, nitrogen and oxygen atoms, and the basis aug-cc-pVDZ-PP EMSL for iodine atom. Reed, A.E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899-926. "Intermolecular interactions from anatural bond orbital, donor-acceptor view point".

[119] Cyanogen iodide is a stable solid, readily available in multigram scale from sodium cyanide and molecular iodine: Bak, B.; Hillebert, A. *Org. Synth. Coll. Vol.* **1963**, *4*, 207-208. "Cyanogen iodide".

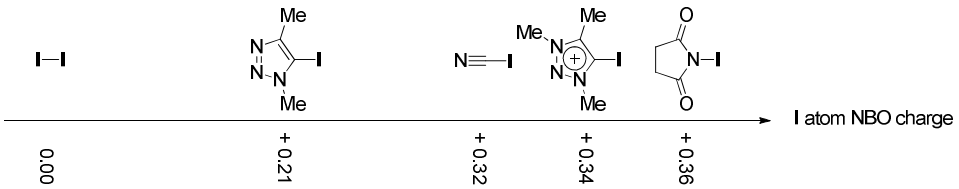


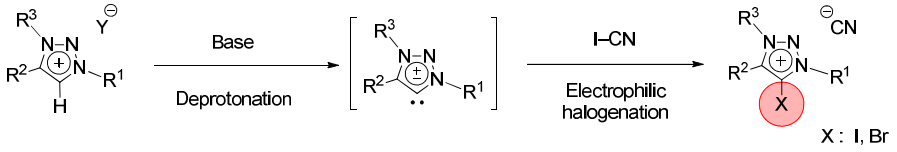

**Figure 4. 1.** Natural bonding orbital (NBO) charges calculated for iodine atom in different iodinated species.

Considering these computational results, we judged interesting to study the reaction of triazole mesoionic carbenes or their silver complexes with molecular iodine, *N*-halosuccinimides and cyanogen halides.

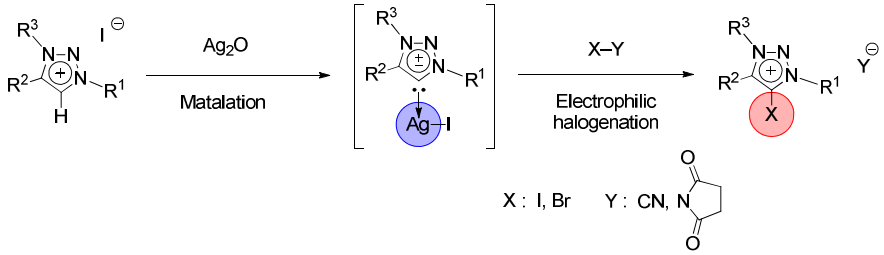
## 4.3 Objectives

According to the hypothesis discussed above, we stablished the following objectives for this part of the thesis work:

1. To study the metal-free synthesis of 5-halo-3-methyl-1,2,3-triazolium salts following a C5 deprotonation-halogenation sequence, using cyanogen halides as halogenating reagents.




2. To study the electrophilic halogenations reaction of silver 1,2,3-triazole carbene complexes using several halogenating reagents, including iodine, *N*-halosuccinimides or cyanogen halides.

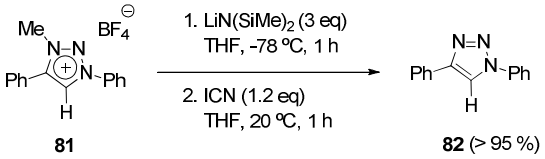


A computational analysis of the likely reaction pathways will be undertaken to gain insight on the mechanistic details of the reaction and to compare it with the silver-free transformation.

## 4.4 Results and discussion

### 4.4.1 Deprotonative halogenation of *N*-alkyl-1,2,3-triazolium salts

To address the first objective of this chapter, we studied the deprotonation of a 3-methyl-1,2,3-triazolium salts to the corresponding carbenes in the presence of an halogenating reagent. We selected the 1,4-diaryl triazolium tetrafluoroborate **81**[120] as a model to prevent unwanted deprotonations at 1,4- positions by the strong base required to form the mesoionic carbene intermediate (tipically, KHMDS or LiHMDS). Among the potential halogenating agents (see **Figure 4. 1** in the introduction section), we selected cyanogen iodide for its lack of potentially acidic hydrogen atoms. Thus, following a standard protocol to prepare mesoionic carbenes,[116b] the triazolium salt **81** was treated with 3 equivalents of lithium bis(trimethylsilyl)amide in THF at -78 ºC for 1 hour, followed by the addition of cyanogen iodide and warming of the mixture to room temperature (**Scheme 4. 4**).




**81** **82** (> 95 %)

**Scheme 4. 4.** Demethylation reaction of 1,4-diaryl-3-methyl-1,2,3-triazolium salt **81**.

Surprisingly, instead of the expected C5-halogenation product, we observed a clean and quasi-quantitatine *N*-demethylation of the triazolium ring to the parent triazole. The transformation was confirmed unambiguously by comparing the $^{1}$H NMR spectra of **81** and the reaction product **82** (**Figure 4. 2**). An upfield shift of the triazolic proton from 8.8 ppm to 8.2 ppm and the disappearance of the methyl protons at 4.4 ppm were fully consistent with the proposed reaction.

[120] Nakamura, T.; Terashima, T.; Ogata, K.; Fukuzawa, S. *Org. Lett.* **2011**, *13*, 620-623. "Copper(I) 1,2,3-triazol-5-ylidene complexes as efficient catalysts for click reactions of azides with alkynes".

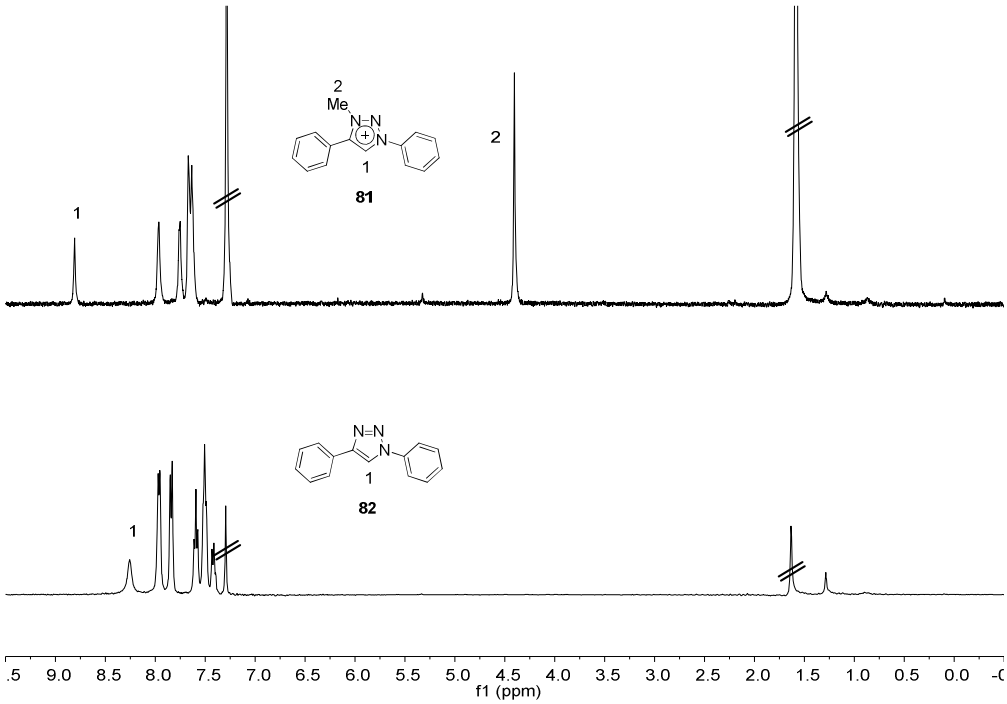
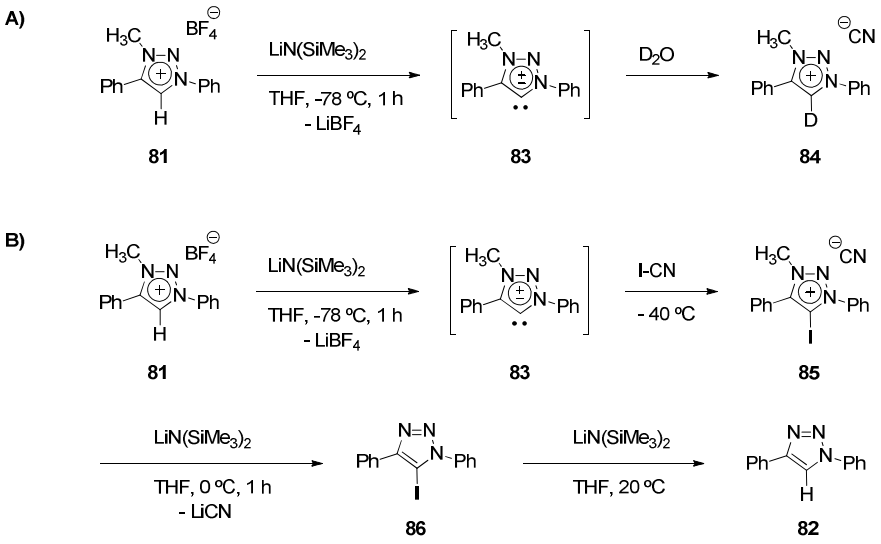



**Figure 4. 2.** $^{1}$H NMR (500 MHz, $CDCl_3$) spectra of the triazole derivatives **81** and **82** (see **Scheme 4. 4**).

The intriguing nature of the transformation and the smooth reaction conditions required to perform it (compare, for example, with the *N*-demethylation described in **section 2.4.4**, pages 71-72) prompted us to conduct a more in depth study carrying out a few additional experiments (**Scheme 4. 5**). First, we repeated the reaction in the absence of cyanogen iodide, replacing it with $D_2O$. The disappearance of CH protons at 8.8 ppm in the $^{1}$H NMR spectrum of the product and the unchanged presence of the *N*-methyl group at 4.5 ppm, denoted the formation of the C5-deuterated triazolium salt **84**. The deuteration proved the formation of the carbene intermediate **83** under the conditions used and confirmed the necessity of cyanogen iodide to complete the *N*-demethylation of the triazolium ring. Next, (**Scheme 4. 5**, **B**) we repeated the experiment treating the *in situ* generated carbene **83** with cyanogen iodide and increasing the temperature. Reaction aliquots were quenched periodically with a diluted solution of trimethylsilyl chloride and acetic acid in THF. At -78 ºC, the starting triazolium cation **81** was only partially converted into 5-iodotriazolium **85**. Raising the temperature to -40 ºC, 5-iodotriazolium cyanide **85** was obtained as the only product (see the $^{1}$H NMR spectrum of **Figure 4. 3**).




**Scheme 4. 5.** Deuteration reaction (A) and sequential outcome (B) of the *N*-demethylation reaction of the triazolium salt **81** to put into evidence the formation of reaction intermediates.

Warming the mixture to 0 ºC, resulted in a complete demethylation of **85** to the 5-iodotriazole **86**. Finally, adding one equivalent of LiHMDS and keeping the mixture at room temperature, led to the total deiodination reaction of **86** to **82**.

These experiments clearly established the reaction intermediates involved in the *N*-demethylation sequence of the triazolium salt **81** and confirmed the demethylation of the 5-iodotriazolium cyanide **85** into the 5-iodotriazole **86** at temperatures around 0 ºC as the key reaction step.

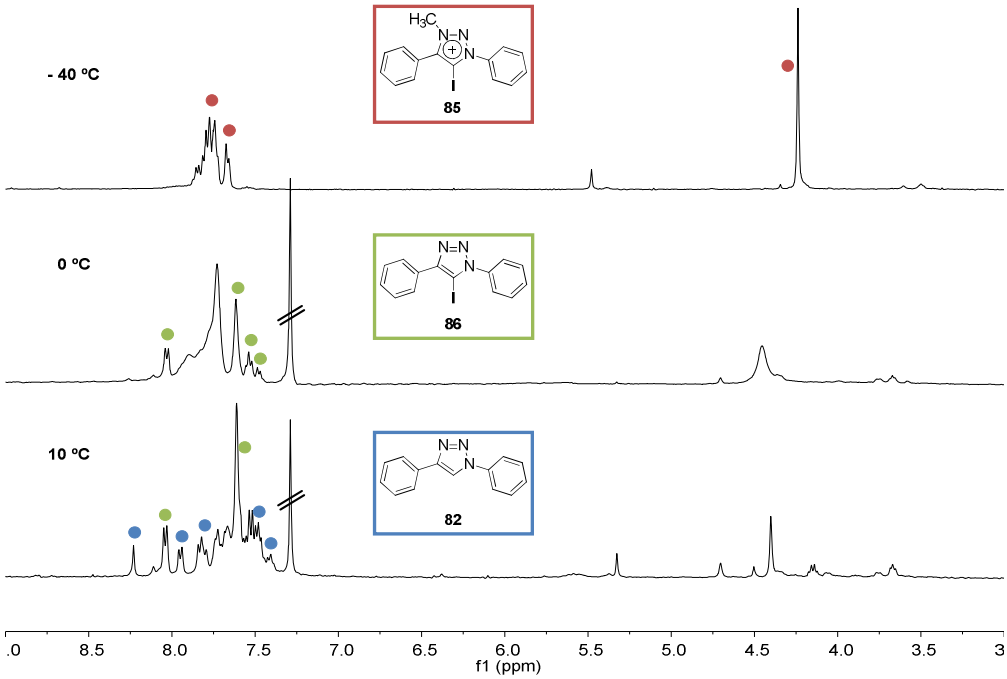



**Figure 4. 3.** $^{1}$H NMR (400 MHz, MeCN-$d_3$ and $CDCl_3$) spectra of reaction aliquots quenched at different temperatures from the demethylation reaction of **81** with LiHMDS and cyanogen iodide (**Scheme 4. 5**).

In parallel with the experimental exploration, a collaboration was stablished with Prof. Enrique Gómez-Bengoa and Béla Fiser (Departamento de Química Orgánica-I UPV/EHU) to gain insight on the mechanism of the aforementioned demethylation step (**85** → **86**).

We guessed at least two plausible pathways to explain the *N*-demethylation of **85** (**Figure 4. 4**). The first obvious option was the $S_N^2$ attack of cyanide anion to the electrophilic *N*-methyl group in **85** to form the iodotriazole **86** and acetonitrile (**TS-I**). Alternatively, the strongly basic bis(trimethylsilylamide) anion could deprotonate the relatively acidic methyl group (**TS-II**) to generate a transient ylide intermediate **87** that would subsequently envolve to the iodotriazole **86** (see **Figure 4. 4**).

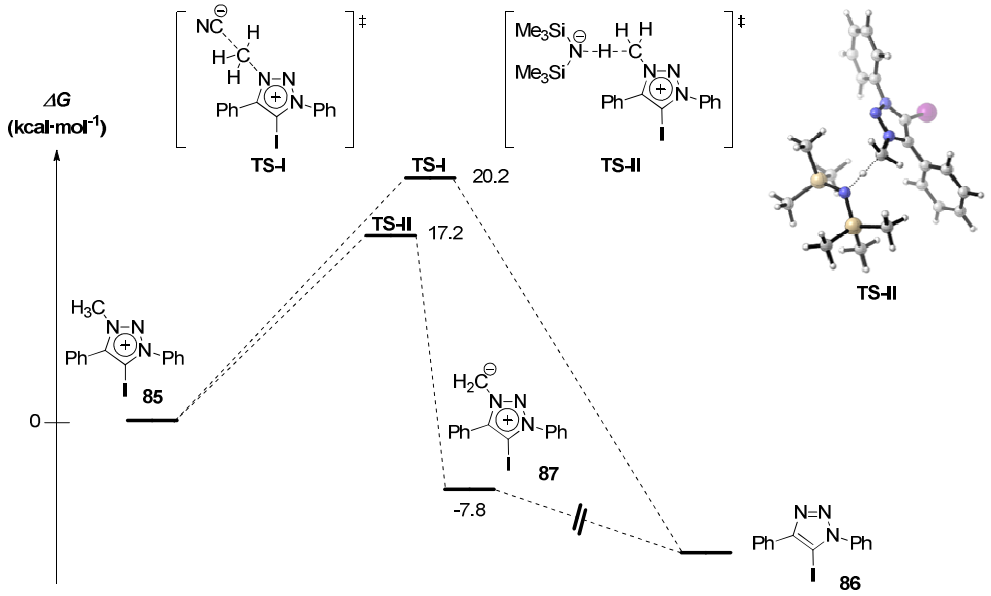



**Figure 4. 4.** Free-energy profiles of two alternative reaction pathways for the *N*-demethylation of **85**.

All reported structures were optimized at DFT level by using the B3LYP[121] hybrid functional as implemented in Gaussian 09.[122] Optimizations were carried out in a solvent model[123] (IEFPCM, solvent = acetonitrile), using the standard 6-31G(d,p) basis set for C, H, N and Si atoms. The LANL2DZ basis set was used for I atom.[124]

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[121] (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. "Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density". (b) Becke, A. D. *J. Chem. Phys*. **1993**, *98*, 5648–5652. "Density-functional thermochemistry. III. The role of exact exchange". (c) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem*. **1996**, *100*, 12974–12980. "Density Functional Theory of electronic structure".

[122] Gaussian 09, Revision D.01; M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2013**.

[123] (a) Cancès, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys*. **1997**, *107*, 3032–3047. "A new integral equation formalism for the polarizable continuum model: theoretical background and applications to isotropic and anisotropic dielectrics". (b) Cossi, M.; Barone, V.; Mennuci, B.; Tomasi, J. *Chem. Phys. Lett*. **1998**, *286*, 253–260. "*Ab initio* study of ionic solutions by a polarizable continuum

Although both mechanisms provided consistent transition states, the $S_N^2$ pathway through **TS-I** was about 3 kcal·mol$^{-1}$ higher in energy than the alternative deprotonation mechanism. In addition, the neutral electronic character of ylide **87** likely contributed to its stability. Besides, we concluded that transition state **TS-II** was the preferred pathway to the demethylated iodotriazole **86**. The detailed structure of the transition state **TS-II** it shown in **Figure 4. 4**. Finally, the activation energy for the C5-H deprotonation of the parent triazolium proton in **81** (**Scheme 4. 5**) was found to be only 4.4 kcal·mol$^{-1}$, which was consistent with the easy carbene formation observed at -78 ºC.

On the basis of the results discussed above, we concluded that the deprotonation-halogenation of *N*-alkyl-1,2,3-triazolium salts was not a synthetically convenient approach to prepare 5-halo-1,2,3-triazolium salts. Conversely, the deprotonation-halogenation approach provided a potentially usefull method for the mild *N*-dealkylation of 1,2,3-triazolium salts by the abstraction of an α-alkyl proton with a base in the presence of cyanogen halides.

### 4.4.2 Synthesis of 5-halo-1,2,3-triazolium salts from silver carbenes

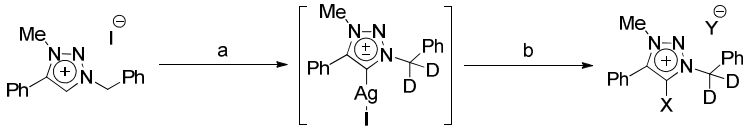
Next, we addressed the synthesis of 5-halo-1,2,3-triazolium salts from the readily available silver carbenes by reaction with electrophilic halogen sources. Since silver triazole carbenes are compatible with a considerable number of functional groups, this approach was expected to have a wider scope than the deprotonation-halogenation method. For the successful preparation of silver carbene complexes from 3-methyl-1,2,3-triazolium cations and $Ag_2O$, the counteranion of the starting salt was of crucial importance. Iodide and similar halides strongly stabilize the silver cation in the carbene complex **89**, whereas $BF_4^-$ or $TfO^-$ nucleofuge anions favour the formation of cationic silver complexes coordinated with two carbene ligands.

dielectric model". (c) Tomasi, J.; Mennucci, B.; Cancès, E. *J. Mol. Struct. (Theochem)*, **1999**, *464*, 211–226. "The IEF version of the PCM solvation method: an overview of a new method addressed to study molecular solutes at the QM ab initio level".

[124] (a) Hay, P. J.; Wadt, W. R. *J. Chem. Phys*. **1985**, *82*, 270-283. "*Ab initio* effective core potentials for molecular calculations. Potentials for the transition metal atoms scandium to mercury". (b) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284-298. "*Ab initio* effective core potentials for molecular calculations. Potentials for main group elements Na to Bi". (c) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299-310. "*Ab initio* effective core potentials for molecular calculations. Potentials for potassium to gold including the outermost core orbitals".

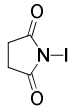
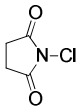
To start our study, we screened the halogenation reaction of the triazolium iodide **88**[125] with several electrophilic halogen sources under different conditions (**Table 4. 1**). Reactions were conducted in NMR sample tubes using MeCN-$d_3$ as solvent.

**Table 4. 1.** Reaction screening for the halogenation of carbene **89** with electrophilic halogen sources.




**88** **89** **90**

Reagents and conditions: (a) $Ag_2O$ (1.5 eq), MeCN-$d_3$, r.t., 16 h; (b) reagent (1.2 eq), r.t.

| Entry | Reagent | Time (h) | X | Y | Product | Conversion[a] (%) |
|---|---|---|---|---|---|---|
| 1 | $I_2$ | 5 | I | I | **90a** | 60 |
| 2 |  | 3 | I | I | **90a** | <10 |
| 3 |  | 3 | -- | -- | -- | --[b] |
| 4 |  | 3 | -- | -- | -- | --[b] |
| 5 | ICN | 1 | I | CN | **90b** | >98 |
| 6 | BrCN | 1 | Br | CN | **90c** | >98 |
| 7[c] | ICN | 1 | I | CN | **90d** | 90[d] |

[a]Conversion calculated by integration of the $^1$H NMR signals of *N*-methyl groups of the carbene and the halotriazolium salt. [b]No conversion observed. [c]One-pot synthesis using a mixture of $Ag_2O$/ICN. [d]Yield of isolated pure product.

Unexpectedly, the metalation reaction of 1,2,3-triazolium iodide **88** with silver oxide took place with concomitant deuteration at the benzylic position providing the carbene **89**. This observation was in agreement with the easy α-deprotonation predicted for triazolium

[125] Mathew, P.; Neels, A.; Albrecht, M. *J. Am. Chem. Soc.* **2008**, *130*, 13534-13535. "1,2,3-Triazolylidenes as versatile abnormal carbene ligands for late transition metals".

cation *N*-substituents (**Figure 4. 4**) and was an additional demonstration of the acidity-enhancement caused by the triazolium moiety. Consequently, all the halogenation reactions of silver carbene complexes conducted in deuterated solvents furnished the corresponding deuterated 5-halo-1,2,3-triazolium salts **90**.

Regarding the silver-halogen exchange ability of the electrophilic halogen sources tested, results collected in **Table 4. 1** clearly revealed the superiority of cyanogen iodide and cyanogen bromide (entries 5-7) compared to molecular iodine (entry 1) and *N*-halosuccinimides (entries 2-4). Importantly, product **90d** was obtained in 90 % isolated yield (entry 7) when the reaction was carried out in a single operation reacting the triazolium salt **88** with a mixture of $Ag_2O$ and cyanogen iodide.[126] Besides, the reaction products obtained from cyanogen halides were particularly easy to purify. Actually, a simple filtration through celite and sublimation of the low-boiling halogen cyanides during the evaporation of the solvents provided practically pure 5-halo-1,2,3-triazolium salts. Therefore, we selected cyanogen halides to conduct further experiments.

The deuterated nature of 5-iodo-1,2,3-triazolium salt **90a** was confirmed by comparison with the protonated product obtained by conducting the same reaction in normal acetonitrile. In **Figure 4. 5** are compared the assigned $^1$H NMR spectra of the 5-iodo-1,2,3-1,2,3-triazolium salt **78a** and the deuterated analog **90b**.

[126] The $^{13}$C NMR spectra of a mixture of cyanogen iodide and silver oxide in MeCN-$d_3$ showed no change over a period of 24 hours at room temperature, excluding a reaction between these reagents under such conditions.

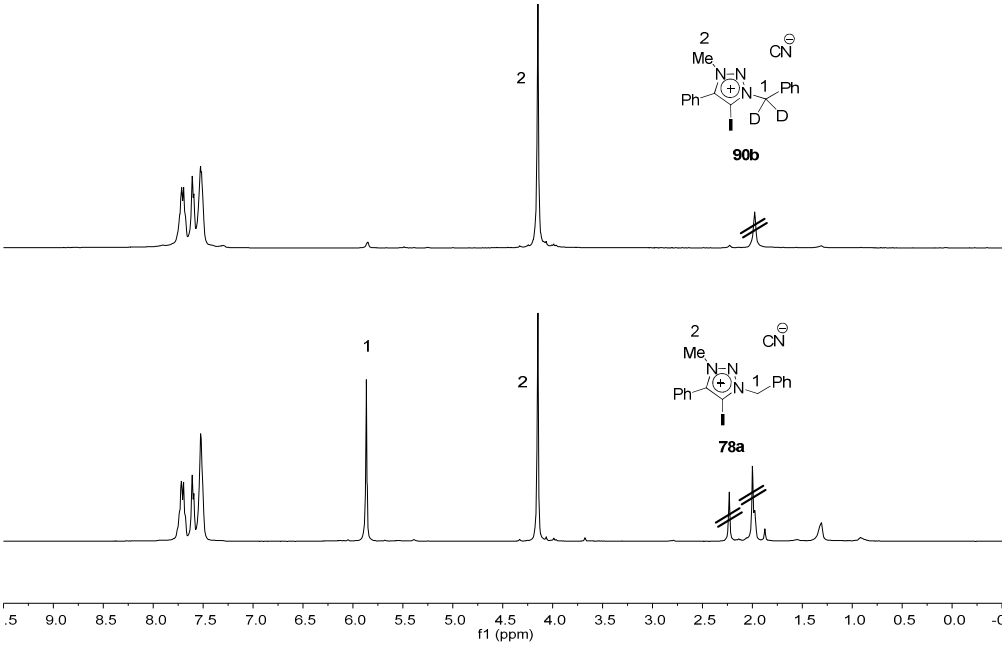



**Figure 4. 5.** $^{1}$H NMR (400 MHz, MeCN-$d_3$) spectra of iodinated triazolium salts **90b** and **78a**.

The deuteration of **90b** was also assessed from its HMRS spectrum (**Figure 4. 6**). A base peak at m/z= 378.0444, consistent with the molecular formula $C_{16}H_{13}D_2IN_3$, and a fragmentation peak at m/z= 252.1478 ($C_{16}H_{13}D_2N_3$) arising from the loss of the iodine atom, fully confirmed the proposed structure.

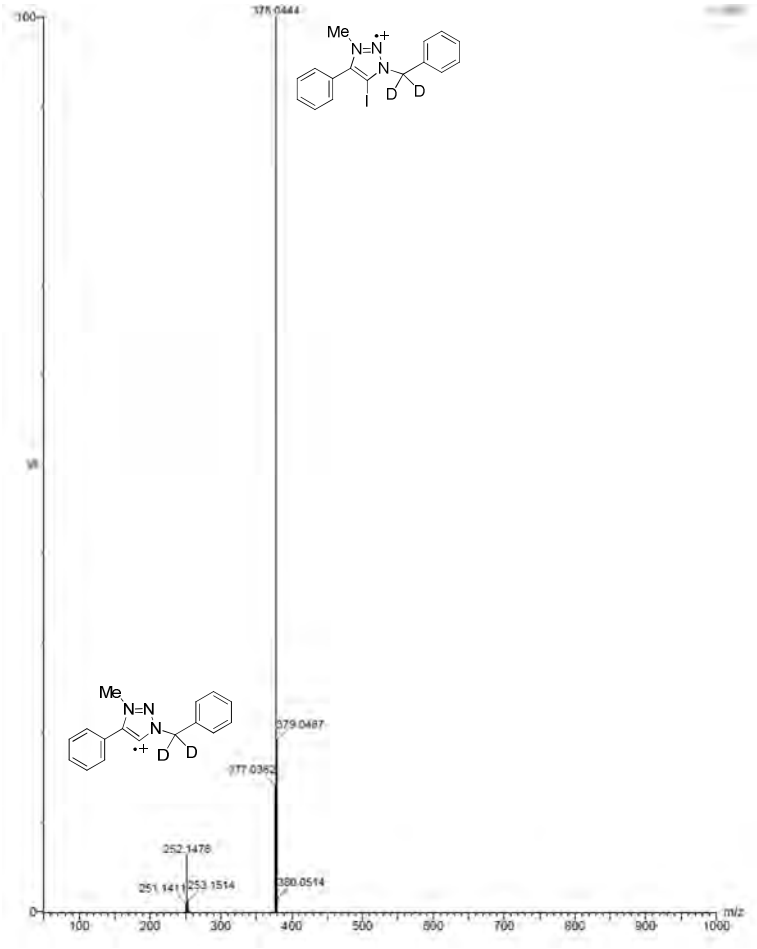
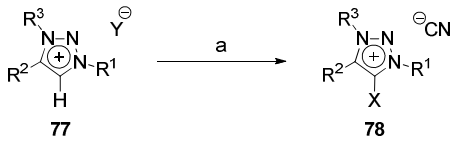


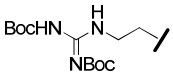
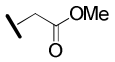
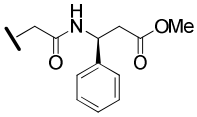
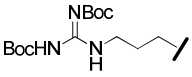
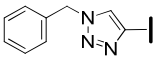

**Figure 4. 6.** HMRS spectrum of deuterated triazolium cation **90b**.

With the optimized conditions in hand, we studied the scope of the synthesis of 5-halo-3-methyl-1,2,3-triazolium salts **78** following the one-pot metalation-halogenation procedure described above (**Table 4. 2**).

**Table 4. 2.** One-pot metalation-halogenation synthesis of iodinated triazolium salts **78**.




Reagents and conditions: (a) $Ag_2O$ (1.5 eq), XCN (1.2 eq), $MeCN/CH_2Cl_2$ 1:1, r.t., 5-18 h.

| Entry | Substrate | X | $R^1$ | $R^2$ | $R^3$ | X | Product | Yield[a] 78 (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **77a** | I | Bn | Ph | Me | I | **78a** | 99 |
| 2 | **77b** | Cl | Bn | Ph | Me | Br | **78b** | 99 |
| 3 | **77c** | I | Bn | $HOCH_2$- | Me | I | **78c** | 96 |
| 4 | **77d** | I | Bn | 4-MeO-$C_6H_4$- | Me | I | **78d** | 89 |
| 5 | **77e** | I | Bn |  | Me | I | **78e** | 98 |
| 6 | **77f** | I | Ph | Ph | Me | I | **78f** | 98 |
| 7 | **77g** | Cl | Ph | Ph | Ph | Br | **78g** | 96 |
| 8 | **77h** | I |  | Ph | Me | I | **78h** | --[b] |
| 9 | **77i** | I |  |  | Me | I | **78i** | --[b] |
| 10 | **77j** | I | Bn |  | Me | I | **78j** | 92 |

[a]Yield of isolated pure product. [b]No reaction was observed.

The reaction provided excellent isolated yields of most 5-halo-1,2,3-triazolium cyanides and was tolerant with several functional groups including alcohols (entry 3) or carbamate NH functions (entry 5). All the products showed characteristic cyanide IR absorption bands at 2130-2138 $cm^{-1}$. Both 5-iodo-triazolium and 5-bromo-triazolium salts were obtained by just changing the halogenating reagent from cyanogen iodide to the commercially available cyanogen bromide (entries 1-2). It is noteworthy that only the halogen atom of the cyanogen halides was bonded to the triazole carbene intermediate,

according to the $^{13}C$ RMN and HRMS spectra. The method also allowed for the preparation of 1,3,4-triarylated-1,2,3-triazolium halides (entry 7) or the bistriazole salt **78j** (entry 10). Only the substrates containing *N*1-substituents with markedly acidic α-protons (entries 8-9) failed to give the desired iodinated triazolium salt. Instead, unidentified reaction by-products were formed, probably araising from the decomposition of an unstable triazolium ylide intermediate.

As an example of the formation of functionalized 5-iodo-1,2,3-triazolium salts, the $^1H$ NMR spectra of **78e** and its precursor **77e** are shown in **Figure 4. 7**.

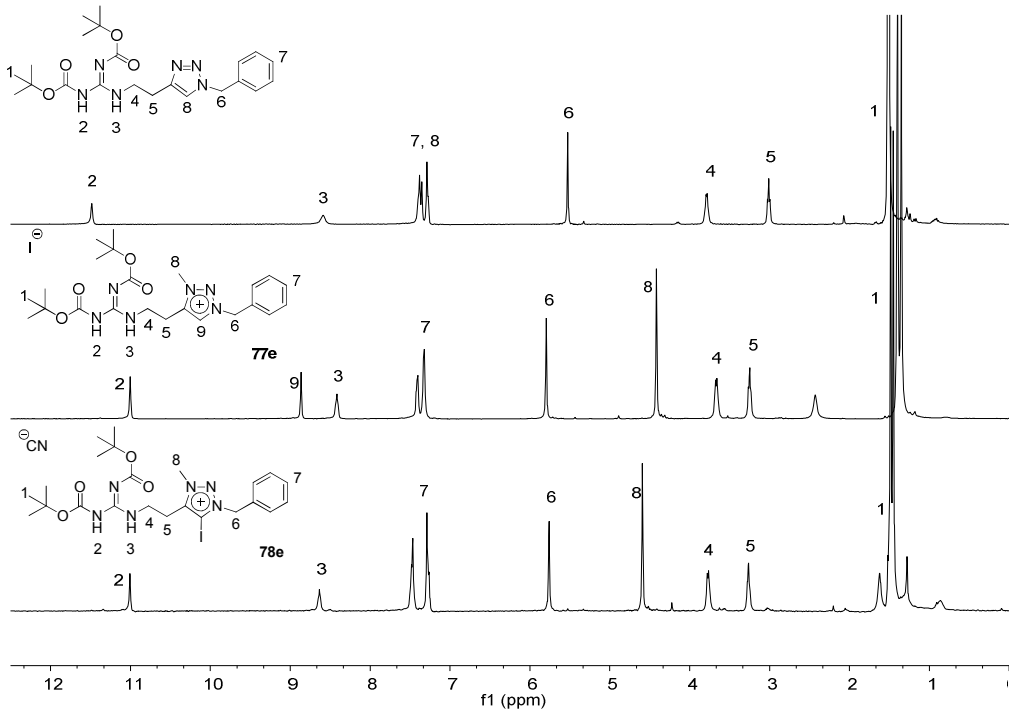
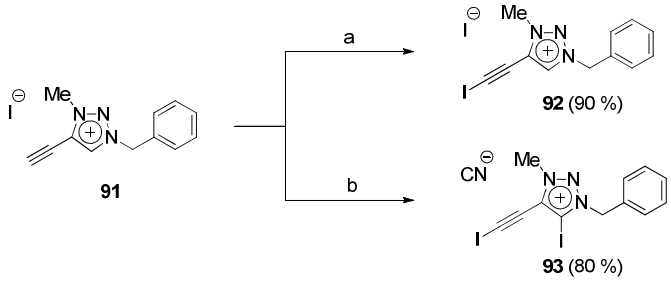



**Figure 4. 7.** $^1H$ NMR (400 MHz, $CDCl_3$) spectra of triazolium compounds **77e** and **78e**.

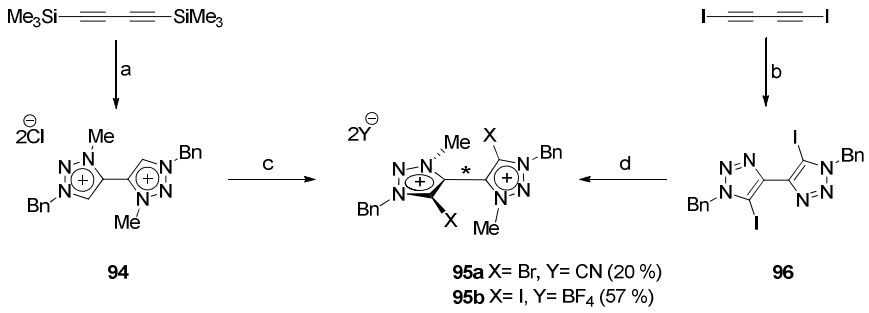
Looking for chemoselective triazolium halogenation reactions, we investigated the 4-ethynyl-1,2,3-triazolium iodide **91**, containing a potentially competitive C-H bond (**Scheme 4. 6**). Performing the reaction in the presence of 1.1 equivalents of $Ag_2O$ and 2.0 equivalents of ICN, the iodoalkyne **92** was obtained as the exclusive reaction product. This result suggests a stronger acidity of the alkyne proton compared to the triazolium proton and, hence, the faster formation of a silver acetylide intermediate than the triazole carbene.

Besides, performing the halogenation of **91** with 2.2 equivalents of $Ag_2O$ 2.0 and 4.0 equivalents of ICN, resulted in the high yield formation of the dihalogenated product **93**.




**Scheme 4. 6.** Chemoselective iodination reaction of the cationic alkyne **91**. Reagents and conditions: (a) $Ag_2O$ (1.1 eq), ICN (2.0 eq), MeCN/$CH_2Cl_2$ 1:1, r.t., 18 h.; (b) $Ag_2O$ (2.2 eq), ICN (4.0 eq), MeCN:$CH_2Cl_2$ 1:1, r.t., 18 h.

Finally, we checked the dihalogenation of bistriazolyl silver dicarbenes to prepare bis-(5,5'-dihalo-1,2,3-triazolium) salts **95** incorporating an induced axial chirality element into their structures (**Scheme 4. 7**). This transformation was achieved treating the bis-triazolium salt **94** with $Ag_2O$ in the presence of cyanogen bromide. Alternatively, the *N*,*N*'-dialkylation reaction of the 5,5'-diiodinated bistriazole **96** also gave the same type of unprecedented chiral compounds. The bis-triazole precursors **94** and **96** required to conduct the study were obtained by double CuAAC cycloadditions of benzylazide with 1,4-bis(trimethylsilyl)-1,3-butadiine[127] and 1,4-diiodo-1,3-butadiyne,[115] respectively.




**Scheme 4. 7.** Synthesis of 5,5'-dihalogenated bis(1,2,3-triazolium) salts **95** incorporating a chiral axis. Reagents and conditions: (a) i) Bn-$N_3$, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, pyridine, $K_2CO_3$, *t*BuOH/$H_2O$ 1:1, r.t., 24 h; ii) $Me_3OBF_4$, $CH_2Cl_2$, r.t., 16 h; iii) Amberlist.HCl; (b) Bn-$N_3$, CuI, TBTA, THF, r.t., 18 h; (c) $Ag_2O$, Br-CN, MeCN, r.t., 16 h; (d) $Me_3OBF_4$, $CH_2Cl_2$, r.t, 18 h.

[127] Flecher, J. T.; Bumgarner, B. J.; Engels, N. D. Skoglund, D. A. *Organometallics*, **2008**, *27*, 5430-5433. "Multidentate 1,2,3-triazole-containing chelators from tandem deprotection/click reactions of (trimethylsilyl)alkynes and comparison of their ruthenium(II) complexes".

In **Figure 4. 8** are compared the assigned $^{1}$H NMR spectra of the iodinated triazole **96** and the bis-triazolium salt **95b**. The magnetically equivalent benzylic protons of **96** resonating at 5.7 ppm turned into diastereotopic nonequivalent protons at 6.0 ppm for the salt **95b**. This fact clearly indicated the creation of an important rotation restriction around the 5,5'-C-C bond and, hence, the incorporation of a chiral axis to the atropoisomeric racemic bis-triazolium salt **95b**.

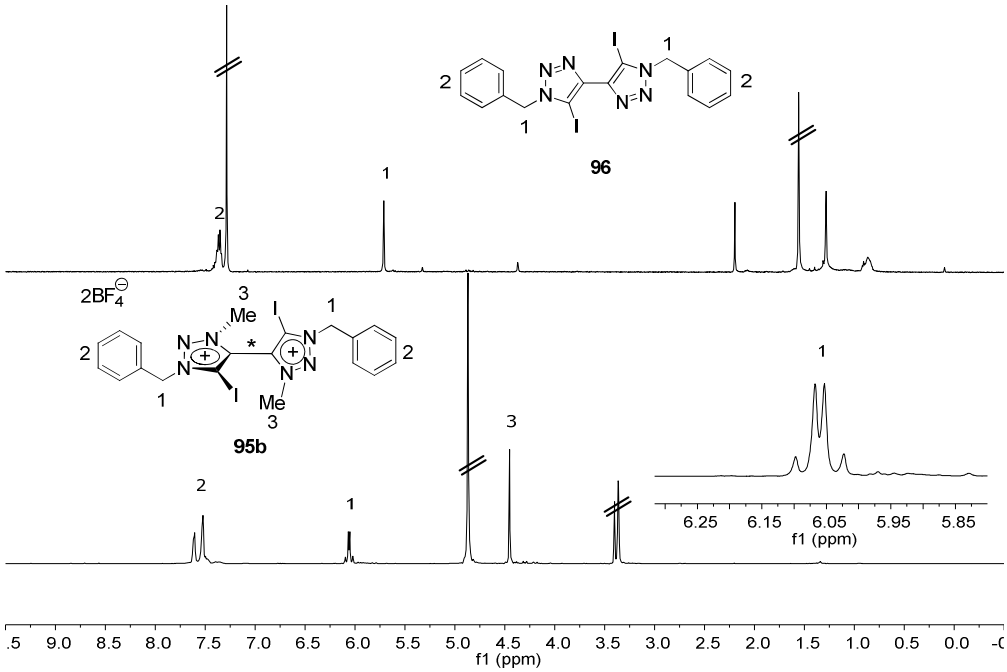



**Figure 4. 8.** $^{1}$H NMR (500 MHz, $CDCl_3$ and MeOH-$d_4$) spectra of the iodinated bis-triazoles **95b** and **96**.

According to our previous observation (see **Table 4. 1**), dibromination of **94** with silver oxide and cyanogen bromide should take place through a chiral bis-triazolylidene silver dicarbene intermediate **97**. To confirm this aspect, we monitored by $^{1}$H NMR the reaction of bis-triazolium salt **94** with silver oxide in MeCN-$d_3$ at different conversion stages (see **Figure 4. 9**).

The analysis of spectra revealed a stepwise formation of the silver dicarbene **97** through a monometalated transient intermediate, which was clearly detectable at ≈50 % reaction conversion. This observation also suggested a significantly slower reaction rate for

the second metalation step, as a consequence of the electron donating effect of the neighboring carbene, which should weaken the acidity of the triazolium ring. Importantly, the benzylic methylene protons became diastereotopic in the biscarbene complex **97** as a result of the formation of a chiral axis during the double metalation reaction.

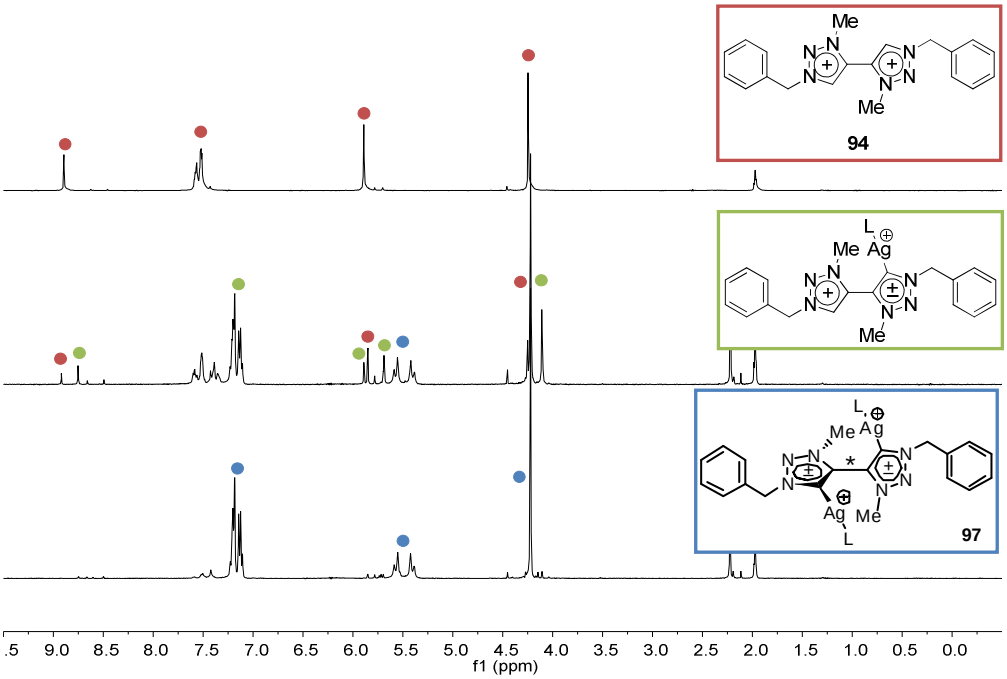



**Figure 4. 9.** $^{1}$H NMR (500 MHz, MeCN-$d_3$) spectra of the conversion of **94** into the chiral racemic silver dicarbene **97** (L= NC-Me-$d_3$).

In order to get insight on the specific role exerted by the silver cation in these transformations and the remarkable effectiveness shown by cyanogen halides compared to other electrophilic halogen sources, we decided to perform a computational mechanistic exploration.

### 4.4.2.1 Computational study of the iodination of silver triazolylidenes with cyanogen iodide

To conduct a computational investigation of the mechanism of the halogenation reaction of silver 1,2,3-triazole carbenes with cyanogen iodide, we selected the trimethylated structure **98** as a model. Calculation were conducted by Prof. Enrique Gómez-Bengoa and

Béla Fiser (Departamento de Química Orgánica-I, UPV-EHU) using the same methodology described in **section 4.4.1** with the solvent model (IEFPCM, solvent= acetonitrile) and the LANL2DZ basis set for the Ag atom. After extensive computation, the sequential mechanism shown in **Figure 4. 10** was proposed.

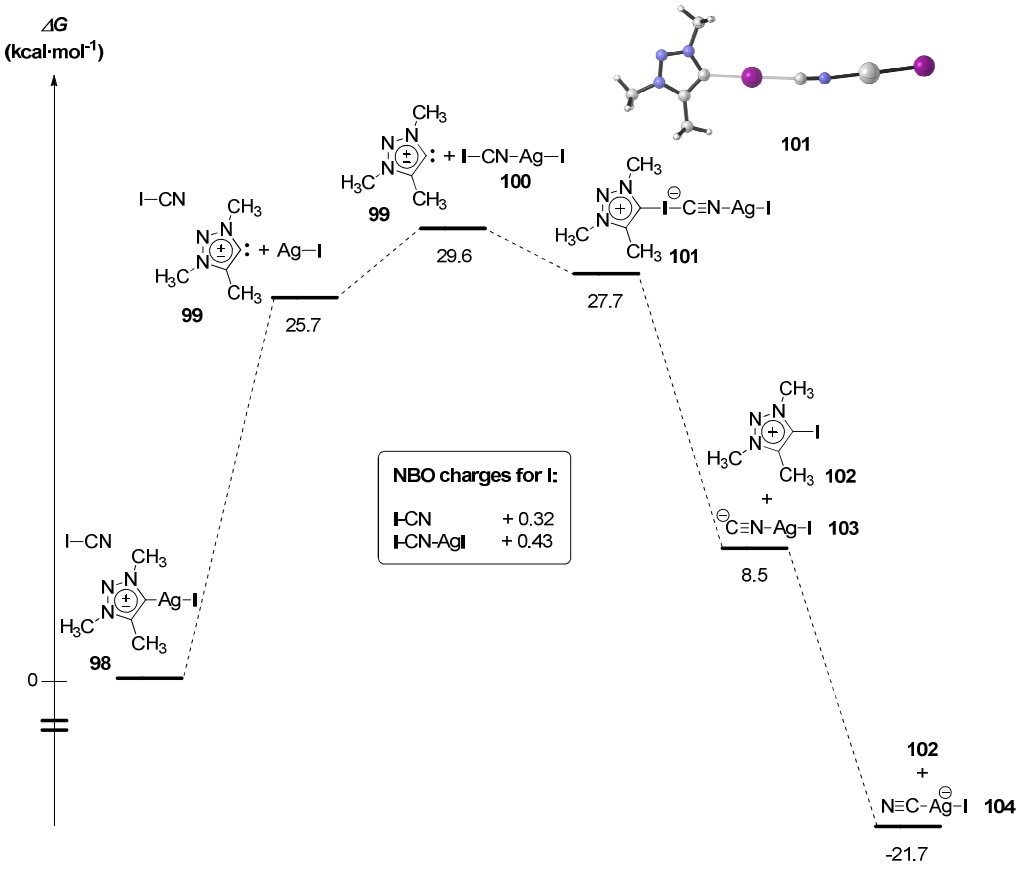



**Figure 4. 10.** Free-energy profile for the iodination reaction of the silver carbene **98** with cyanogen iodide.

Initially, silver complex **98** dissociated to the free carbene **99** and silver iodide in an endothermic process. Coordination of the freshly freed AgI ion pair with the cyanogen iodide nitrogen atom resulted in the formation of complex **100**. This species had an electrophilic iodide atom which accepted the carbene electron lone pair to form the complex **101** possessing a partial triazolium ylide character. The exothermic dissociation (-19.2 kcal·mol$^{-1}$) of the I-C bond in **101** delivered the final 5-iodo-triazolium product **102**, together with a transient silver iodide-isocyanide complex **103** which inmediatly rearranged to the cyanoiodoargentate (I) anion **104** liberating an additional -30.2 kcal·mol$^{-1}$.

All the intermediates involved in the mechanism were accessible through very low barrier transition states. Therefore, the free energy values quoted in **Figure 4. 10** correspond to the energy minima of such intermediates. The reaction rate-determining step was the addition of the silver complex **100** to carbene **99** to form the intermediate **101**. This step was almost barrierless, slightly exothermic and highly favoured by the strong electrophilic character of the iodine atom in complex **100**. Indeed, one could assume an alternative reaction pathway involving the interaction of triazole carbene **99** with cyanogen iodide to form directly the silver free product **102** and cyanide anion. However, a comparison of the NBO charges of the iodine atom in **100** (+ 0.43) and in cyanogen iodide (+ 0.32), clearly, precluded the direct attack of cyanogen iodide to carbene **99** when silver salts were present in the reaction.

Finally, an alternative three center mechanism involving the interaction of cyanogen iodide and the carbene complex **98** was also examined, but it was discarded because it required an activation barrier energy of 67 kcal·mol$^{-1}$.

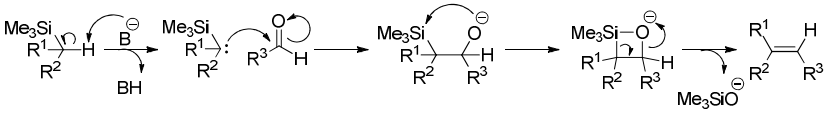
### 4.4.3 Peterson olefination of *N*1-(α-silylalkyl)-1,2,3-triazolyl carbanions

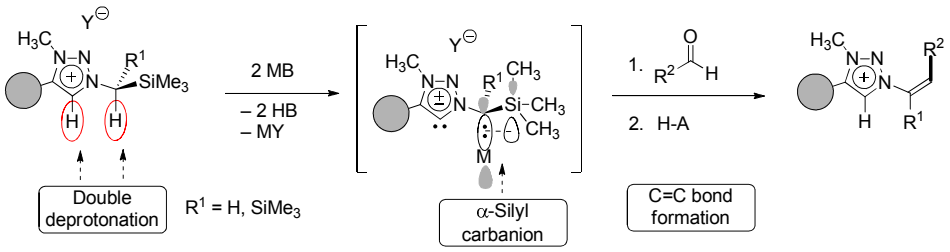
As detailed in the previous section (**Table 4. 1**, page 116), α-deprotonation of *N*-(alkyl)-1,2,3-triazolium cations with suitable bases provides triazolyl carbenes with the concomitant formation of transient *N1*-(α-alkyl)-1,2,3-triazolium carbanions able to experience α-deuteration reactions.

We hypothesized that a double deprotonation of triazolium cations bearing suitable carbanion-stabilizing groups should lead to carbene-carbanion intermediates that could be trapped with carbonyl compounds to form carbon-carbon bonds adjacent to the triazolium ring (**Scheme 4. 8**). Trialkylsilyl group are known to be excellent α-carbanion stabilizing substituents, and they add to carbonyl compounds to form C=C bonds (Peterson olefination).[128]

[128] van Staden, L. F.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev.* **2002**, *31*, 195-200. "*New developments in the Peterson olefination reaction*".

Peterson reaction mechanism:



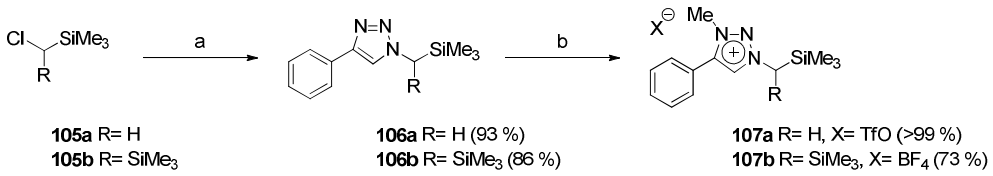



**Scheme 4. 8.** Silicon-stabilized 1,2,3-triazolylidene-α-carbanions as potential substrates for Peterson olefination.

We selected the trimethylsilylmethyl- and bis(trimethylsilyl)methyl groups[129] as substituents of choice at position *N*1 of 1,2,3-triazolium heterocycles to study the double deprotonation in the presence of strong bases. Although one silyl group is lost in this reaction, the use of bis(trimethylsilyl)methyl triazolium salts ($R^1$= $SiMe_3$) as substrates would allow to keep one silyl group attached to the final product. In this way, novel α-silylalkyl triazoles would be accessible from a single triazole skeleton. It is worth mentioning that some silicon-containing azaheterocyclic compounds display remarkable biological activities.[130]

To conduct our exploratory study, we first carried out the synthesis of silicon-containing triazoles **106** and triazolium salts **107** from the commercially available chloromethyltrimethylsilane **105a** and chlorobis(trimethylsilyl)methane **105b**. First, the chloromethylsilanes were reacted with sodium azide in HMPA to form the corresponding trimethylsilylmethyl azides, followed by the *in situ* addition of phenylacetylene, DIPEA and CuI catalyst. Then, the resulting 1-(trimethylsilyl)methyl-1,2,3-triazoles **106** were *N*-alkylated with trimethyloxonium tetrafluoroborate or methyl triflate in anhydrous $CH_2Cl_2$ to afford good overall yields of triazolium salts **107** (**Scheme 4. 9**).

[129] Picard, J. P. *Adv. Organomet. Chem.* **2005**, *52*, 175-375. "Silylmethylamines and their derivatives: chemistry and biological activities".
[130] Franz, A. K.; Wilson, S. O. *J. Med. Chem.* **2013**, *56*, 388-405. "Organosilicon molecules with medicinal applications"



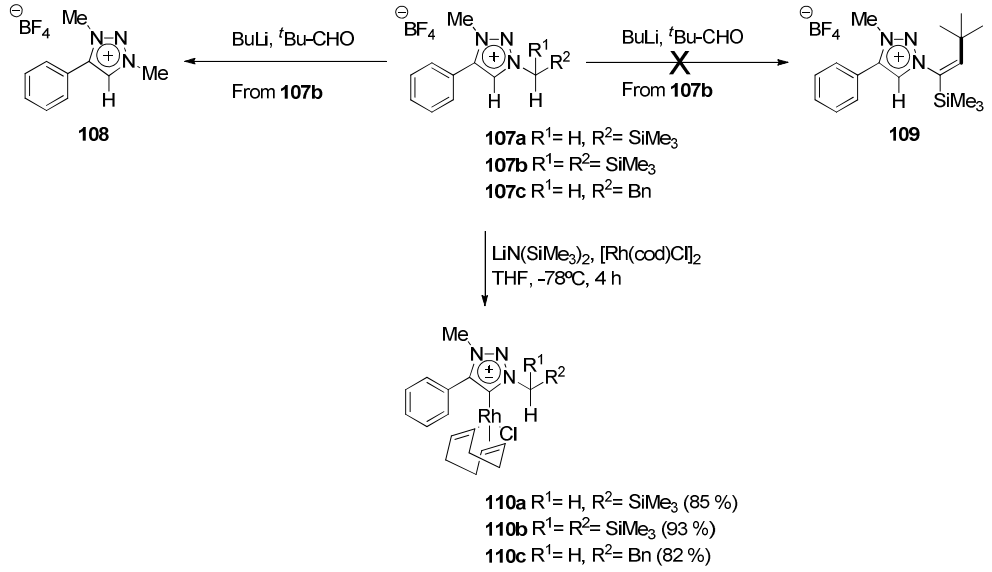

**105a** R= H
**105b** R= $SiMe_3$

**106a** R= H (93 %)
**106b** R= $SiMe_3$ (86 %)

**107a** R= H, X= TfO (>99 %)
**107b** R= $SiMe_3$, X= $BF_4$ (73 %)

**Scheme 4. 9.** Synthesis of silylated 1,2,3-triazoles **106** and triazolium salts **107**. Reagents and conditions: (a) i) $NaN_3$, HMPA, r.t., 2 h; ii) phenylacetylene, CuI, DIPEA, r.t., 18 h; (b) $Me_3OBF_4$ or MeOTf, $CH_2Cl_2$, rt., 18 h.

To check out the deprotonation reaction of *N*1-alkyl-triazolium cations, we first treated compounds **107a-c** with two equivalents of LiHMDS at low temperature in the presence of the carbene-trapping rhodium(I) complex $[Rh(cod)Cl]_2$ (**Scheme 4. 10**). In all cases, the silylated *N*1-alkyl chains remained uncharged and only the rhodium carbene complexes **105a-c**, arising from the C5-H monodeprotonation, were obtained in good yields, Then, we conducted a similar reaction using a stronger base (BuLi) and adding one equivalent of pivalaldehyde to the preformed anion of **107b**. Dissapointingly, the reaction only gave the desilylated triazolium salt **108**, but no trace of the expected olefination product **109**. Similar results were obtained from triazolium salts **107a**, and benzylic compounds **107c** gave only decomposition side products.




**108**

**107a** $R^1$= H, $R^2$= $SiMe_3$
**107b** $R^1$= $R^2$= $SiMe_3$
**107c** $R^1$= H, $R^2$= Bn

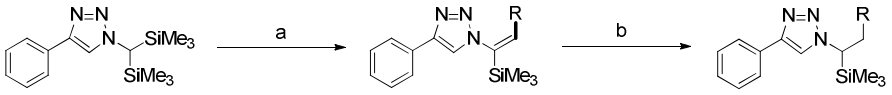
**109**

**110a** $R^1$= H, $R^2$= $SiMe_3$ (85 %)
**110b** $R^1$= $R^2$= $SiMe_3$ (93 %)
**110c** $R^1$= H, $R^2$= Bn (82 %)

**Scheme 4. 10.** Attemped double deprotonation of *N*-alkyl-1,2,3-triazolium salts **107**, followed by trapping with pivalaldehyde or $[Rh(cod)Cl]_2$.

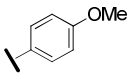
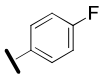
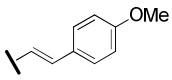
To establish whether the failure of the α-deprotonation reactions of triazolium salts **107** was caused by the cationic heterocyclic ring, we tested the same transformation starting from the neutral *N*-[bis(trimethylsilyl)methyl)]-1,2,3-triazole **106b**. This compound was deprotonated with BuLi in THF for 1 hour at -78ºC and the resulting bis(trimethylsilyl) α-carbanion was olefinated with a few nonenolizable aldehydes (see **Table 4. 3**). Mixtures of *Z*:*E* isomers of the unprecedent α-triazolyl vinylsilanes **111** were obtained in fair to good yields and, in some instances (entry 2), each isomer could be separated by column chromatography or crystallization. Besides, the catalytic hydrogenation of isomeric mixtures allowed the quantitative transformation into the novel silylated triazoles **112**.

**Table 4. 3** Peterson olefination of silyl-triazole **106b** with aldehydes.




**106b** **111** **112**

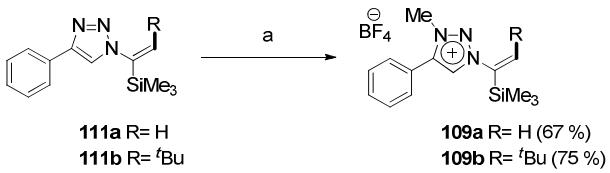
Reagents and conditions: (a) i) BuLi, THF, -78 ºC, 1 h; ii) R-CHO, - 78 ºC to 0 ºC, 18 h; (b) $H_2$, Pd/C, MeOH, r.t., 18 h.

| Entry | R | Product | Yield[a] (%) | Product | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | H[b] | **111a** | 83 | -- | -- |
| 2 |  | **111b** | 77[c] | **112b** | >99 |
| 3 |  | **111c** | 77[d] | **112c** | >99 |
| 4 |  | **111d** | 75[e] | **112d** | >99 |
| 5 |  | **111e** | 64[f] | -- | -- |

[a]Yield of isolated pure product. [b]Anhydrous formaldehyde gas was prepared by thermal depolymerization of paraformaldehyde. [c]Z/E ratio: 69/31. [d]Z/E ratio was not measured. [e]Z/E ratio: 44/56. [f]Z/E ratio: 50/50.

As discussed above (**Scheme 4. 10**) our attemps to prepare α-(1,2,3-triazolium)-vinylsilanes **109** by double deprotonation/Peterson olefination of *N*-(silylalkyl)-triazolium

salts met with failure. In contrast, we found that *N*-alkylation of α-triazolyl-vinylsilanes **111** with trimethyloxonium tetrafluoroborate provided the triazolium salt **109** in good yields (**Scheme 4. 11** and **Figure 4. 11**).




**111a** R= H
**111b** R= $^t$Bu

**109a** R= H (67 %)
**109b** R= $^t$Bu (75 %)

**Scheme 4. 11.** Synthesis of α-(1,2,3-triazolium)-vinylsilanes **109**. Reagents and conditions: (a) $Me_3OBF_4$, $CH_2Cl_2$, r.t., 16 h.

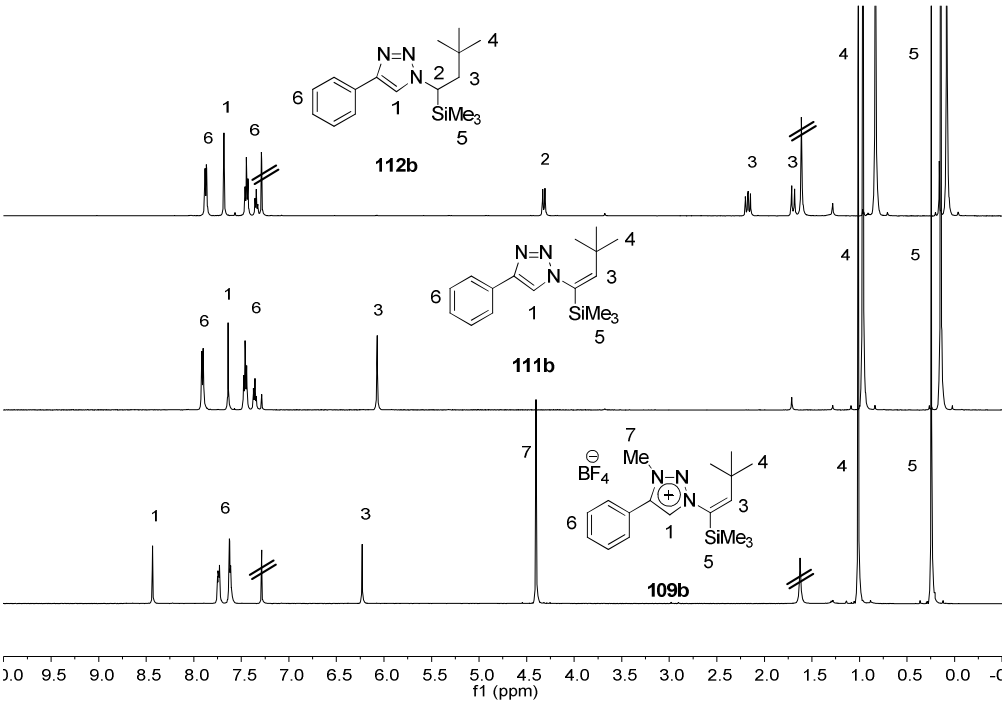



**Figure 4. 11.** $^1$H NMR (400 MHz, $CDCl_3$) spectra of silylated triazole compounds **111b**, **112b** and **109b**.

## 4.5 Conclusions

Halogenation of 1,2,3-triazole-5-ylidene carbenes with cyanogen iodide or cyanogen bromide provides a novel general entry to 1,4,3-trisubstituted 5-halo-1,2,3-triazolium cyanides.

When the intermediate carbenes are formed by deprotonation of 1,2,3-triazolium salts at C5-H position with strong bases in the presence of cyanogen halides, the triazole ring may experience a *N*3-dealkylation reaction to provide 5-halo-1,2,3-triazoles. According to computational calculations, this reaction occurs by α-deprotonation of the *N*3-alkyl group.

Alternatively, silver carbene complexes prepared *in situ* from 1,4,3-trisubstituted 1,2,3-triazolium salts in the presence of cyanogen halides also provide 5-halo-1,2,3-triazoles in a *one-pot* manner. If this transformation is conducted in MeCN-$d_3$, 5-halo-1,2,3-triazolium salts deuterated at the *N*1-substituent α-position can be obtained. The computationally calculated mechanism for this reaction suggests that I–CN-AgI intermediate is the more likely electrophilic halide source to iodinate 1,2,3-triazolylidene carbenes.

# 5

*General conclusions*

# 5 General conclusions

Easily accessible “click” 3-alkyl-1,2,3-triazolium salts provide a novel platform to perform unprecedented synthetic transformation taking advantage of their strongly electron deficient nature.

Cationic triazolium C4-alkynes react with alkyl- and aryl azides under Huisgen thermal activation conditions to give mixtures of bicyclic 4-(1,2,3-triazolyl)-3-methyl-1,2,3-triazolium salts about $10^2$ times faster than nonactivated alkynes. Cationic triazolium alkynes act as strong LUMO-lowering dipolarophiles, narrowing the HOMO–LUMO energy gap of the azide–alkyne interaction, and favoring the reaction with nucleophilic azides. This reaction occurs with high 1,4/1,5- regioselectivity (typically > 95%) caused by the orthogonal geometry adopted by the transition state TS-1,5 (but not by TS-1,4) around the newly created N-alkyl-1,2,3-triazolium ring. Cationic triazolium alkynes also react with azides under “ultra-fast” CuAAC conditions (< 5min) to give bicyclic 4-(1,2,3-triazolyl)-3-methyl-1,2,3-triazolium salts in a completely chemoselective way, compatible with neutral alkynes.

A general route to prepare *N*3-alkyl-1,2,3-triazolium salts with an additional labeled or functionalized *N*3-substituent has been developed for the first time. Solvent-free *N*3-alkylation of 1,2,3-triazoles with functionalized alkyl triflates provides *N*1,*N*3,C4-trisubstituted-1,2,3-triazolium salts with great operational simplicity. The latent reactivity of some model *N*3-(ω-azidoalkyl)-1,2,3-triazolium salts has been demonstrated by a CuAAC coupling with alkynes to which affords multisubstituted bis(1,2,3-triazolium) salts with total positional control. When the method is applied to 4-ethynyl-1,2,3-triazoles using short ω-azidoalkyl triflates, a novel tandem reaction involving an intramolecular thermal [3+2] azide-alkyne cycloaddition, leads to unprecedented tricyclic bis-triazole-triazolium systems.

The enhanced C5-H acidity of 3-alkyl-1,2,3-triazolium salts can been exploited to form intermediate 1,2,3-triazole-5-ylidene carbenes or their silver(I) complexes, which react with cyanogen iodide or cyanogen bromide to give 1,4,3-trisubstituted 5-halo-1,2,3-triazolium salts. Computational calculations suggest that halogenation of silver carbenes occurs through highly electrophilic X–CN-AgI intermediates. In the presence of strong bases, 5-halo-1,2,3-triazolium salts may experience a *N*3-dealkylation reaction to provide 5-halo-1,2,3-triazoles.

# 6

*Experimental*

# 6 Experimental

## General

All reagents and solvents were obtained from commercial sources (Aldrich, Acros, Merck, Sigma and Fluka) and were used without further purification unless stated otherwise. Tetrahydrofuran (THF) and diethyl ether ($Et_2O$) were dried through PS-MD-2columns. Extra pure dichloromethane ($CH_2Cl_2$), acetonitrile (MeCN), hexane (Hex) and ethyl acetate (EtOAc) were bought from Sharlau.

Moisture sensitive reactions were carried out under an atmosphere of nitrogen in oven or flame-dried glassware with magnetic stirring.

Purification of reaction products was carried out by flash chromatography using silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and phosphomolybdic acid-ammonium cerium (IV) nitric-sulfuric acid-water reagent, followed by heating.

$^1$H NMR spectra were recorded on a Bruker 500, 400 and 300 MHz; and $^{13}$C NMR spectra at 125, 101 and 75 MHz. The chemical shifts are reported as δ values (ppm) relative to residual deuterated solvent as internal standards: for $CDCl_3$ δH (7.26 ppm) and δC (77.16 ppm), respectively; for MeOH-$d_4$ δH (3.31 ppm) and δC (49.0 ppm), respectively; for MeCN-$d_3$ δH (1.94 ppm) and δC (118.26 ppm, 1.32 ppm), respectively; for DMSO-$d_6$ δH (2.50 ppm) and δC (39.52 ppm), respectively.

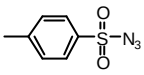
Mass spectra were acquired on a time of flight (TOF) mass spectrometer (SYNAPT G2 HDMS from Waters, Milford, MA, USA) equipped with an electrospray source in positive mode (ESI+). Melting points were measured with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a *Bruker Alpha P*. Optical rotations were measured on an *Jasco P-200* polarimeter using a sodium lamp (589 nm, D line) at 25 ±0.2 °C.

Analytical HPLC was performed on a Waters-600E chromatograph (diode array UV detector), using a Diacel Chiralpak OD-H column. The mobile phase was iPrOH/Hex 70:30 with a flow rate of 0.5-1 ml/min monitored by UV detection at 227 nm.

## 6.1 Preparation of precursors, reagents and known compounds

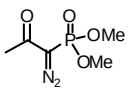
### 6.1.1 Preparation of Ohira-Bestmann reagent[131]

**_p_-Toluenesulfonyl azide (tosyl azide)**[132]



_p_-Toluenesulfonyl chloride (10.50 mmol, 2.00 g) and $NaN_3$ (10.50 mmol, 682 mg) were taken in acetone:water (1:1, 60 mL) at 0 ºC and were stirred for 2 hours. Acetone was evaporated and the water phase was extracted with $Et_2O$ (30 mL x 3). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The product was stored in the fridge (-15 ºC). Yield: quantitative. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.85 (d, 2H, _J_ = 8.3 Hz, Ar), 7.41 (d, 2H, _J_ = 8.3 Hz, Ar), 2.48 (s, 3H, C$H_3$).

**Dimethyl 1-diazo-2-oxopropylphosphonate**[133]



To a solution of tosyl azide (11.12 mmol, 2.08 g) in anhydrous THF (50 mL) cooled at 0 ºC was added successively NaH (18.50 mmol, 445 mg) and a solution of dimethyl-(2-oxopropyl)-phosphonate (9.27 mmol, 1.57 mL) in THF (10 mL). The mixture was stirred at 0 ºC for 1 hour and at ambient temperature for another 1 hour. After this time the reaction mixture was filtered through a celite pad and the solvent was evaporated under reduced pressure keeping the water bath of the rotary evaporator below 30 ºC. The product was purified by column chromatography (silica gel, Hex/EtOAc 1:1). Yield: 356 mg (90 %). $^1$H NMR (200 MHz, $CDCl_3$) δ 3.87 (s, 3H, OC$H_3$), 3.81 (s, 3H, OC$H_3$), 2.27 (s, 3H, C$H_3$).

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[131] a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561-564. "Methanolysis of dimethyl (1-diazo-2-oxopropyl)phosphonate: generation of dimethyl (diazomethyl)phosphonate and reaction with carbonyl compounds". b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521-522. "An improves one-pot procedure for the synthesis of alkynes from aldehydes".

[132] Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693-11712. "Hydrazines and azides via the metal-catalyzed hydrohydrazination and hydroazidation of olefins".

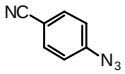
[133] Bélanger, D.; Tong, X.; Soumaré, S.; Dory, Y. L.; Zhao, Y. *Chem. Eur. J.* **2009**, *15*, 4428-4436. "Cyclic peptide-polymer complexes and their self-asembly".

### 6.1.2 Preparation of azides[134]

#### 6.1.2.1 General procedure for the synthesis of aromatic azides[135]

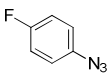
To a solution of the corresponding aromatic amine (1.00 mmol) in MeCN (2.5 mL) cooled at 0ºC was added $^t$BuONO (1.50 mmol) followed by the dropwise addition of TMS-$N_3$ (1.20 mmol). The resulting yellow solution was stirred at ambient temperature for 2 hours and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, Hex/EtOAc).

**4-Azidobenzonitrile**[135a]



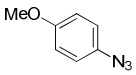
The general procedure 6.1.2.1 was followed starting from 4-aminobenzonitrile (10.00 mmol, 1.18 g), $^t$BuONO (20.00 mmol, 2.37 mL) and TMS-$N_3$ (11.00 mmol, 1.46 mL) in MeCN (30 mL). The product was purified by column chromatography (silica gel, Hex/EtOAc 1:10). Yield: 1.20 g (83 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.6 Hz, 2H, Ar), 7.14 (d, *J* = 8.6 Hz, 2H, Ar).

**4-Fluorophenyl azide**[136]



The general procedure 6.1.2.1 was followed starting from 4-fluoroaniline (10.00 mmol, 1.11 g), $^t$BuONO (20.00 mmol, 2.37 mL) and TMS-$N_3$ (11.00 mmol, 1.46 mL) in MeCN (30 mL). The product was purified by column chromatography (silica gel, Hex). Yield: 1.25 g (91 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.08 (t, *J* = 8.5 Hz, 2H, Ar), 7.05 – 6.94 (m, 2H, Ar).

**4-Methoxyphenyl azide**[135a]



The general procedure 6.1.2.1 was followed starting from 4-methoxyaniline (10.00 mmol, 1.23 g), $^t$BuONO (20.00 mmol, 2.37 mL) and TMS-$N_3$ (11.00

[134] Care must be taken during the synthesis of low molecular weight organic azides.

[135] a) Liu, Q.; Tor, Y. *Org. Lett.* ***2003***, 5, 2571-2572. "Simple conversion of aromatic amines into azides". b) Barral, A. K.; Moorhouse, A. D.; Moses, J. E. *Org. Lett.* **2007**, *9*, 1809-1811. "Efficient conversion of aromatic amines into azides: a one-pot synthesis of triazole linkages".

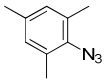
[136] Hu, H.; Zhang, A.; Ding, L.; Lei, X.; Zhang, L. *Molecules* **2008**, *13*, 556-566. "Regioselective synthesis of 1-(2,6-dichloro-4-trifluoromethyl-phenyl)-4-alkyl-1*H*-[1,2,3]-triazoles)".

mmol, 1.46 mL) in MeCN (30 mL). The product was purified by column chromatography (silica gel, Hex/EtOAc 1:10). Yield: 1.47 g (98 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.6 Hz, 2H, Ar), 6.91 (d, *J* = 8.5 Hz, 2H, Ar), 3.82 (s, 3H, OC*H*$_3$).

**Phenylazide**[135b]

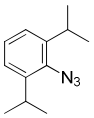
The general procedure 6.1.2.1 was followed starting from aniline (10.00 mmol, 931 mg), $^t$BuONO (20.00 mmol, 2.37 mL) and TMS-$N_3$ (11.00 mmol, 1.46 mL) in MeCN (30.00 mL). The product was purified by column chromatography (silica gel, Hex). Yield: 893 mg (75 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.3 Hz, 2H, Ar), 7.17 (t, *J* = 7.4 Hz, 1H, Ar), 7.06 (d, *J* = 7.6 Hz, 2H, Ar).

**2,4,6-Trimethylphenylazide**[137]



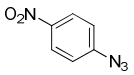
The general procedure 6.1.2.1 was followed starting from 2,4,6-trimethylaniline (10.00 mmol, 1.40 mL), $^t$BuONO (20.00 mmol, 2.37 mL) and TMS-$N_3$ (11.00 mmol, 1.46 mL) in MeCN (30 mL). The product was purified by column chromatography (silica gel, Hex). Yield: 1.46 g (91 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 2H, Ar), 2.35 (s, 6H, *CH*$_3$), 2.28 (s, 3H, *CH*$_3$).

**2,6-Diisopropylphenylazide**[135a]



The general procedure 6.1.2.1 was followed starting from 2,6-diisopropylaniline (10.00 mmol, 1.88 mL), $^t$BuONO (20.00 mmol, 2.37 mL) and TMS-$N_3$ (11.00 mmol, 1.46 mL) in MeCN (30 mL). The product was purified by column chromatography (silica gel, Hex). Yield: 1.81 g (89 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.21 (m, 3H, Ar), 3.39 (hept, *J* = 6.8 Hz, 2H, *CH*), 1.30 (d, *J* = 6.8 Hz, 12H, *CH*$_3$).

**4-Nitrophenylazide**[135b]



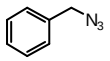
The general procedure 6.1.2.1 was followed starting from 4-nitroaniline (10.00 mmol, 1.11 mL), $^t$BuONO (20.00 mmol, 2.37 mL) and TMS-$N_3$ (11.00 mmol, 1.46 mL) in MeCN (30 mL). The product was purified by column chromatography (silica gel, Hex/EtOAc 1:3). Yield: 1.51 g (92 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.9 Hz, 2H, Ar), 7.17 (d, *J* = 8.9 Hz, 2H, Ar).

[137] Kwok, S. W.; Fotsing, J. R.; Fraser, R. J.; Rodionov, V. O.; Fokin, V. V. *Org. Lett.* **2010**, *12*, 4217-4219. "Transition metal-free catalytic synthesis of 1,5-diaryl-1,2,3-triazoles".

### 6.1.2.2 General procedure for the synthesis of aliphatic azides

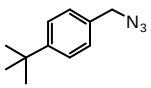
The corresponding alkyl bromide (1.00 mmol) was added to a solution of $NaN_3$ (1.10 mmol) in DMSO (2.2 mL) and the reaction mixture was stirred for 18 hours at ambient temperature. Then, the reaction mixture was quenched with water (5 mL) and the product was extracted with $Et_2O$ (10 mL x 3). The organic phase was washed with water, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The product was purified by column chromatography (silica gel, Hex/EtOAc).

**Benzyl azide**[138] **(6b)**



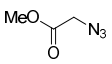
The general procedure 6.1.2.2 was followed starting from benzyl bromide (3.00 mmol, 0.35 mL) and $NaN_3$ (3.30 mmol, 215 mg) in DMSO (6.6 mL). Yield: 379 mg (95 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 5H, Ar), 4.33 (s, 2H, C*H*$_2$).

**4-*tert*-Butylbenzyl azide**[139]



The general procedure 6.1.2.2 was followed starting from 4-*tert*-butylbenzyl bromide (2.60 mmol, 587 mg) and $NaN_3$ (2.90 mmol, 188 mg) in DMSO (5 mL). Yield: 482 mg (98 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, 2H, *J* = 7.9 Hz, Ar), 7.34 (d, 2H, *J* = 7.9 Hz, Ar), 4.38 (s, 2H, C*H*$_2$), 1.42 (s, 9H, C*H*$_3$).

**Methyl azidoacetate**[140]



Methyl bromoacetate (21.25 mmol, 3.22 g) was taken in anhydrous DMF (5 mL) and $NaN_3$ (22.50 mmol, 1.46 mg) was added. The mixture was stirred at ambient temperature for 3 hours, then water was added (2 mL) and the solution was extracted with $Et_2O$ (2 mL x 3). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. Yield: 2.32 g (95 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 3.89 (s, 2H, C*H*$_2$), 3.81 (s, 3H, C*H*$_3$).

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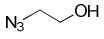
138 Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 413-414. "A practical procedure for the synthesis of alkyl azides at ambient temperature in dimethyl sulfoxide in high purity and yield".

139 Barr, L.; Lincoln, S. F.; Easton, C. J. *Supramol. Chem.* **2005**, *17*, 547-555. "A cyclodextrin molecular reactor for the regioselective synthesis of 1,5-disubstituted-1,2,3-triazoles".

140 van Berkel, S. S.; van der Lee, B.; van Delf, F. L.; Wagenvoord, R.; Hemker, H. C.; Rutjes, F. P. J. T. *Chem. Med. Chem.* **2012**, 7, 606-617. "Fluorogenic peptide-based substrates for monitoring thrombin activity".

**2-Azidoethanol**[141]

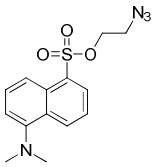


2-Bromoethanol (3.00 mmol, 375 mg) was taken in $H_2O$ (2 mL) and $NaN_3$ (3.30 mmol, 214 mg) was added. The mixture was stirred at 80 ºC for 8 hours, then cooled at ambient temperature and the solution was extracted with $Et_2O$ (2 mL x 3). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. Yield: 222 mg (87 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 3.92 (t, 2H, *J* = 5.3 Hz, C*H*$_2$OH), 3.55 (t, 2H, *J* = 5.3 Hz, N$_3$C*H*$_2$).

**3-Azidopropan-1-ol**[142]

A mixture of 3-bromopropan-1-ol (7.19 mmol, 0.65 mL) and $NaN_3$ (14.38 mmol, 935 mg) in $H_2O$ (20 mL) was stirred at 80 °C for 18 hours, then cooled at ambient temperature and the solution was extracted with EtOAc (20 mL x 5). The combined organic layers were washed with brine (20 mL x 1), dried over $MgSO_4$ and concentrated under reduced pressure. Yield: 698 mg (96 %). $^1$H NMR (400 MHz, $CDCl_3$) δ 3.79 (t, *J* = 6.0 Hz, 2H, C*H*$_2$OH), 3.49 (t, *J* = 6.7 Hz, 2H, N$_3$C*H*$_2$), 1.94-1.76 (m, 2H, CH$_2$C*H*$_2$CH$_2$).

**2-Azidoethyl 5-(*N*,*N*-dimethylamino)naphthalene-1-sulfonate**[143]



Triethylamine (4.00 mmol, 540 µL) was added to a solution of 5-(dimethylamino)naphthalene-1-sulfonyl chloride (dansyl chloride) (1.67 mmol, 500 mg) and 2-azidoethanol (4.00 mmol, 278 mg) in anhydrous $CH_2Cl_2$ (5 mL), and the mixture was stirred at room temperature for 16 hours. Then, it was washed with a sodium phosphate buffer solution (pH = 7.4) (3 mL x 2) and the aqueous layers were extracted with $CH_2Cl_2$ (5 mL x 3). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Yield: 0.55 g (99 %). $^1$H

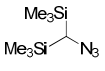
[141] Dowlut, M.; Hall, D. G.; Hindsgaul, O. *J. Org. Chem.* **2005**, *70*, 9809-9813. "Investigation of non-specific effects of different dyes in the screening of labeled carbohydrates against inmobilized proteins".

[142] Aucagne, V., Hänni, K. D.; Leigh, D. A.; Lusby, P. J.; Walker D. B. *J. Am. Chem. Soc.* **2006**, *128*, 2186-2187. "Catalytic "Click" rotaxanes: a substoichiometric metal-template pathway to mechanically interlocked architectures".

[143] Aizpurua Iparraguirre, J. M.; Sagartzazu Aizpurua, M.; Braceras Izaguirre, I.; Azpiroz Dorronsoro, F. J.; Oyarbide Vicuna, J. Eur. Pat. Appl. 2014, EP 2749300 A1 20140702. PCT Int. Appl. 2014, WO 2014102435 A2 20140703. "Modified polyaryletherketone (paek) polymer and method for obtaining it".

NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 8.6 Hz, 1H, Ar), 8.30 (d, *J* = 8.1 Hz, 2H, Ar), 7.65 (t, *J* = 8.1 Hz, 1H, Ar), 7.58 (t, *J* = 7.9 Hz, 1H, Ar), 7.25 (d, *J* = 7.5 Hz, 1H, Ar), 4.14 (t, *J* = 5.3 Hz, 2H, C*H*$_2$), 3.47 (t, *J* = 5.3 Hz, 2H, C*H*$_2$), 2.92 (s, 6H, N(C*H*$_3$)$_2$).

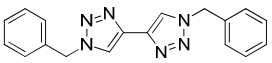
**Bis(trimethylsilyl)methyl azide**[144]




To a solution of sodium azide (5.04 mmol, 328 mg) in anhydrous HMPA (2.3 mL), bis(trimethylsilyl)chloromethane (4.58 mmol, 1.00 mL) was added and the mixture was stirred at room temperature for 5 hours. Water (0.5 mL) was added and the mixture was extracted with hexane (1 mL x 3). The combined organic solutions were washed with a saturated aqueous solution of $NH_4Cl$ (1 mL x 2) and dried over $MgSO_4$. Yield: 830 mg (90 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 2.21 (s, 1H, *CH*), 0.16 (s, 18H, *CH*$_3$).

### 6.1.3 Synthesis of symmetrically substituted 4,4'-bis(1*H*-1,2,3-triazoles)

**1,1'-Dibenzyl-4,4'-bis-(1*H*-1,2,3-triazole)**[145]



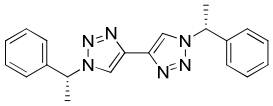
To a solution of 1,4-bis(trimethylsilyl)-1,3-butadiyne (2.00 mmol, 389 mg) and benzyl azide (4.20 mmol, 559 mg) in $H_2O$/*t*BuOH 1:1 (30 mL), $CuSO_4 \cdot 5H_2O$ (0.80 mmol, 200 mg), sodium ascorbate (1.60 mmol, 317 mg), $K_2CO_3$ (4.00 mmol, 553 mg) and pyridine (20.00 mmol, 1.60 ml) were added and the reaction mixture was stirred vigorously at room temperature for 24 hours. The solvent was evaporated under reduced pressure, the residue was suspended in aqueous 10% $NH_3$ (10 mL) and extracted with $CH_2Cl_2$ (15 mL x 3). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to afford the product. Yield: 500 mg (80 %). $^1$H NMR (500 MHz, $CDCl_3$): δ 7.96 (s, 2H, triazole), 7.40 (d, *J* = 6.8

[144] Prepare according to procedure: Palomo, C.; Aizpurua, J. M.; García, J. M.; Legido, M. *J. Chem. Soc., Chem. Commun*. **1991**, 524-526. "A novel highly stereoselective synthesis of pyrrolidines and their derivatives through thermal cyclization reaction of *N*-[bis(trimethylsilyl)methyl]-1-aza-1,3-dienes".

[145] Monkowius, U.; Ritter, S.; König, B.; Zabel, M.; Yersin, H. *Eur. J. Inorg. Chem.* **2007**, 4597-4606. "Synthesis, characterization and ligand properties of novel bi-1,2,3-triazole ligands".

Hz, 6H, Ar), 7.35 – 7.31 (m, 4H, Ar), 5.59 (s, 4H, C$H_2$). $^{13}$C NMR (126 MHz, $CDCl_3$): δ 140.4, 134.3, 129.2, 128.9, 128.2, 120.5, 54.4.

**1,1'-Bis((*R*)-α-methylbenzyl)-4,4'-bis(1*H*-1,2,3-triazole)**



To a solution of 1,4-bis(trimethylsilyl)-1,3-butadiyne (1.37 mmol, 266 mg) and (*R*)-(+)-α-methylbenzylazide (2.87 mmol, 422 mg) in $H_2O$/*t*BuOH 1:1 (20 mL), $CuSO_4 \cdot 5H_2O$ (1.15 mmol, 402 mg), sodium ascorbate (2.30 mmol, 456 mg), $K_2CO_3$ (2.74 mmol, 379 mg) and pyridine (13.70 mmol, 1.10 mL) were added and the reaction mixture was stirred vigorously at ambient temperature for 24 hours. The solvent was evaporated *in vacuo*, the residue was suspended in aqueous 10% $NH_3$ (10 mL) and extracted with $CH_2Cl_2$ (10 mL x 3). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to afford the product. Yield: 414 mg (88 %). White solid (mp = 168 ºC). $[\alpha]_D^{20}$ = – 37.8º (c= 1.05, $CH_2Cl_2$). IR ($cm^{-1}$): 1456 (triazole). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 2H, triazole), 7.43 - 7.30 (m, 10H, Ar), 5.89 (q, *J* = 7.1 Hz, 2H, C*H*$CH_3$), 2.00 (d, *J* = 7.1 Hz, 6H, CHC$H_3$). $^{13}$C NMR (126 MHz, $CDCl_3$): δ 139.5, 129.0, 128.6, 126.5, 119.4, 60.4, 29.7, 21.2. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{20}H_{21}N_6$: 345.1828; found: 345.1840.

### 6.1.4 General procedure for the synthesis of 1*H*-1,2,3-triazoles

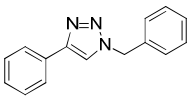
**Method A:**

To a solution of the corresponding azide (1.00 mmol) and alkyne (1.10 mmol) in THF/*t*BuOH/$H_2O$ 1:1:1 (5 mL), sodium ascorbate (0.40 mmol) and $CuSO_4 \cdot 5H_2O$ (0.20 mmol) were added. The reaction mixture was stirred for 18 hours at ambient temperature. The organic solvents were evaporated under reduced pressure and the aqueous residue was extracted with EtOAc/$NH_3$ 20% ($H_2O$). The organic layer was separated, dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, Hex/EtOAc).

**Method B:**

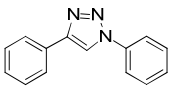
To a solution of the corresponding azide (1.00 mmol) and alkyne (1.10 mmol) in MeCN (15 mL), was added a solution of CuOAc (0.20 mmol) and NaOAc (1.00 mmol) in MeCN/$H_2O$ 1:1 (3 mL). The reaction mixture was stirred at room temperature for 18 hours and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH 95:5).

**1-Benzyl-4-phenyl-1*H*-1,2,3-triazole**[146]



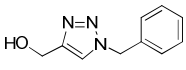
The general procedure 6.1.4 A was followed starting from benzyl azide (7.51 mmol, 1.00 g), phenylacetylene (8.26 mmol, 0.91 mL), $CuSO_4$ $5H_2O$ (1.50 mmol, 0.38 g) and sodium ascorbate (3.00 mmol, 0.60 g). Yield: 1.76 g (99 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6 Hz, 2H, Ar), 7.69 (s, 1H, triazole), 7.44 – 7.38 (m, 4H, Ar), 7.33 (t, *J* = 5.5 Hz, 4H, Ar), 5.58 (s, 2H, Ar$CH_2$).

**1,4-Diphenyl-1*H*-1,2,3-triazole**[135b]



The general procedure 6.1.4 A was followed starting from phenyl azide (0.84 mmol, 100 mg), phenylacetylene (0.92 mmol, 0.10 mL), $CuSO_4$ $5H_2O$ (0.34 mmol, 84 mg) and sodium ascorbate (0.67 mmol, 133 mg). Yield: 146 mg (78 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H, triazole), 7.93 (d, *J* = 7.9 Hz, 2H, Ar), 7.81 (d, *J* = 7.8 Hz, 2H, Ar), 7.56 (t, *J* = 7.7 Hz, 2H, Ar), 7.52 – 7.43 (m, 4H, Ar), 7.39 (t, *J* = 7.4 Hz, 1H, Ar). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 148.6, 137.2, 130.4, 130.0, 129.1, 129.0, 128.6, 126.0, 120.7, 117.9.

**1-Benzyl-4-hydroxymethyl-1*H*-1,2,3-triazole**[147]



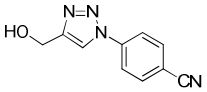
The general procedure 6.1.4 A was followed starting from benzyl azide (10.00 mmol, 1.33 g), propargyl alcohol (11.00 mmol, 0.64 mL), $CuSO_4$

[146] Jlalia, I.; Meganem, F.; Herscovici, J.; Girard, C. *Molecules* **2009**, *14*, 528-539. ""Flash" solvent-free synthesis of triazoles using a supported catalyst".

[147] Girard, C; Önen, E.; Aufort, M.; Beauvière, S.; Samson, E.; Herscovici, J. *Org. Lett.* **2006**, *8*, 1689-1692. "Reusable polymer-supported catalyst for the [3+2] Huisgen cycloaddition in automation protocols".

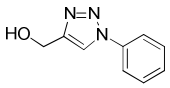
$5H_2O$ (2.00 mmol, 499 mg) and sodium ascorbate (4.00 mmol, 792 mg). Yield: 1.65 g (87 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, 1H, triazole), 7.38-7.28 (m, 5H, Ar), 5.51 (s, 2H, *CH*$_2$), 4.76 (s, 2H, HOC*H*$_2$), 3.29 (s, 1H, *H*OCH$_2$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 148.4, 134.7, 129.3, 129.0, 128.3, 121.9, 56.5, 54.4.

**1-(4-Cyanophenyl)-4-hydroxymethyl-1*H*-1,2,3-triazole**[148]




The general procedure 6.1.4 A was followed starting from 4-azidobenzonitrile (6.94 mmol, 1.00 g), propargyl alcohol (7.63 mmol, 0.51 mL), $CuSO_4$ $5{\cdot}H_2O$ (1.39 mmol, 347 mg) and sodium ascorbate (2.78 mmol, 548 mg). Yield: 1.17 g (84 %). $^1$H NMR (500 MHz, DMSO) δ 8.83 (s, 1H, triazole), 8.16-8.07 (m, 4H, Ar), 5.35 (t, *J* = 5.3 Hz, 1H, *H*OCH$_2$), 4.63 (d, 2H, *J* = 5.3 Hz, HOC*H*$_2$). $^{13}$C NMR (125 MHz, DMSO) δ 149.5, 139.5, 134.1, 121.0, 120.1, 117.9, 110.7, 54.8.

**1-Phenyl-4-hydroxymethyl-1*H*-1,2,3-triazole**[149]



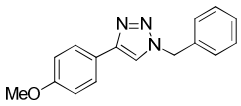

The general procedure 6.1.4 A was followed starting from phenyl azide (7.61 mmol, 907 mg), propargyl alcohol (8.36 mmol, 0.49 mL), $CuSO_4$ $5H_2O$ (1.52 mmol, 380 mg) and sodium ascorbate (3.04 mmol, 602 mg). Yield: 988 mg (74 %). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H, triazole), 7.79 – 7.72 (m, 2H, Ar), 7.60 – 7.44 (m, 3H, Ar), 4.93 (d, *J* = 5.7 Hz, 2H, HOC*H*$_2$), 2.75 (t, *J* = 5.9 Hz, 1H, *H*OCH$_2$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 148.6, 137.3, 130.0, 129.1, 120.8, 120.3, 56.8.

**1-Benzyl-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole**[150]

[148] Aizpurua, J. M.; Azcune, I.; Fratila, R. M.; Balentova, E.; Sagartzazu-Aizpurua, M.; Miranda, J. I. *Org. Lett.* **2010**, *12*, 1584-1587. ""Click" synthesis of nonsymmetrical bis(1,2,3-triazoles)".

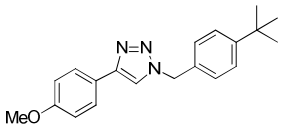
[149] Stefani, H. A.; Canduzini, H. A.; Manarin, F. *Tetrahedron Lett.* **2011**, *52*, 6086-6090. "Modular synthesis of mono, di and tri-1,4-disubstituted-1,2,3-triazoles through copper-catalyzed alkyne-azide cycloaddition: *in situ* reactIR spectroscopic monitoring".

[150] Chassaing, S.; Sido, A. S. S.; Alix, A.; Kumarraja, M.; Pale, P.; Sommer, J. *Chem. Eur. J.* **2008**, *14*, 6713-6721. ""Click chemistry" in zeolites: copper(I) zeolites as new heterogeneous and ligand-free catalysts for the Huisgen [3+2] cycloaddition".



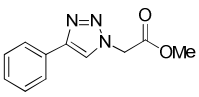
The general procedure 6.1.4 A was followed starting from benzyl azide (1.00 mmol, 133 mg), 4-ethynylanisole (1.10 mmol, 132 µL), $CuSO_4$ $5H_2O$ (0.40 mmol, 100 mg) and sodium ascorbate (0.80 mmol, 158 mg) in THF/$^t$BuOH/$H_2O$ 1:1:1 (6 mL). Yield: 260 mg (98 %). $^1$H RMN (400 MHz, $CDCl_3$) δ 7.75 (d, 2H, *J* = 8.8 Hz, Ar), 7.60 (s, 1H, triazole), 7.44 – 7.32 (m, 5H, Ar), 6.69 (d, 2H, *J* = 8.8 Hz, Ar), 5.59 (s, 2H, C*H*$_2$), 3.86 (s, 3H, OC*H*$_3$). $^{13}$C RMN (126 MHz, $CDCl_3$) δ 159.6, 148.1, 134.8, 129.1, 128.7, 128.0, 127.0, 123.3, 118.6, 114.2, 54.2, 55.3.

**1-(4-*tert*-Butylbenzyl)-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole**



The general procedure 6.1.4 A was followed starting from 4-*tert*-butylbenzyl azide (1.00 mmol, 189 mg), 4-ethynylanisole (1.10 mmol, 132 µL), $CuSO_4$ $5H_2O$ (0.40 mmol, 100 mg) and sodium ascorbate (0.80 mmol, 158 mg) in THF/$^t$BuOH/$H_2O$ 1:1:1 (6 mL). Yield: 288 mg (90 %). White solid (mp = 118-120 ºC). IR (cm$^{-1}$): 1454 (triazole), 1250, 1219 (arC-O-alC). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H, Ar), 7.63 (s, 1H, triazole), 7.40 (d, *J* = 7.9 Hz, 2H, Ar), 7.25 (d, *J* = 7.9 Hz, 2H, Ar), 6.94 (d, *J* = 8.2 Hz, 2H, Ar), 5.51 (s, 2H, C*H*$_2$), 3.81 (s, 3H, OC*H*$_3$), 1.33 (s, 9H, $(CH_3)_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 159.7, 151.9, 148.1, 132.0, 128.0, 127.1, 126.1, 123.5, 119.0, 114.3, 55.4, 54.0, 34.8, 31.4. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{20}H_{24}N_3O$: 322.1919; found: 322.1924.

**1-(Methoxycarbonylmethyl)-4-phenyl-1*H*-1,2,3-triazole**[151]

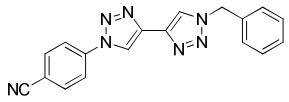


The general procedure 6.1.4 A was followed starting from methyl azidoacetate (5.00 mmol, 575 mg), phenylacetylene (5.00 mmol, 0.5 mL), $CuSO_4$ $5H_2O$ (1.00 mmol, 250 mg) and sodium ascorbate (2.00 mmol, 396 mg) in THF/$^t$BuOH/$H_2O$ 1:1:1 (15 mL). Yield: 1.00 g (93 %). $^1$H NMR (400

[151] Buckley, B. R.; Dann, S. E.; Harris, D. P.; Heaney, H.; Stubbs, E. C. *Chem. Commun.* **2010**, *46*, 2274-2276. "Alkynylcopper(I) polymers and their use in a mechanistic study of alkyne-azide click reactions".

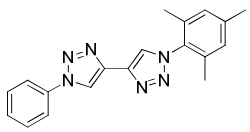
MHz, $CDCl_3$) δ 7.94 (s, 1H, triazole), 7.88 (d, *J* = 7.6 Hz, 2H, Ar), 7.47 (t, *J* = 7.5 Hz, 2H, Ar), 7.38 (t, *J* = 7.5 Hz, 1H, Ar), 5.26 (s, 2H, C*H*$_2$), 3.87 (s, 3H, OC*H*$_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.8, 148.3, 130.4, 128.9, 128.4, 125.9, 121.2, 53.1, 50.9.

**1-Benzyl-1'-(4-cyanophenyl)-4,4'-bis(1*H*-1,2,3-triazole) ($8_{1,4}$)**



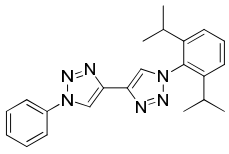
The general procedure 6.1.4 A was followed starting from 1-(4-cyanophenyl)-4-ethynyl-1*H*-1,2,3-triazole (0.10 mmol, 20 mg), benzylazide (0.19 mmol, 26 mg), $CuSO_4$ $5H_2O$ (0.02 mmol, 7 mg) and sodium ascorbate (0.04 mmol, 8 mg). Yield: 21 mg (67 %). White solid (mp = 206 ºC dec). IR ($cm^{-1}$): 3134, 3092, 2228 (C≡N), 1604, 1496, 1455 (triazole), 1051, 989, 834, 730, 696, 575. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.40 (s, 1H, triazole), 8.69 (s, 1H, triazole), 8.25 (d, *J* = 8.2 Hz, 2H, Ar), 8.12 (d, *J* = 8.2 Hz, 2H, Ar), 7.41 (s, 5H, Ar), 5.71 (s, 2H, C*H*$_2$). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 141.0, 139.9, 139.0, 136.4, 134.8, 129.3, 128.7, 128.5, 122.9, 121.0, 120.5, 118.6, 111.6, 53.5. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{18}H_{14}N_7$: 328.1311; found: 328.1313.

**1-Phenyl-1'-(2,4,6-trimethylphenyl)-4,4'-bis(1*H*-1,2,3-triazole)**



The general procedure 6.1.4 A was followed starting from 4-ethynyl-1-phenyl-1*H*-1,2,3-triazole (0.12 mmol, 20 mg), 2,4,6-trimethylphenyl azide (0.24 mmol, 39 mg), $CuSO_4$ $5H_2O$ (0.02 mmol, 8 mg) and sodium ascorbate (0.05 mmol, 10 mg). Yield: 30 mg (76 %). White solid (mp = 201-202 ºC). IR ($cm^{-1}$): 3135, 3087, 1596, 1503, 1464 (triazole), 1038, 756, 681. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H, triazole), 8.21 (s, 1H, triazole), 7.85 (d, *J* = 7.9 Hz, 2H, Ar), 7.59 (t, *J* = 7.8 Hz, 2H, Ar), 7.50 (t, *J* = 7.4 Hz, 1H, Ar), 7.05 (s, 2H, Ar), 2.40 (s, 3H, ArC*H*$_3$), 2.05 (s, 6H, ArC*H*$_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 140.7, 140.2, 139.6, 136.9, 135.0, 133.2, 129.9, 129.2, 129.0, 122.8, 120.5, 118.8, 21.1, 17.3. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{19}H_{19}N_6$: 331.1671; found: 331.1674.

**1-(2,6-Diisopropylphenyl)-1'-phenyl-4,4'-bis(1*H*-1,2,3-triazole)**

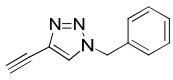


The general procedure 6.1.4 A was followed starting from 4-ethynyl-1-phenyl-1*H*-1,2,3-triazole (0.12 mmol, 20 mg), 2,6-diisopropylphenyl azide (0.24 mmol, 49 mg), $CuSO_4$ $5H_2O$ (0.05 mmol, 17 mg) and sodium ascorbate (0.10 mmol, 19 mg). Yield: 34 mg (76 %). White solid (mp = 234 ºC dec). IR ($cm^{-1}$): 3130, 2962, 1507, 1459 (triazole), 1395, 1387, 1159, 1039, 840, 804, 758, 685. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H, triazole), 8.28 (s, 1H, triazole), 7.85 (d, *J* = 7.8 Hz, 2H, Ar), 7.66 – 7.47 (m, 4H, Ar), 7.35 (d, *J* = 7.8 Hz, 2H, Ar), 2.36 (m, 2H, C*H*$CH_3$), 1.20 (d, *J* = 6.6 Hz, 6H, CHC*H*$_3$), 1.18 (d, *J* = 6.6 Hz, 6H, CHC*H*$_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 146.3, 137.2, 133.2, 131.2, 130.1, 129.2, 124.1, 120.9, 28.7, 24.33 (d, *J* = 16.4 Hz). HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{22}H_{25}N_6$: 373.2141; found: 373.2139.

### 6.1.5 General procedure for Swern oxidation and Ohira-Bestmann alkynylation of 4-hydroxymethyl-1*H*-1,2,3-triazoles

To a solution of oxalyl chloride (1.10 mmol) in $CH_2Cl_2$ (10 mL) cooled at -55 ºC, anhydrous DMSO (2.40 mmol) was added and the solution was stirred for 5 min. After this time, a solution of the corresponding 4-hydroxymethyl-1,2,3-triazole (1.00 mmol) in $CH_2Cl_2$ (10 mL) was added *via* canula at the same temperature and the mixture was stirred for 15 min. Then, $Et_3N$ (5.00 mmol) was added and the mixture was stirred at ambient temperature for 1 hour. The reaction was quenched with aqueous 1M HCl and the product was extracted with $CH_2Cl_2$. The organic layer was dried over $MgSO_4$, the solvent was evaporated under reduced pressure and the product was submitted to the Bestmann-Ohira alkynylation without any further purification. Thus, to a solution of the so-obtained aldehyde in MeOH cooled at 0 ºC, dimethyl acetyldiazomethylphosphonate (1.00 mmol) and $K_2CO_3$ (2.00 mmol) were added. The reaction was stirred for 1 hour at 0 ºC and then, at ambient temperature for 3-5 hours. After this time, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel, Hex/EtOAc).

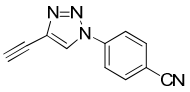
**1-Benzyl-4-ethynyl-1*H*-1,2,3-triazole**[148]



The general procedure 6.1.5 was followed starting from 1-benzyl-4-hydroxymethyl-1*H*-1,2,3-triazole (9.05 mmol, 1.71 g), oxalyl chloride (9.96 mmol, 0.83 mL), DMSO (21.73 mmol, 1.55 mL), $Et_3N$ (45 mmol, 6.40 mL), $K_2CO_3$ (18.10 mmol, 2.50 g) and dimethyl acetyldiazomethylphosphonate reagent (9.05 mmol, 1.74 g). Yield: 2.34 g (75 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H, triazole), 7.44 – 7.29 (m, 5H, Ar), 5.55 (s, 2H, C$H_2$), 3.23 (s, 1H, C≡C*H*). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 133.9, 130.4, 129.2, 129.0, 128.1, 126.5, 81.1, 73.0, 54.3.

[**Aldehyde**: $^1$H NMR (500 MHz, $CDCl_3$) δ 10.08 (s, 1H, C*H*O), 8.07 (s, 1H, triazole), 7.42 – 7.22 (m, 5H, Ar), 5.59 (s, 2H, C$H_2$)].

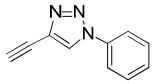
**1-(4-Cyanophenyl)-4-ethynyl-1*H*-1,2,3-triazole**[148] **(1c)**



The general procedure 6.1.5 was followed starting from 1-(4-cyanophenyl)-4-hydroxymethyl-1*H*-1,2,3-triazole (9.27 mmol, 1.98 g), oxalyl chloride (10.20 mmol, 0.85 mL), DMSO (22.25 mmol, 1.58 mL), $Et_3N$ (6.50 mL), $K_2CO_3$ (18.50 mmol, 2.50 g) and dimethyl acetyldiazomethylphosphonate reagent (9.27 mmol, 1.78 g). Yield: 1.62 g (80 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1H, triazole), 7.92-7.85 (m, 4H, Ar), 3.35 (s, 1H, C≡C*H*). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 138.9, 134.1, 130.0, 126.6, 120.7, 117.8, 111.4, 84.9, 72.8.

[**Aldehyde**: $^1$H NMR (200 MHz, $CDCl_3$) δ 10.15 (s, 1H, C*H*O), 9.01 (s, 1H, triazole), 8.05 (d, 2H, *J* = 8.6 Hz, Ar), 7.83 (d, 2H, *J* = 8.6 Hz, Ar)].

**4-Ethynyl-1-phenyl-1*H*-1,2,3-triazole**[152]



The general procedure 6.1.5 was followed starting from 4-hydroxymethyl-1-phenyl-1*H*-1,2,3-triazole (5.64 mmol, 988 mg), oxalyl chloride (6.20 mmol, 0.54 mL), DMSO (13.54 mmol, 0.96 mL), $Et_3N$ (28.2 mmol, 3.93 mL), $K_2CO_3$ (11.28 mmol, 1.56 g) and dimethyl acetyldiazomethylphosphonate reagent (8.46 mmol, 1.62 g). Yield: 788 mg (83 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H, triazole), 7.76-7.74 (m,

[152] Sokolyanskaya, L. V.; Volkov, A. N.; Trofimov, B. A. *Khimiya Geterotsiklicheskikh Soedinenii* **1979**, 849. "Cycloaddition of phenyl azide to diacetylene".

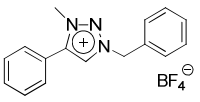
2H, Ar), 7.60 – 7.47 (m, 3H, Ar), 3.34 (s, 1H, C≡C*H*). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 136.5, 130.8, 129.9, 129.2, 124.7, 120.7, 81.7, 72.8.

[**Aldehyde**: $^1$H NMR (500 MHz, $CDCl_3$) δ 10.26 (s, 1H, C*H*O), 8.55 (s, 1H, triazole), 7.80 (d, *J* = 7.9 Hz, 2H, Ar), 7.63-7.54 (m, 3H, Ar)].

### 6.1.6 General procedure for the synthesis of 3-*N*-alkyl-1,2,3-triazolium salts

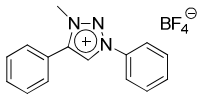
A solution of the corresponding 1,2,3-triazole (1.00 mmol) and the alkylating reagent (1.30 mmol) in anhydrous $CH_2Cl_2$ (5 mL) was stirred under nitrogen atmosphere at room temperature for 5 hours. Then, anhydrous MeOH (1 mL) was added and the solution was stirred for another 5 hours. The solvents were removed under reduced pressure and the crude product was purified by either precipitation with $Et_2O$ or by column chromatography (silica gel, $CH_2Cl_2$/MeOH).

**1-Benzyl-3-methyl-4-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate**[153]



The general procedure 6.1.6 was followed starting from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (1.23 mmol, 290 mg) and $Me_3OBF_4$ (1.60 mmol, 304 mg). Yield: 331 mg (80 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H, triazole), 7.59 – 7.46 (m, 7H, Ar), 7.43-7.38 (m, 3H, Ar), 5.73 (s, 2H, C$H_2$), 4.21 (s, 3H, C$H_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 143.4, 131.8, 131.3, 129.9, 129.7, 129.6, 129.4, 129.4, 128.2, 121.9, 57.5, 38.4.

**1,4-Diphenyl-3-methyl-1*H*-1,2,3-triazolium tetrafluoroborate**[154]



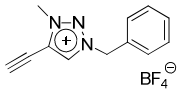
The general procedure 6.1.6 was followed starting from 1,4-diphenyl-1*H*-1,2,3-triazole (0.45 mmol, 100 mg) and $Me_3OBF_4$ (0.59 mmol, 112 mg). Yield: 118 mg (81 %). $^1$H NMR (400 MHz, MeOH-$d_4$) δ 9.51 (s,

[153] Kilpin, K. J.; Paul, U. S. D.; Lee, A.-L.; Crowley, J. D. *Chem. Commun.* **2011**, *47*, 328-330. "Gold(I) "click" 1,2,3-triazolylidenes: synthesis, self-assembly and catalysis".

[154] Nakamura, T.; Terashima, T.; Ogata, K.; Fukuzawa, S. *Org. Lett.* **2011**, *13*, 620-623. "Copper(I) 1,2,3-triazol-5-ylidene complexes as efficient catalysts for click reactions of azides with alkynes".

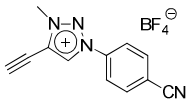
1H, triazole), 8.24 – 7.98 (m, 2H, Ar), 7.96 – 7.57 (m, 8H, Ar), 4.46 (s, 3H, C*H*$_3$). $^{13}$C NMR (126 MHz, MeOH-d$_4$) δ 144.2, 135.3, 131.8, 130.3, 129.4, 129.3, 126.8, 122.4, 121.4, 38.2.

**1-Benzyl-4-ethynyl-3-methyl-1*H*-1,2,3-triazolium tetrafluoroborate**[155]



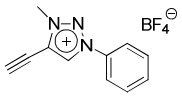
The general procedure 6.1.6 was followed starting from 1-benzyl-4-ethynyl-1*H*-1,2,3-triazole (2.62 mmol, 500 mg) and trimethyloxonium tetrafluoroborate (3.41 mmol, 647 mg). Yield: 574 mg (84 %). $^1$H NMR (500 MHz, MeOH-d$_4$) δ 8.98 (s, 1H, triazole), 7.57 – 7.43 (m, 5H, Ar), 5.85 (s, 2H, C*H*$_2$), 4.98 (s, 1H, C≡C*H*), 4.36 (s, 3H, C*H*$_3$). $^{13}$C NMR (126 MHz, MeOH-d$_4$) δ 133.6, 133.0, 130.9, 130.4, 127.8, 95.7, 65.4, 58.7, 39.3.

**1-(4-Cyanophenyl)-4-ethynyl-3-methyl-1*H*-1,2,3-triazolium tetrafluoroborate**[155] **(2c)**



The general procedure 6.1.6 was followed starting from 1-(4-cyanophenyl)-4-ethynyl-1*H*-1,2,3-triazole (0.48 mmol, 100 mg) and trimethyloxonium tetrafluoroborate (0.62 mmol, 117 mg). Yield: 99 mg (70 %). $^1$H NMR (500 MHz, MeOH-d$_4$) δ 9.74 (s, 1H, triazole), 8.21 (d, *J* = 8.6 Hz, 2H, Ar), 8.15 (d, *J* = 8.5 Hz, 2H, Ar), 5.17 (s, 1H, C≡C*H*), 4.53 (s, 3H, C*H*$_3$). $^{13}$C NMR (126 MHz, MeOH-d$_4$) δ 139.1, 135.6, 132.6, 128.8, 123.9, 118.1, 116.9, 96.6, 65.2, 39.9.

**4-Ethynyl-3-methyl-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate**

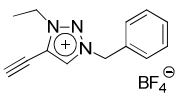


The general procedure 6.1.6 was followed starting from 4-ethynyl-1-phenyl-1*H*-1,2,3-triazole (1.77 mmol, 300 mg) and trimethyloxonium tetrafluoroborate (2.30 mmol, 437 mg). Yield: 398 mg (83 %). White solid (mp = 170 ºC dec). IR (cm$^{-1}$): 3552, 3241 (≡CH), 2133 (C≡C), 1445 (triazole), 1035 (BF$_4$). $^1$H NMR (500 MHz, MeCN-d$_3$) δ 9.01 (s, 1H, triazole), 7.91 – 7.84 (m, 2H, Ar), 7.79 – 7.72 (m, 3H, Ar), 4.59 (s, 1H, C≡C*H*), 4.40 (s, 3H, C*H*$_3$). $^{13}$C NMR (126 MHz, MeCN-d$_3$)

[155] Aizpurua, J. M.; Sagartzazu-Aizpurua, M.; Azcune, I.; Miranda, J. I.; Monasterio, Z.; García-Lecina, A.; Fratila, R. M. *Synthesis* **2011**, 2737-2742. ""Click" synthesis of nonsymmetrical 4,4'-bis(1,2,3-triazolium) salts".

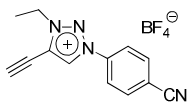
δ 134.5, 132.1, 130.8, 130.3, 126.6, 121.6, 94.4, 63.6, 38.8. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{11}H_{10}N_3$: 184.0875; found: 184.0880.

**1-Benzyl-4-ethynyl-3-ethyl-1*H*-1,2,3-triazolium tetrafluoroborate**



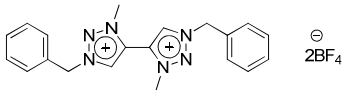
The general procedure 6.1.6 was followed starting from 1-benzyl-4-ethynyl-1*H*-1,2,3-triazole (1.09 mmol, 200 mg) and triethyloxonium tetrafluoroborate (1.64 mmol, 310 mg). Yield: 233 mg (72 %). Oil. IR ($cm^{-1}$): 3244 (≡CH), 3151, 3105, 2136 (C≡C), 1738, 1564, 1458 (triazole), 1030 ($BF_4$). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H, triazole), 7.45 (ddd, *J* = 67.7, 5.6, 3.2 Hz, 5H, Ar), 5.74 (s, 2H, Ar$CH_2$), 4.60 (q, *J* = 7.3 Hz, 2H, $CH_3CH_2N_{tri}$), 4.26 (s, 1H, C≡C*H*), 1.60 (t, *J* = 7.3 Hz, 3H, $CH_3$). $^{13}$C NMR (101 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-Cyanophenyl)-4-ethynyl-3-ethyl-1*H*-1,2,3-triazolium tetrafluoroborate**



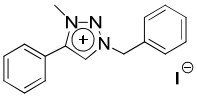
The general procedure 6.1.6 was followed starting from 1-(4-cyanophenyl)-4-ethynyl-1*H*-1,2,3-triazole (0.51 mmol, 150 mg) and triethyloxonium tetrafluoroborate (0.76 mmol, 144 mg). Yield: 117 mg (78 %). White solid (mp = 153-156 ºC). IR ($cm^{-1}$): 3239.2 (≡CH), 3159, 3113, 2231 (C≡N), 2137 (C≡C), 1737, 1603, 1565, 1436 (triazole), 1035 ($BF_4$). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.05 (s, 1H, triazole), 8.34 – 8.20 (m, 4H, Ar), 4.83 (q, *J* = 7.3 Hz, 2H, $CH_3CH_2N_{tri}$), 2.09 (s, 1H, C≡C*H*), 1.65 (t, *J* = 7.3 Hz, 3H, $CH_3$). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 137.5, 134.7, 132.3, 127.5, 122.5, 117.4, 114.5, 97.1, 64.7, 48.8, 13.3.

**1,1'-Dibenzyl-3,3'-dimethyl-4,4'-bis(1*H*-1,2,3-triazolium) tetrafluoroborate**[155]



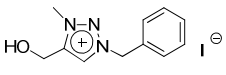
The general procedure 6.1.6 was followed starting from 1,1'-dibenzyl-4,4'-bis(1*H*-1,2,3-triazole) (1.23 mmol, 390 mg) and trimethyl oxonium tetrafluoroborate (4.93 mmol, 729 mg). Yield: 596 mg (92 %). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.47 (s, 2H, triazole), 7.65 – 7.41 (m, 10H, Ar), 6.04 (s, 4H, $CH_2$), 4.33 (s, 6H, $CH_3$). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 133.5, 133.1, 130.0, 129.7, 129.6, 127.5, 57.4, 39.9.

**1-Benzyl-3-methyl-4-phenyl-1*H*-1,2,3-triazolium iodide**[156]



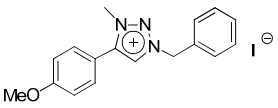
The general procedure 6.1.6 was followed starting from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (5.52 mmol, 1.30 g) and MeI (64.24 mmol, 4 mL). Yield: 2.00 g (96 %). $^{1}$H NMR (500 MHz, MeCN-$d_3$) δ 8.95 (s, 1H, triazole), 7.74 – 7.57 (m, 7H, Ar), 7.55 – 7.43 (m, 3H, Ar), 5.92 (s, 2H, C$H_2$), 4.21 (s, 3H, C$H_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 143.2, 131.8, 131.0, 129.7, 129.7, 129.4, 129.3, 129.2, 129.2, 121.3, 57.5, 39.3.

**1-Benzyl-4-hydroxymethyl-3-methyl-1*H*-1,2,3-triazolium iodide**[157]



The general procedure 6.1.6 was followed starting from 1-benzyl-4-hydroxymethyl-1*H*-1,2,3-triazole (0.50 mmol, 94 mg) and MeI (16.10 mmol, 1.00 mL). Yield: quantitative. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H, triazole), 7.52 (d, *J* = 5.1 Hz, 2H, Ar), 7.46 – 7.20 (m, 3H, Ar), 5.84 (s, 2H, C$H_2$Ph), 4.91 (d, *J* = 6.1 Hz, 2H, C$H_2$OH), 4.77 (t, *J* = 6.1 Hz, 1H, $CH_2$O*H*), 4.32 (s, 3H, C$H_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 143.6, 131.0, 129.7, 129.3, 129.3, 57.3, 52.5, 39.7.

**1-Benzyl-4-(4-methoxyphenyl)-3-methyl-1*H*-1,2,3-triazolium iodide**

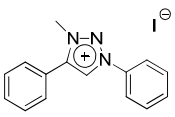


The general procedure 6.1.6 was followed starting from 1-benzyl-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (0.67 mmol, 179 mg) and MeI (21.52 mmol, 1.34 mL). Yield: 268 mg (98 %). Yellow solid (mp = 140-141 ºC). IR ($cm^{-1}$): 1446 (triazole), 1256 (Ar-O), 1072 (O-$CH_3$). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H, triazole), 7.94-7.68 (m, 4H, Ar), 7.55-7.31 (m, 3H, Ar), 7.07 (d, *J* = 8.3 Hz, 2H, Ar), 6.08 (s, 2H, C$H_2$), 4.41 (s, 3H, C$H_3$), 3.88 (s, 3H, OC$H_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.1, 142.0, 130.4, 130.2, 128.8, 128.3, 127.5, 114.1, 112.5, 56.2, 54.8, 38.9. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{17}H_{18}N_3O$: 280.1450; found: 280.1463.

[156] Mathew, P.; Neels, A.; Albrecht, M. *J. Am. Chem. Soc.* **2008**, *130*, 13534-13535. "1,2,3-Triazolylidenes as versatile abnormal carbene ligands for late transition metals".

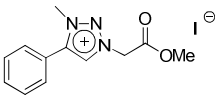
[157] Khan, S. S.; Hanelt, S.; Liebscher, J. *ARKIVOC* **2009**, *xii*, 193-208. "Versatile synthesis of 1,2,3-triazolium-based ionic liquids".

**1,4-Dibenzyl-3-methyl-1*H*-1,2,3-triazolium iodide**[158]



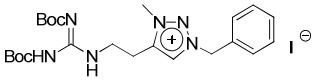
The general procedure 6.1.6 was followed starting from 1,4-dibenzyl-1*H*-1,2,3-triazole (1.36 mmol, 300 mg) and MeI (32.13 mmol, 1.34 mL). Yield: 350 mg (71 %). $^{1}$H NMR (400 MHz, MeCN-$d_3$) δ 9.03 (s, 1H, triazole), 8.06 – 7.55 (m, 10H, Ar), 4.32 (s, 3H, C$H_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 144.1, 134.6, 131.9, 131.9, 130.3, 130.0, 129.5, 127.2, 121.9, 121.3, 40.0.

**1-(Methoxycarbonylmethyl)-3-methyl-4-phenyl-1*H*-1,2,3-triazolium iodide**



The general procedure 6.1.6 was followed starting from 1-(methoxycarbonylmethyl)-4-pheny-1*H*-1,2,3-triazole (0.23 mmol, 50 mg) and MeI (16.06 mmol, 1.00 mL) in anhydrous $CH_2Cl_2$ (1.00 mL). Yield: quantitative. Colorless oil. IR (cm$^{-1}$): 1749 (C=O), 1436 (triazole), 1227, 1159 (C-O). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H, triazole), 7.69 (d, *J* = 7.2 Hz, 2H, Ar), 7.61-7.49 (m, 3H, Ar), 5.90 (s, 2H, C$H_2$), 4.34 (s, 3H, C$H_3$), 3.81 (s, 3H, OC$H_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 164.8, 143.0, 132.2, 131.0, 129.9, 129.7, 121.5, 54.7, 54.0, 39.9. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{12}H_{14}N_3O_2$: 232.1086; found: 232.1093.

**1-Benzyl-4-{2-[*N*,*N*'-di(*tert*-butoxycarbonyl)-guanidyl]-ethyl}-3-methyl-1*H*-1,2,3-triazolium iodide**

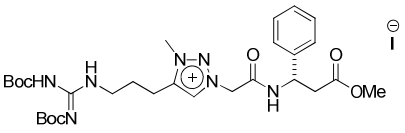


The general procedure 6.1.6 was followed starting from 1-benzyl-4-{2-[*N*,*N*'-di(*tert*-butoxycarbonyl)-guanidyl]-ethyl}-1*H*-1,2,3-triazole (0.22 mmol, 100 mg) and MeI (21.52 mmol, 1.34 mL) in anhydrous $CH_2Cl_2$ (1.34 mL). Yield: quantitative. Yellow solid (mp = 67-68 ºC). IR (cm$^{-1}$): 3326 (NH), 1723 (C=O), 1151, 1126. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H, N*H*Boc), 8.86 (s, 1H, triazole), 8.42 (t, *J* = 6.8 Hz, 1H, N*H*), 7.45-7.37 (m, 2H, Ar), 7.37-7.28 (m, 3H, Ar), 5.80 (s, 2H, C$H_2$Ar), 4.42 (s, 3H, C$H_3$), 3.67 (q, *J* = 6.9 Hz, 2H, NHC$H_2$CH$_2$), 3.25 (t, *J* = 6.9 Hz, 2H, NHCH$_2$C$H_2$), 1.40 (s, 9H, Boc), 1.35 (s, 9H, Boc). $^{13}$C

[158] Poulain, A.; Canseco-Gonzalez, D.; Hynes-Roche, R.; Müller-Bunz, H.; Schuster, O.; Stoeckli-Evans, H.; Neels, A.; Albrecht, M. *Organometallics* **2011**, *30*, 1021-1029. "Synthesis and tunability of abnormal 1,2,3-triazolylidene palladium and rhodium complexes".

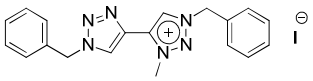
NMR (101 MHz, $CDCl_3$) δ 160.3, 154.1, 150.4, 139.4, 129.3, 127.6, 127.5, 127.2, 127.0, 81.5, 77.0, 55.1, 36.9, 35.7, 26.0, 25.9, 22.2. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{23}H_{35}N_6O_4$: 459.2720; found: 459.2721.

**(*S*)-4-{3-[*N*,*N*'-Di(*tert*-butoxycarbonyl)-guanidyl]-propyl}-3-methyl-1-{*N*-[1-phenyl-2-(methoxycarbonyl)ethyl]carbamoylmethyl}-1*H*-1,2,3-triazolium iodide**



The general procedure 6.1.6 was followed starting from (*S*)-4-{3-[*N*,*N*'-di(*tert*-butoxycarbonyl)-guanidyl]-propyl}-1-{*N*-[1-phenyl-2-(methoxycarbonyl)ethyl]carbamoylmethyl}-1*H*-1,2,3-triazole (0.15 mmol, 90 mg) and MeI (16.1 mmol, 1.00 mL) in anhydrous $CH_2Cl_2$ (1 mL). Yield: 81 mg (73 %). Yellow solid (mp = 95-97 ºC). $[\alpha]_D^{20}$ = –19.56º (c= 1.78, $CH_2Cl_2$). IR ($cm^{-1}$): 3326 (NH), 1722, 1621 (C=O), 1152, 1130. $^1$H NMR (400 MHz, $CDCl_3$) δ 11.44 (s, 1H, N*H*Boc), 8.99 (d, *J* = 8.3 Hz, 1H, N*H*CO), 8.89 (s, 1H, triazole), 8.47 (t, *J* = 6.4 Hz, 1H, N*H*$CH_2CH_2CH_2$), 7.47 (d, *J* = 7.4 Hz, 2H, Ar), 7.28 (t, *J* = 7.7 Hz, 2H, Ar), 7.20 (t, *J* = 7.4 Hz, 1H, Ar), 5.65 (dd, *J* = 49.5, 15.5 Hz, 2H, C*H*$_2$CONH), 5.40 (q, *J* = 7.6 Hz, 1H, C*H*Ph), 4.21 (s, 3H, C*H*$_3$), 3.58 (s, 3H, COOC*H*$_3$), 3.52 – 3.37 (m, 2H, NHC*H*$_2$$CH_2CH_2$), 3.22 – 2.81 (m, 4H, $NHCH_2CH_2CH_2$, C*H*$_2$$CO_2$Me), 2.14 – 1.93 (m, 2H, $NHCH_2CH_2CH_2$), 1.48 (s, 9H, Boc), 1.42 (s, 9H, Boc). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 171.0, 163.3, 162.1, 156.9, 153.3, 143.6, 140.6, 130.8, 128.8, 127.8, 127.4, 83.7, 79.7, 55.9, 52.0, 51.6, 40.6, 39.0, 38.7, 28.4, 28.2, 26.8, 21.2. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{29}H_{44}N_7O_7$: 602.3302; found: 602.3302.

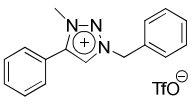
**4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1-benzyl-3-methyl-1H-1,2,3-triazolium iodide**



The general procedure 6.1.6 was followed starting from 1,1'-dibenzyl-4,4'-bis-(1*H*-1,2,3-triazole) (0.19 mmol, 60 mg) and MeI (16.06 mmol, 1.00 mL) in anhydrous MeCN (1 mL). Yield: 70 mg (81%). White solid (mp = 140-142 ºC). IR ($cm^{-1}$): 3436, 3034, 1629, 1454 (triazole). $^1$H NMR (500 MHz, $CDCl_3$) δ 10.07 (s, 1H, triazole), 9.26 (s, 1H, triazole), 7.66 – 7.25 (m, 10H, Ar), 5.90 (s, 2H, C*H*$_2$), 5.61 (s, 2H, C*H*$_2$), 4.57 (s, 3H, C*H*$_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 134.3, 133.5,

131.3, 130.8, 129.9, 129.5, 129.3, 129.1, 129.0, 128.8, 128.3, 127.2, 57.7, 54.5, 41.0. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{19}H_{19}N_6$: 331.1666; found: 331.1657.

**1-Benzyl-3-methyl-4-phenyl-1*H*-1,2,3-triazolium trifluoromethanesulfonate**



The general procedure 6.1.6 was followed starting from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (1.23 mmol, 290 mg) and MeOTf (1.35 mmol, 153 µL). Yield: quantitative. Colorless oil. IR ($cm^{-1}$): 1458 (triazole), 1255, 1223, 1058, 1028 ($SO_2$), 697, 634. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H, triazole), 7.83 – 7.31 (m, 10H, Ar), 5.82 (s, 2H, C*H*$_2$), 4.26 (s, 3H, C*H*$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 142.9, 131.3, 130.8, 129.3, 129.0, 128.8, 128.8, 127.7, 121.3, 120.2 (q, *J* = 320.0 Hz), 56.8, 38.1. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{16}H_{16}N_3$: 250.1344; found: 250.1352.

## 6.2 Experimental section of chapter 2

### 6.2.1 General procedure for the synthesis of nonsymmetrically substituted 4,4'-bis(1*H*-1,2,3-triazolium) salts

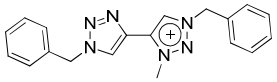
**Method A:**

To a solution of the corresponding azide (1.10 mmol) and 4-ethynyl-1*H*-1,2,3-triazolium salt (1.00 mmol) in *t*BuOH/THF/$H_2O$ 1:1:1 (7 mL) at ambient temperature, sodium ascorbate (0.40 mmol) and $CuSO_4 \cdot 5H_2O$ (0.20 mmol) were added and the mixture was vigorously stirred overnight. The organic volatiles were evaporated at reduced pressure, the aqueous residue was extracted with EtOAc (5 mL x 3) and the combined extracts were dried ($MgSO_4$) and evaporated to afford the crude product, which was purified by column chromatography. In some instances, TBTA (1 mol %) catalyst was used.

**Method B:**

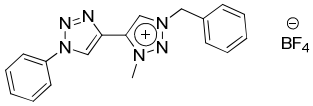
CuOAc (0.20 mmol) and NaOAc (1.00 mmol) were added to a solution of the corresponding azide (1.50 mmol) and 4-ethynyl-1*H*-1,2,3-triazolium salt (1.00 mmol) in MeCN/$H_2O$ 1:1 (2 mL) at ambient temperature and the mixture was stirred vigorously for 5 min. The organic layer was evaporated under vacuo and the crude product was purified by column chromatography.

**4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1-benzyl-3-methyl-1*H*-1,2,3-triazolium tetrafluoroborate**[155]



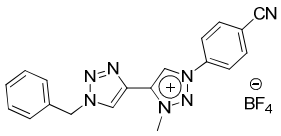
The general procedure 6.2.1 A was followed starting from 1-benzyl-4-ethynyl-3-methyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.18 mmol, 50 mg), benzyl azide (0.20 mmol, 38 mg), $CuSO_4 \cdot 5H_2O$ (0.04 mmol, 9 mg) and sodium ascorbate (0.07 mmol, 14 mg). Yield: 83 mg (95 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 9.00 (s, 1H, triazole), 8.67 (s, 1H, triazole), 7.55 – 7.30 (m, 10H, Ar), 5.71 (s, 2H, C*H*$_2$), 5.55 (s, 2H, C*H*$_2$), 4.55 (s, 3H, C*H*$_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 134.7, 133.7, 131.7, 131.0, 130.1, 129.5, 129.5, 129.1, 129.0, 128.4, 128.2, 126.8, 57.9, 54.6, 40.5.

**1-Benzyl-3-methyl-4-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-1*H*-1,2,3-triazolium tetrafluoroborate**



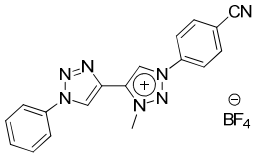
The general procedure 6.2.1 A was followed starting from 1-benzyl-4-ethynyl-3-methyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.18 mmol, 50 mg), phenyl azide (0.20 mmol, 23 mg), $CuSO_4 \cdot 5H_2O$ (0.04 mmol, 9 mg) and sodium ascorbate (0.08 mmol, 14 mg). Yield: 60 mg (83 %). White solid (mp = 184-185 ºC). IR (cm$^{-1}$): 3163, 3128, 1644, 1595, 1457 (triazole), 1022 ($BF_4$). $^1$H NMR (500 MHz, $CDCl_3$) δ 9.33 (s, 1H, triazole), 9.24 (s, 1H, triazole), 7.89 (d, *J* = 8.0 Hz, 2H, Ar), 7.64 – 7.44 (m, 8H, Ar), 5.78 (s, 2H, C*H*$_2$), 4.69 (s, 3H, C*H*$_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 135.9, 134.6, 132.2, 130.8, 130.3, 130.0, 129.8, 129.7, 129.6, 128.9, 125.0, 120.6, 58.2, 40.8. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{18}H_{17}N_6$: 317.1509; found: 317.1513.

**4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1-(4-cyanophenyl)-3-methyl-1*H*-1,2,3-triazolium tetrafluoroborate ($9_{1,4}$)**



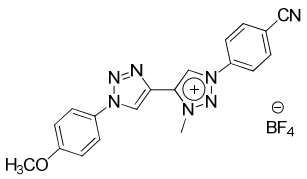
The general procedure 6.2.1 A was followed starting from 1-(4-cyanophenyl)-4-ethynyl-3-methyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.05 mmol, 15 mg), benzyl azide (0.10 mmol, 13 mg), $CuSO_4 \cdot 5H_2O$ (0.01 mmol, 3 mg) and sodium ascorbate (0.02 mmol, 4 mg). Yield: 15 mg (73 %). White solid (mp = 60-61 ºC). IR ($cm^{-1}$): 2234 (C≡N), 1661, 1456, 1435 (triazole), 1048, 996 ($BF_4$), 845,723. $^1$H NMR (500 MHz, MeOH-$d_4$) δ 8.82 (s, 1H, triazole), 8.26 (d, *J* = 8.8 Hz, 2H, Ar), 8.17 (d, *J* = 8.8 Hz, 2H, Ar), 7.44 (m, 5H, Ar), 5.81 (s, 2H, C$H_2$), 4.74 (s, 3H, C$H_3$). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 138.0, 135.9, 135.7, 135.2, 132.0, 129.4, 129.0, 128.7, 127.5, 127.0, 122.8, 118.0, 114.9, 54.0, 41.0. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{19}H_{16}N_7$: 342.1467; found: 342.1470.

**1-(4-Cyanophenyl)-3-methyl-4-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-1*H*-1,2,3-triazolium tetrafluoroborate**



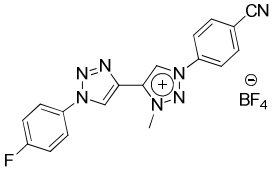
The general procedure 6.2.1 A was followed starting from 1-(4-cyanophenyl)-4-ethynyl-3-methyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.19 mmol, 58 mg), phenyl azide (0.37 mmol, 44 mg), $CuSO_4 \cdot 5H_2O$ (0.04 mmol, 13 mg) and sodium ascorbate (0.08 mmol, 15 mg). Yield: 57 mg (70 %). White solid (mp = 204 ºC dec). IR ($cm^{-1}$): 2228 (C≡N), 1490, 1460 (triazole), 1047, 1031 ($BF_4$), 854, 813, 771, 687, 552. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.25 (s, 1H, triazole), 9.70 (s, 1H, triazole), 8.39 – 8.30 (m, 4H, Ar), 8.06 (d, *J* = 7.9 Hz, 2H, Ar), 7.73 (t, *J* = 7.8 Hz, 2H, Ar), 7.64 (t, *J* = 7.4 Hz, 1H, Ar), 4.71 (s, 3H, C$H_3$). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 138.1, 136.0, 135.2, 132.5, 131.8, 130.6, 130.3, 127.7, 125.0, 123.0, 121.3, 118.0, 114.9, 40.9. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{18}H_{14}N_7$: 328.1311; found: 328.1300.

**1-(4-Cyanophenyl)-4-[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]-3-methyl-1*H*-1,2,3-triazolium tetrafluoroborate**



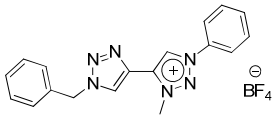
The general procedure 6.2.1 A was followed starting from 1-(4-cyanophenyl)-4-ethynyl-3-methyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.18 mmol, 56 mg), 4-metoxyphenyl azide (0.36 mmol, 54 mg), $CuSO_4 \cdot 5H_2O$ (0.04 mmol, 13 mg) and sodium ascorbate (0.07 mmol, 14 mg). Yield: 58 mg (72 %). White solid (mp = 214 ºC dec). IR ($cm^{-1}$): 2239 (C≡N), 1518, 1505, 1470, 1443 (triazole), 1052, 1033 ($BF_4$), 849, 565, 542, 523. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.23 (s, 1H, triazole), 9.60 (s, 1H, triazole), 8.33 (s, 4H, Ar), 7.96 (d, *J* = 8.6 Hz, 2H, Ar), 7.26 (d, *J* = 8.6 Hz, 2H, Ar), 4.70 (s, 3H, C*H*$_3$), 3.89 (s, 3H, C*H*$_3$O). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 160.6, 138.1, 136.0, 135.2, 132.3, 129.7, 127.6, 124.9, 123.0, 118.0, 115.6, 114.93, 56.2, 40.9. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{19}H_{16}N_7O$: 358.1416; found: 358.1414.

**1-(4-Cyanophenyl)-4-[1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl]-3-methyl-1*H*-1,2,3-triazolium tetrafluoroborate**



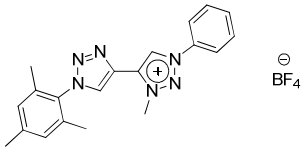
The general procedure 6.2.1 A was followed starting from 1-(4-cyanophenyl)-4-ethynyl-3-methyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.06 mmol, 20 mg), 4-fluorophenyl azide (0.13 mmol, 18 mg), $CuSO_4 \cdot 5H_2O$ (0.01 mmol, 4 mg) and sodium ascorbate (0.02 mmol, 5 mg). Yield: 19 mg (70 %). White solid (mp = 126-127 ºC). IR ($cm^{-1}$): 2234 (C≡N), 1441 (triazole), 1236, 1187 (C-F), 1066, 1033 ($BF_4$), 842, 832, 578, 520, 496. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.27 (s, 1H, triazole), 9.70 (s, 1H, triazole), 8.38 – 8.29 (m, 4H, Ar), 8.17 – 8.07 (m, 2H, Ar), 7.60 (t, *J* = 8.7 Hz, 2H, Ar), 4.70 (s, 3H, C*H*$_3$). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 162.2 (d, *J* = 247.2 Hz), 137.5, 135.3, 134.7, 132.4, 131.9, 127.2, 124.8, 123.3 (d, *J* = 9.0 Hz), 122.4, 117.4, 117.0 (d, *J* = 23.5 Hz), 114.4, 40.4. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{18}H_{13}FN_7$: 346.1216; found: 346.1213.

**4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-3-methyl-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate**



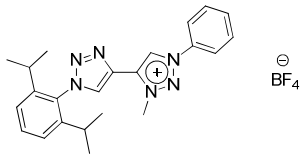
The general procedure 6.2.1 B was followed starting from 4-ethynyl-3-methyl-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.07 mmol, 20 mg), benzylazide (0.11 mmol, 15 mg), CuOAc (0.02, 2 mg) and NaOAc (0.07 mmol, 6 mg) in MeCN/$H_2O$ 1:1 (0.15 mL). Yield: 21 mg (89 %). White solid (mp = 68-70 ºC). IR ($cm^{-1}$): 1491, 1441 (triazole), 1050, 1012 ($BF_4$), 762, 722, 670. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H, triazole), 9.01 (s, 1H, triazole), 8.08 – 7.90 (m, 2H, Ar), 7.73 – 7.54 (m, 3H, Ar), 7.53 – 7.33 (m, 5H, Ar), 5.59 (s, 2H, C$H_2$), 4.74 (s, 3H, C$H_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 135.6, 134.5, 133.7, 132.2, 131.6, 130.6, 129.2, 129.0, 128.6, 127.6, 125.8, 121.2, 54.8, 41.1. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{18}H_{17}N_6$: 317.1515; found: 317.1523.

**3-Methyl-1-phenyl-4-[1-(2,4,6-trimethylphenyl)-1*H*-1,2,3-triazol-4-yl]-1*H*-1,2,3-triazolium tetrafluoroborate**



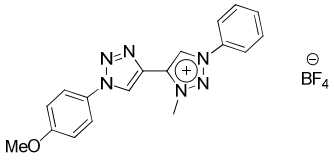
The general procedure 6.2.1 A was followed starting from 4-ethynyl-3-methyl-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.18 mmol, 50 mg), 2,4,6-trimethylphenyl azide (0.36 mmol, 58 mg), $CuSO_4 \cdot 5H_2O$ (0.04 mmol, 13 mg) and sodium ascorbate (0.07 mmol, 14 mg). Yield: 40 mg (64 %). White solid (mp = 226-227 ºC). IR ($cm^{-1}$): 1495, 1468, 1438 (triazole), 1053, 1035, 1021 ($BF_4$), 850, 775, 581. $^1$H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H, triazole), 9.10 (s, 1H, triazole), 8.11 (d, *J* = 6.4 Hz, 2H, Ar), 7.72 (m, 3H, Ar), 7.05 (s, 2H, Ar), 4.92 (s, 3H, C$H_3N_{tri}$), 2.41 (s, 3H, C$H_3$Ar), 2.04 (s, 6H, C$H_3$Ar). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 140.8, 135.6, 134.8, 134.6, 134.5, 132.4, 132.2, 130.6, 130.0, 129.4, 126.2, 121.2, 41.4, 21.1, 17.3. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{20}H_{21}N_6$: 345.1828; found: 345.1820.

**4-[1-(2,6-Diisopropylphenyl)-1*H*-1,2,3-triazol-4-yl]-3-methyl-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate**



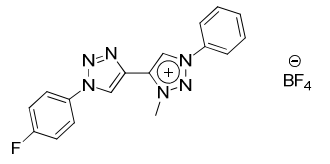
The general procedure 6.2.1 A was followed starting from 4-ethynyl-3-methyl-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.18 mmol, 50 mg), 2,6-diisopropylphenyl azide (0.36 mmol, 73 mg), $CuSO_4 \cdot 5H_2O$ (0.04 mmol, 13 mg) and sodium ascorbate (0.07 mmol, 14 mg). Yield: 59 mg (66 %). White solid (mp = 177-178 ºC). IR ($cm^{-1}$): 1496, 1468 (triazole), 1055, 1028 ($BF_4$), 803, 764, 686. $^1$H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H, triazole), 9.07 (s, 1H, triazole), 8.08 (d, *J* = 2.8 Hz, 2H, Ar), 7.64 (s, 3H, Ar), 7.56 (t, *J* = 7.8 Hz, 1H, Ar), 7.34 (d, *J* = 7.8 Hz, 2H, Ar), 4.90 (s, 3H, C*H*$_3$N$_{tri}$), 2.21 (m, 2H, C*H*CH$_3$), 1.18 (d, *J* = 6.7 Hz, 6H, CHC*H*$_3$), 1.16 (d, *J* = 6.7 Hz, 6H, CHC*H*$_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 146.0, 135.7, 134.8, 132.5, 132.3, 131.9, 131.7, 130.9, 130.8, 126.5, 124.3, 121.5, 41.8, 28.8, 24.4, 24.0. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{23}H_{27}N_6$: 387.2297; found: 387.2301.

**4-[1-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]-3-methyl-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate**



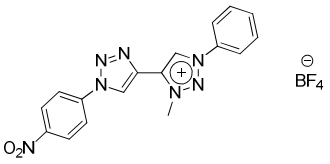
The general procedure 6.2.1 B was followed starting from 4-ethynyl-3-methyl-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.07 mmol, 20 mg), 4-methoxyphenylazide (0.11 mmol, 17 mg), CuOAc (0.02, 2 mg) and NaOAc (0.07 mmol, 6 mg) in MeCN/$H_2O$ 1:1 (0.15 mL). Yield: 26 mg (84 %). White solid (mp = 205-207 ºC). IR ($cm^{-1}$): 1443 (triazole), 1253 (Ar-OMe), 1037 ($BF_4$). $^1$H NMR (500 MHz, MeCN-$d_3$) δ 9.28 (s, 1H, triazole), 9.00 (s, 1H, triazole), 8.04 – 7.92 (m, 2H, Ar), 7.85 (d, *J* = 8.6 Hz, 2H, Ar), 7.82 – 7.69 (m, 3H, Ar), 7.19 (d, *J* = 8.6 Hz, 2H, Ar), 4.66 (s, 3H, C*H*$_3$), 3.91 (s, 3H, OC*H*$_3$). $^{13}$C NMR (126 MHz, MeCN-$d_3$) δ 160.7, 135.6, 135.0, 132.3, 132.0, 130.7, 129.6, 126.3, 124.5, 122.8, 121.8, 115.1, 55.6, 40.6. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{18}H_{17}N_6O$: 333.1464; found: 333.1464.

**4-[1-(4-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl]-3-methyl-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate**



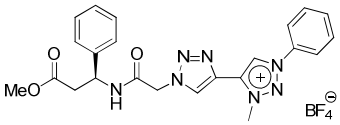
The general procedure 6.2.1 A was followed starting from 4-ethynyl-3-methyl-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.07 mmol, 20 mg), 4-fluorophenyl azide (0.15 mmol, 20 mg), $CuSO_4 \cdot 5H_2O$ (0.01 mmol, 4 mg) and sodium ascorbate (0.03 mmol, 6 mg). Yield: 15 mg (63 %). White solid (mp = 204-205 ºC). IR ($cm^{-1}$): 3139, 1473, 1439 (triazole), 1210, 1559 (C-F), 1035 ($BF_4$), 846, 762, 623, 534. $^1$H NMR (500 MHz, MeCN-$d_3$) δ 9.27 (s, 1H, triazole), 9.04 (s, 1H, triazole), 8.02 – 7.94 (m, 5H, Ar), 7.81 –7.77 (m, 3H, Ar), 7.44 (t, *J* = 8.7 Hz, 2H, Ar), 4.67 (s, 3H, C*H*$_3$). $^{13}$C NMR (126 MHz, MeCN-$d_3$) δ 162.7 (d, *J* = 247.8 Hz), 135.1, 134.6, 132.5, 132.0, 131.9, 130.3, 126.1, 124.4, 123.2 (d, *J* = 9.0 Hz), 121.4, 116.6 (d, *J* = 23.7 Hz), 40.2. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{17}H_{14}FN_6$: 321.1264; found: 321.1265.

**3-Methyl-4-[1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate**



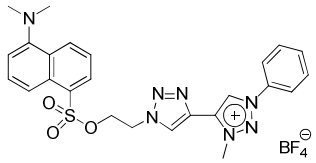
The general procedure 6.2.1 B was followed starting from 4-ethynyl-3-methyl-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.07 mmol, 20 mg), 4-nitrophenylazide (0.11 mmol, 18 mg), CuOAc (0.02, 2 mg) and NaOAc (0.07 mmol, 6 mg) in MeCN/$H_2O$ 1:1 (0.15 mL). Yield: 25 mg (78 %). Yellow solid (mp = 150 ºC dec). IR ($cm^{-1}$): 1527 (Ar-$NO_2$), 1466 (triazole), 1345 (Ar-$NO_2$), 1031 ($BF_4$), 854 (Ar-$NO_2$). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.18 (s, 1H, triazole), 9.90 (s, 1H, triazole), 8.59 (d, *J* = 9.0 Hz, 2H, Ar), 8.39 (d, *J* = 9.0 Hz, 2H, Ar), 8.22 – 8.02 (m, 2H, Ar), 7.88 – 7.73 (m, 3H, Ar), 4.69 (s, 3H, C*H*$_3$). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 147.5, 140.1, 134.8, 134.7, 132.6, 131.9, 130.5, 126.9, 125.7, 124.9, 121.6, 121.4, 40.2. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{17}H_{14}N_7O_2$: 348.1209; found: 348.1205.

**4-{1-[*N*-(1-phenyl-3-methoxycarbonylethyl)carbamoylmethyl]-1*H*-1,2,3-triazol-4-yl}-3-methyl-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate**



The general procedure 6.2.1 A was followed starting from 4-ethynyl-3-methyl-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.11 mmol, 30 mg), (3*S*)-3-(azidoacetamido)-3-phenylpropionic acid methyl ester (0.11 mmol, 29 mg), $CuSO_4 \cdot 5H_2O$ (0.02 mmol, 6 mg) and sodium ascorbate (0.04 mmol, 9 mg). Yield: 40 mg (70 %). Waxy solid. $[\alpha]_D^{20}$ = -35.37º (c= 0.77, $CH_2Cl_2$). IR ($cm^{-1}$): 3365 (NH), 1733 (C=O), 1656 (C=O), 1046, 1027 ($BF_4$). $^1$H NMR (500 MHz, MeCN-$d_3$) δ 9.18 (s, 1H, triazole), 8.60 (s, 1H, triazole), 8.04 – 7.88 (m, 2H, Ar), 7.88 – 7.68 (m, 3H, Ar), 7.55 (d, *J* = 8.2 Hz, 1H, N*H*), 7.48 – 7.25 (m, 5H, Ar), 5.40 – 5.24 (m, 3H, C$H_2$CO, C*H*), 4.61 (s, 3H, C$H_3$), 3.63 (s, 3H, OC$H_3$), 3.04 – 2.80 (m, 3H, C$H_2$COOC$H_3$). $^{13}$C NMR (126 MHz, MeCN-$d_3$) δ 170.5, 164.0, 140.6, 135.1, 134.6, 131.9, 131.0, 130.3, 128.3, 127.4, 127.4, 126.2, 125.9, 121.3, 52.0, 51.1, 50.3, 40.2, 39.7. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{23}H_{24}N_7O_3$: 446.1941; found: 446.1946.

**4-{1-[2-(5-*N*,*N*-Dimethylaminonaphthyl-1-sulfonyloxy)ethyl]-1*H*-1,2,3-triazol-4-yl}-3-methyl-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate**



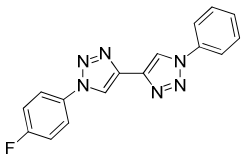
The general procedure 6.2.1 B was followed starting from 4-ethynyl-3-methyl-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.07 mmol, 20 mg), 2-azidoethyl 5-(*N*,*N*-dimethylamino)naphthalene-1-sulfonate (0.11 mmol, 35 mg), CuOAc (0.02, 2 mg) and NaOAc (0.07 mmol, 6 mg) in MeCN/$H_2O$ 1:1 (0.15 mL). Yield: 36 mg (82 %). Yellow solid (mp = 183-184 ºC). IR ($cm^{-1}$): 1466 (triazole), 1350 (C-$SO_2$-OC), 1061, 1023 ($BF_4$). $^1$H NMR (500 MHz, MeCN-$d_3$) δ 9.09 (s, 1H, triazole), 8.63 (d, *J* = 8.6 Hz, 1H, Ar), 8.40 (s, 1H, triazole), 8.27 (d, *J* = 7.4 Hz, 1H, Ar), 8.03 – 7.96 (m, 2H, Ar), 7.94 (d, *J* = 8.8 Hz, 1H, Ar), 7.89 – 7.73 (m, 3H, Ar), 7.66 (t, *J* = 8.0 Hz, 1H, Ar), 7.52 (t, *J* = 8.2 Hz, 1H, Ar), 7.17 (d, *J* = 7.6 Hz, 1H, Ar), 4.78 (t, *J* = 4.9 Hz, 2H), 4.53 (s, 5H, C$H_2$O, C$H_3$), 2.83 (s, 6H, (C$H_3$)$_2$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 152.0, 135.4, 134.9, 132.4, 132.1, 131.2, 131.0, 130.7, 130.3, 129.5, 129.5, 128.9, 126.6, 126.0, 123.5, 121.8, 118.3, 115.2,

68.4, 49.6, 44.7, 40.6. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{25}H_{26}N_7O_3S$: 504.1818; found: 504.1822.

### 6.2.2 General procedure for the synthesis of nonsymmetrically substituted 4,4'-bis(1*H*-1,2,3-triazoles) by *N*-demethylation of 4,4´-bis(1,2,3-triazolium) salts

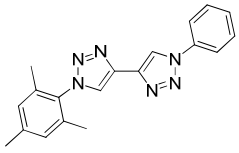
To a solution of the corresponding bis(1,2,3-triazolium) salt (1.00 mmol) and $K_2CO_3$ (5.00 mmol) in $CH_3CN$ (8 mL), thiophenol (10.00 mmol) was added and the mixture was stirred at 100 ºC for 3 hours or at 50 ºC for 18 hours. After this time, the volatiles were evaporated under vacuo, the product was trated with 3M NaOH, extracted with $CH_2Cl_2$ and the organic layers were dried over $MgSO_4$. The product was purified by column chromatography.

**1'-(4-Fluorophenyl)-1-phenyl-4,4'-bis(1*H*-1,2,3-triazole)**



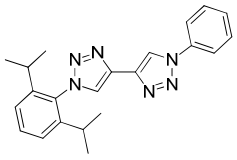
The general procedure 6.2.2 was followed starting from 4-[1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl]-3-methyl-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.06 mmol, 25 mg), $K_2CO_3$ (0.30 mmol, 42 mg) and thiophenol (0.61 mmol, 62 µL). Yield: 14 mg (73 %). White solid (mp = 198-199 ºC). IR ($cm^{-1}$): 1514 (triazole), 1232, 1184 (C-F), 1039, 828, 755, 686, 624, 519. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.32 (s, 1H, triazole), 9.31 (s, 1H, triazole), 8.06 (m, 4H, Ar), 7.65 (t, *J* = 7.2 Hz, 2H, Ar), 7.59 – 7.39 (m, 3H, Ar). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 162.2 (d, *J* = 246.0 Hz), 140.2, 140.1, 137.0, 133.6, 130.4, 129.4, 123.1 (d, *J* = 8.8 Hz), 120.9, 120.7, 120.6, 117.2 (d, *J* = 23.3 Hz). HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{12}FN_6$: 307.1107; found: 307.1112.

**1-Phenyl-1'-(2,4,6-trimethylphenyl)-4,4'-bis(1*H*-1,2,3-triazole)**



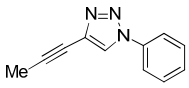
The general procedure 6.2.2 was followed starting from 3-methyl-1-phenyl-4-[1-(2,4,6-trimethylphenyl)-1*H*-1,2,3-triazol-4-yl]-1*H*-1,2,3-triazolium tetrafluoroborate (0.06 mmol, 20 mg), $K_2CO_3$ (0.29 mmol, 40 mg) and thiophenol (0.58 mmol, 59 µL). Yield: 13 mg (68 %). For characterization see section 6.2.2.

**1'-(2,6-Diisopropylphenyl)-1-phenyl-4,4'-bis(1*H*-1,2,3-triazole)**



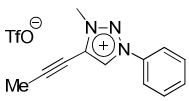
The general procedure 6.2.2 was followed staring from 4-[1-(2,6-diisopropylphenyl)-1*H*-1,2,3-triazol-4-yl]-3-methyl-1-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.04 mmol, 20 mg), $K_2CO_3$ (0.21 mmol, 29 mg) and thiophenol (0.42 mmol, 43 µL). Yield: 13 mg (88 %). For characterization see section 6.2.2.

**1-Phenyl-4-(1-propyn-1-yl)-1*H*-1,2,3-triazole**



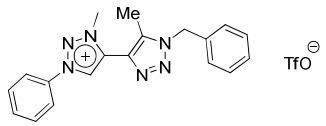
To a solution of 4-ethynyl-1-phenyl-1*H*-1,2,3-triazole (0.59 mmol, 100 mg) in THF (0.6 mL) at -78ºC was added a solution of BuLi in hexane 1.6 M (0.59 mmol, 370 µL) and the reaction mixture was stirred for 1 hour. Then, MeI (0.71 mmol, 44 µL) was added and the reaction mixture was warmed to ambient temperature in 1 h. The mixture was filtered through a celite:silica pad. Yield: 99 mg (92 %). White solid (mp = 103-105 ºC). IR ($cm^{-1}$): 3138 (≡CH), 1631, 1543, 1465 (triazole). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H, triazole), 7.74 (d, *J* = 7.6 Hz, 2H, Ar), 7.56 (t, *J* = 7.6 Hz, 2H, Ar), 7.52-7.44 (m, 1H, Ar), 2.13 (s, 3H, C*H*$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 136.7, 132.3, 129.9, 129.0, 123.5, 120.6, 90.6, 69.0, 4.5. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{11}H_{10}N_3$: 184.0875; found: 184.0879.

**3-Methyl-1-phenyl-4-(1-propyn-1-yl)-1*H*-1,2,3-triazolium trifluoromethanesulfonate (4)**



The general procedure 6.1.6 was followed starting from 1-phenyl-4-(1-propyn-1-yl)-1*H*-1,2,3-triazole (0.23 mmol, 50 mg) and methyl trifluoromethanesulfonate (0.30 mmol, 33 µL) in $CH_2Cl_2$ (1 mL). Yield: quantitative. White solid (mp = 129-130 ºC). IR ($cm^{-1}$): 2263 (C≡C), 1443 (triazole), 1255, 1220, 1158, 1028 ($SO_2$), 633. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H, triazole), 8.06-7.83 (m, 2H, Ar), 7.78-7.45 (m, 3H, Ar), 4.39 (s, 3H, NC*H*$_3$), 2.21 (s, 3H, C≡CC*H*$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 134.5, 132.0, 130.3, 129.4, 128.6, 121.6, 105.1, 60.9, 38.9, 4.9. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{12}H_{12}N_3$: 198.1031; found: 198.1036.

**4-[1-Benzyl-5-methyl-1*H*-1,2,3-triazol-4-yl]-3-methyl-1-phenyl-1*H*-1,2,3-triazolium trifluoromethanesulfonate**

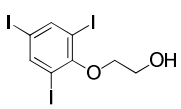


To a solution of 3-methyl-1-phenyl-4-(1-propyn-1-yl)-1*H*-1,2,3-triazolium trifluoromethanesulfonate (0.10 mmol, 35 mg) in toluene (0.6 mL), benzyl azide (0.20 mmol, 27 mg) was added and the mixture was stirred at 130 ºC for 18 hours in an Ace pressure tube. Then, the solvent was evaporated under reduced pressure and the product was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH 95:5). Yield: 29 mg (60%). White solid (mp = 42-45 ºC). IR ($cm^{-1}$): 1455 (triazole), 1252, 1222, 1149, 1028 ($SO_2$), 984, 635. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H, triazole), 8.18 – 7.98 (m, 2H, Ar), 7.73 – 7.52 (m, 3H, Ar), 7.44 – 7.32 (m, 3H, Ar), 7.27 – 7.18 (m, 2H, Ar), 5.57 (s, 2H, C*H*$_2$), 4.68 (s, 3H, C*H*$_3$), 2.52 (s, 3H, C*H*$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 136.6, 135.5, 134.6, 133.4, 132.0, 130.4, 129.5, 129.2, 128.8, 127.4, 125.4, 121.5, 52.3, 40.9, 8.8. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{19}H_{19}N_3$: 331.1671; found: 331.1674.

## 6.3 Experimental section of chapter 3

### 6.3.1 General procedure for the synthesis of aryl ether glycols

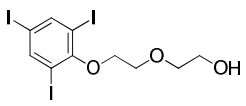
**2-(2,4,6-Triiodophenoxy)ethanol**[159]



To a solution of 2,4,6-triiodophenol (1.27 mmol, 600 mg), NaOH (1.52 mmol, 61 mg) and NaI (1.27 mmol, 190 mg) in EtOH (6.6 mL), 2-bromoethanol (2.54 mmol, 0.18 mL) was added. The reaction mixture was stirred for 6 hours at 150 ºC in an Ace pressure tube. Then, the solvent was evaporated under reduced pressure. A solution of $NH_4Cl$ (sat) (6 mL) was added and the product was extracted with $CH_2Cl_2$ (7 mL x 3). The organic layer was dried over $MgSO_4$ and evaporated to dryness. Yield: quantitative. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 2H, Ar), 4.17 (t, *J* = 4.2 Hz, 2H, C*H*$_2$OAr), 4.13-4.03 (m, 2H, C*H*$_2$OH), 2.27 (t, *J* = 6.3 Hz, 1H, O*H*). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 157.2, 147.3, 91.9, 89.5, 74.4, 62.0.

[159] Prepare according to procedure: Radek, O.; Nemecek, O. Czech Patent **1966**, CS 118450. "Basic 2,4,6-triiodophenol ethers"

**2-[2-(2,4,6-Triiodophenoxy)ethoxy]ethanol**

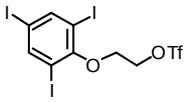


To a solution of 2,4,6-triiodophenol (0.42 mmol, 200 mg) in EtOH (2.2 mL), NaOH (0.38 mmol, 15 mg) was added. The reaction mixture was stirred for 30 min at ambient temperature. Then, the solvent was evaporated under reduced pressure. After that, NaI (0.38 mmol, 57 mg) and 2-(2-chloroethoxy)ethanol (0.38 mmol, 40 µL) in EtOH (2.2 mL) were added. The reaction mixture was stirred for 6 hours at 150 ºC in an Ace pressure tube. Then, the solvent was evaporated under reduced pressure. A solution of NaOH 6M (6 mL) was added and the product was extracted with $CH_2Cl_2$ (7mL x 3). The organic layer was dried over $MgSO_4$ and evaporated to dryness. The product was purified by column chromatography (silica gel, Hex:EtOAc, 1:1). Yield: 103 mg (48 %). White solid (mp = 76-78 ºC). IR ($cm^{-1}$): 1409, 1357, 1236, 1113, 1068, 1042, 1030, 1007 ($CH_2OH$). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 2H, Ar), 4.16 (t, *J* = 4.6 Hz, 2H, C*H*$_2$OAr), 3.99 (t, *J* = 4.6 Hz, 2H, C*H*$_2$CH$_2$OAr), 3.86-3.78 (m, 2H, C*H*$_2$CH$_2$OH), 3.78-3.70 (m, 2H, C*H*$_2$OH). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 158.0, 147.6, 92.2, 89.7, 72.8, 72.5, 70.2, 62.1. HRMS (ESI+): *m/z* $[M+Na]^+$calcd for $C_{10}H_{11}O_3I_3Na$: 582.7740; found: 582.7756.

### 6.3.2 General procedure for the synthesis of alkyl trifluoromethanesulfonates

Trifluoromethanesulfonic anhydride $Tf_2O$ (1.20 mmol) was added to a solution of the corresponding alcohol (1.00 mmol) and $KHCO_3$ (1.40 mmol) in anhydrous $CH_2Cl_2$ (8.6 mL) cooled at 0 ºC and the reaction mixture was stirred for 5-18 hours at ambient temperature. Then, the suspension was filtered through a 0.2 µm PTFE filter and the solvent was evaporated under reduced pressure. Alkyl trifluoromethanesulfonates were isolated but not fully characterized due to their high unstability.

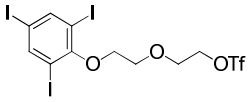
**2-(2,4,6-Triiodophenoxy)ethyl trifluoromethanesulfonate**



The general procedure 6.3.2 was followed starting from 2-(2,4,6-triiodoethoxy)ethanol (0.58 mmol, 300 mg), $KHCO_3$ (0.81 mmol, 81 mg) and $Tf_2O$ (0.70 mmol, 117 µL) in $CH_2Cl_2$ (5 mL). The reaction mixture was stirred for 18 hours. Yield: 355 mg (94 %). White solid (mp = 62-63 ºC). IR ($cm^{-1}$): 1238, 1200, 1141 ($SO_2$), 930, 863, 612. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 2H, Ar), 4.95

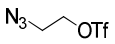
(t, *J* = 4.2 Hz, 2H, C*H*$_2$OTf), 4.32 (t, *J* = 4.2 Hz, 2H, C*H*$_2$OAr). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.6, 147.5, 118.6 (q, *J* = 320.5, 319.9 Hz), 91.5, 90.3, 74.5, 69.2.

**2-[2-(2,4,6-Triiodophenoxy)ethoxy]ethyl trifluoromethanesulfonate**



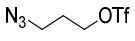
The general procedure 6.3.2 was followed starting from 2-[2-(2,4,6-triiodophenoxy)ethoxy]ethanol (0.05 mmol, 30 mg), $KHCO_3$ (0.08 mmol, 8 mg) and $Tf_2O$ (0.07 mmol, 11 µL) in $CH_2Cl_2$ (1 mL). The reaction mixture was stirred for 18 hours. Yield: quantitative. Black solid (mp = 65-67 ºC). IR (cm$^{-1}$): 1243, 1197, 1138, 1050 ($SO_2$), 915, 860, 608. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 2H, Ar), 4.71 (t, *J* = 4.1 Hz, 2H, C*H*$_2$OAr), 4.18 (t, *J* = 4.6 Hz, 2H, C*H*$_2$CH$_2$OAr), 4.10-3.92 (m, 4H, C*H*$_2$CH$_2$OTf, C*H*$_2$OTf). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 157.7, 147.4, 91.8, 89.5, 75.5, 72.4, 70.4, 68.7.

**2-Azidoethyl trifluoromethanesulfonate**[160]



The general procedure 6.3.2 was followed starting from 2-azidoethanol (1.15 mmol, 100 mg), $KHCO_3$ (1.61 mmol, 161 mg) and $Tf_2O$ (1.44 mmol, 242 µL) in $CH_2Cl_2$ (5 mL). The reaction mixture was stirred for 5 hours. $^1$H NMR (400 MHz, $CDCl_3$) δ 4.63 (t, *J* = 4.8 Hz, 2H, C*H*$_2$OTf), 3.71 (t, *J* = 4.8 Hz, 2H, C*H*$_2$N$_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 118.61 (q, *J* = 319.5 Hz), 74.3, 49.6.

**3-Azidopropyl-1-triflate**[161]

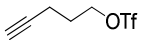


The general procedure 6.3.2 was followed starting from 3-azidopropan-1-ol (0.70 mmol, 72 mg), $KHCO_3$ (0.98 mmol, 98 mg) and $Tf_2O$ (0.88 mmol, 147 µL) in $CH_2Cl_2$ (6 mL). The reaction mixture was stirred for 4 hours. $^1$H NMR (400 MHz, $CDCl_3$) δ 4.66 (t, *J* = 6.2 Hz, 2H, C*H*$_2$OTf), 3.55 (t, *J* = 6.2 Hz, 2H,C*H*$_2$N$_3$), 2.10 (p, *J* = 6.2 Hz, 2H C*H*$_2$CH$_2$N$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 73.7, 46.8, 28.8.

[160] Takaya, T.; Tozuka, Z.; Yasuda, N.; Kawabata, K. 1985, BE 900230 A1 BE 19850128. "Cephem compounds with antimicrobial activity".

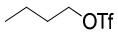
[161] Kramer, J. R.; Deming, T. J. *Biomacromolecules* **2012**, *13*, 1719-1723. "Preparation of multifunctional and multireactive polypeptides via methionine alkylation".

**Hex-5-yn-1-yl triflate**[162]




The general procedure 6.3.2 was followed starting from 4-pentyn-1-ol (0.7 mmol, 65 µL), $KHCO_3$ (0.98 mmol, 91 mg) and $Tf_2O$ (0.88 mmol, 147 µL) in $CH_2Cl_2$ (6 mL). The reaction mixture was stirred for 3 hours. $^1$H NMR (400 MHz, $CDCl_3$) δ 4.70 (t, *J* = 6.2 Hz, 2H, C*H*$_2$OTf), 2.49 – 2.31 (m, 2H C*H*$_2$CCH), 2.15 – 1.97 (m, 3H, C*H*$_2$CHCC*H*). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 120.1 (q, *J* = 324.8 Hz), 82.6, 77.0, 71.7, 29.4, 15.9.

**Butyl triflate**[163]




The general procedure 6.3.2 was followed starting from 1-butanol (0.5 mmol, 46 µL), $KHCO_3$ (0.7 mmol, 70 mg) and $Tf_2O$ (0.62 mmol, 108 µL) in $CH_2Cl_2$ (4 mL). The reaction mixture was stirred for 4 hours. $^1$H NMR (400 MHz, MeCN-$d_3$) δ 4.69 (t, *J* = 6.6 Hz, 2H, C*H*$_2$OTf), 1.84 (p, *J* = 6.6 Hz, 2H, C*H*$_2$CH$_2$OTf), 1.54-1.39 (m, 2H, C*H*$_2$CH$_2$CH$_2$OTf), 0.98 (t, *J* = 7.5 Hz, 3H, C*H*$_3$). $^{13}$C NMR (101 MHz, MeCN-$d_3$) δ 78.9, 30.5, 17.8, 12.3.

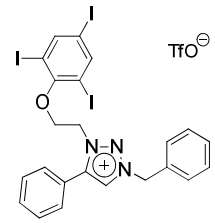
### 6.3.3 General procedure for the synthesis of *N*-alkyl-1*H*-1,2,3-triazolium trifluoromethanesulfonates

To a solution of the corresponding triazole (1.00 mmol) in $CH_2Cl_2$ (8.6 mL) the selected alkyl trifluoromethanesulfonate (1.20 mmol) was added and evaporated under reduced pressure. After 18 hours at 30 ºC the product was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH 95:5).

[162] Hanack, M.; Fuchs, K.-A.; Collins, C. J. *J. Am. Chem. Soc.* **1983**, *105*, 4008-4017. "Vinyl cations. 40. π– and σ-routes to vinyl cations. Solvolyses of 2-methylcyclohexenyl, cyclopentylideneethyl, hex-5-yn-1-yl, and related triflates".

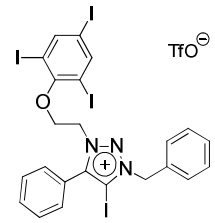
[163] Ross, S. A.; Pitié, M.; Meunier, B. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 571-574. "A straightforward preparation of primary alkyl triflates and their utility in the synthesis of derivatives of ethidium".

**1-Benzyl-4-phenyl-3-[2-(2,4,6-triiodophenoxy)ethyl]-1*H*-1,2,3-triazolium trifluoromethanesulfonate**



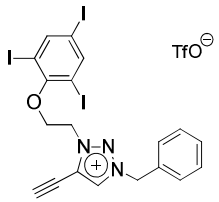
The general procedure 6.3.3 was followed starting from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (0.03 mmol, 8 mg) and 2-(2,4,6-triiodophenoxy)ethyl trifluoromethanesulfonate (0.04 mmol, 25 mg). Yield: 29 mg (98 %). White solid (mp= 67-68 ºC). IR ($cm^{-1}$): 1457 (triazole), 1251, 1223, 1151, 1027 ($SO_2$), 766, 730, 698, 635. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H, triazole), 7.96 (s, 2H, Ar), 7.76 (d, *J* = 7.4 Hz, 2H, Ar), 7.70-7.48 (m, 5H, Ar), 7.48-7.37 (m, 3H, Ar), 5.92 (s, 2H, C*H*$_2$Ar), 5.02 (t, *J* = 4.9 Hz, 2H, C*H*$_2$N$_{trz}$), 4.36 (t, *J* = 5.2 Hz, 2H, C*H*$_2$O). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 155.6, 147.2, 144.9, 131.8, 131.5, 130.2, 130.1, 130.0, 129.5, 128.83, 121.7, 91.5, 90.6, 68.8, 57.9, 50.9. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{23}H_{19}N_3OI_3$: 733.8662; found: 733.8679.

**1-Benzyl-5-iodo-4-phenyl-3-[2-(2,4,6-triiodophenoxy)ethyl]-5-iodo-1*H*-1,2,3-triazolium trifluoromethanesulfonate**



The general procedure 6.3.3 was followed starting from 1-benzyl-5-iodo-4-phenyl-1*H*-1,2,3-triazole (0.03 mmol, 12 mg) and 2-(2,4,6-triiodophenoxy)ethyl trifluoromethanesulfonate (0.04 mmol, 25 mg). Yield: 31 mg (91 %). White solid (mp = 80-83 ºC). IR ($cm^{-1}$): 1455 (triazole), 1235, 1152, 1026 ($SO_2$), 699, 635. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 2H, Ar), 7.71 (d, *J* = 7.3 Hz, 2H, Ar), 7.66-7.52 (m, 5H, Ar), 7.51-7.39 (m, 3H, Ar) 5.85 (s, 2H, C*H*$_2$Ar), 5.04 (t, *J* = 5.0 Hz, 2H, C*H*$_2$N$_{trz}$), 4.30 (t, *J* = 5.0 Hz, 2H, C*H*$_2$O). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.0, 148.9, 147.6, 132.3, 131.6, 131.2, 130.4, 130.1, 129.9, 129.8, 122.7, 91.7, 90.9, 89.8, 68.9, 58.8, 52.4. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{23}H_{18}N_3OI_4$: 859.7629; found: 859.7649.

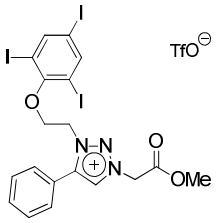
**1-Benzyl-4-ethynyl-3-[2-(2,4,6-triiodophenoxy)ethyl]-1*H*-1,2,3-triazolium trifluoromethane-sulfonate**



The general procedure 6.3.3 was followed starting from 1-benzyl-4-ethynyl-1*H*-1,2,3-triazole (0.05 mmol, 9 mg) and 2-(2,4,6-triiodophenoxy)ethyl trifluoromethanesulfonate (0.06 mmol, 36 mg).

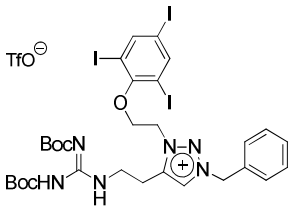
Yield: 35 mg (81 %). White solid (mp = 154-157 ºC). IR ($cm^{-1}$): 2130 (C≡C), 1428 (triazole), 1248, 1223, 1154, 1049 ($SO_2$), 729, 702, 635. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H, triazole), 7.97 (s, 2H, Ar), 7.76-7.54 (m, 2H, Ar), 7.54-7.36 (m, 3H, Ar), 5.93 (s, 2H, C$H_2$Ar), 5.16 (t, *J* = 5.0 Hz, 2H, C$H_2$N$_{trz}$), 4.38 (t, *J* = 5.1 Hz, 2H, C$H_2$O), 4.13 (s, 1H, C≡C*H*). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 155.5, 147.3, 133.0, 131.1, 130.3, 129.9, 129.6, 127.2, 120.6 (q, *J* = 320.2 Hz), 94.4, 91.5, 90.6, 68.2, 64.5, 58.4, 52.3. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{19}H_{15}N_3OI_3$: 681.8349; found: 681.8340.

**1-Methoxycarbonylmethyl-4-phenyl-3-[2-(2,4,6-triiodophenoxy)ethyl]-1*H*-1,2,3-triazolium trifluoromethanesulfonate**




The general procedure 6.3.3 was followed starting from 1-methoxycarbonylmethyl-4-phenyl-1*H*-1,2,3-triazole (0.03 mmol, 7 mg) and 2-(2,4,6-triiodophenoxy)ethyl trifluoromethanesulfonate (0.04 mmol, 25 mg). Yield: 23 mg (79 %). White solid (mp = 52-54 ºC). IR ($cm^{-1}$): 1751 (C=O), 1456 (triazole), 1223, 1153, 1027 ($SO_2$), 674, 635. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H, triazole), 8.04 (s, 2H, Ar), 7.81 (d, *J* = 7.4 Hz, 2H, Ar), 7.70-7.54 (m, 3H, Ar), 5.76 (s, 2H, C$H_2$CO), 5.04 (t, *J* = 5.0 Hz, 2H, C$H_2$N$_{trz}$), 4.43 (t, *J* = 5.0 Hz, 2H, C$H_2$O), 3.90 (s, 3H, C$H_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.6, 155.9, 147.7, 145.3, 132.4, 131.3, 130.6, 130.0, 121.9, 91.9, 91.1, 69.3, 54.5, 54.1, 51.5. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{19}H_{17}N_3O_3I_3$: 715.8404; found: 715.8411.

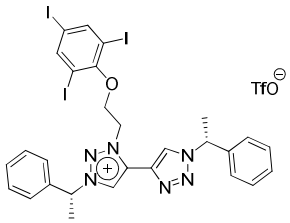
**1-Benzyl-4-{2-[*N*,*N*'-di(*tert*-butoxycarbonyl)guanidyl]ethyl}-3-[2-(2,4,6-triiodophenoxy)ethyl]-1*H*-1,2,3-triazolium trifluoromethanesulfonate**




The general procedure 6.3.3 was followed starting from 1-benzyl-4-{2-[*N*,*N*'-di(*tert*-butoxycarbonyl)guanidyl]ethyl}-1*H*-1,2,3-triazole (0.03 mmol, 15 mg) and 2-(2,4,6-triiodophenoxy)ethyl trifluoromethanesulfonate (0.04 mmol, 25 mg). Yield: 34 mg (92 %). White solid (mp = 73-74 ºC). IR ($cm^{-1}$): 1721, 1638, 1612 (C=O), 1569 (C=O), 1250, 1225, 1150, 1130, 1028 ($SO_2$), 616. $^1$H NMR (400 MHz, $CDCl_3$) δ 11.23 (s, 1H, N*H*Boc), 8.98 (s, 1H, triazole), 8.70 (s, 1H, N*H*), 7.98 (s, 2H, Ar), 7.67-7.51 (m, 2H, Ar), 7.50-7.35 (m, 3H, Ar), 5.83 (s, 2H, C$H_2$Ar), 5.39 (t,

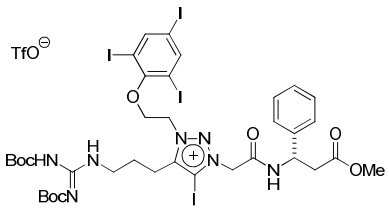
*J* = 4.2 Hz, 2H, C$H_2N_{trz}$), 4.37 (t, *J* = 4.2 Hz, 2H, C$H_2$O), 3.77 (q, *J* = 6.6 Hz, 2H, NHC$H_2CH_2$), 3.38 (t, *J* = 7.0 Hz, 2H, NHC$H_2$C$H_2$), 1.51 (s, 9H, Boc), 1.50 (s, 9H, Boc). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.3, 155.6, 152.6, 147.3, 143.1, 131.5, 130.1, 129.7, 129.6, 91.5, 90.6, 83.8, 79.6, 69.0, 57.8, 50.9, 38.5, 28.4, 28.0, 23.6. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{30}H_{38}N_6O_5I_3$: 943.0038; found: 943.0028.

**4-{1-[(*R*)-α-Methylbenzyl]-1*H*-1,2,3-triazol-4-yl}-1-[(*R*)-α-methylbenzyl]-3-[2-(2,4,6-triiodophenoxy)ethyl]-1*H*-1,2,3-triazolium trifluoromethanesulfonate**



The general procedure 6.3.3 was followed starting from 1,1'-bis[(*R*)-α-methylbenzyl]-3,3'-dimethyl-4,4'-bis(1*H*-1,2,3-triazolium) tetrafluoroborate (0.03 mmol, 12 mg) and 2-(2,4,6-triiodophenoxy)ethyl trifluoromethanesulfonate (0.03 mmol, 22 mg). Yield: 27 mg (81 %). White solid (mp = 54-56 ºC). $[\alpha]_D^{20}$ = -30.16º (c= 0.93, $CH_2Cl_2$). IR ($cm^{-1}$): 1456 (triazole), 1256, 1223, 1150, 1027 ($SO_2$), 698, 636. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H, triazole), 9.16 (s, 1H, triazole), 7.98 (s, 2H, Ar), 7.71-7.56 (m, 3H, Ar), 7.53-7.30 (m, 7H, Ar), 6.14 (q, *J* = 7.2 Hz, 1H, C*H*), 5.92 (q, *J* = 7.2 Hz, 1H, C*H*), 5.64-5.45 (m, 2H, C$H_2N_{trz}$), 4.55-4.37 (m, 2H, C$H_2$Ar), 2.21 (d, *J* = 7.1 Hz, 3H, C$H_3$), 2.06 (d, *J* = 7.1 Hz, 3H, C$H_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 155.6, 147.3, 138.7, 136.0, 135.2, 131.7, 130.2, 129.7, 129.2, 128.9, 127.6, 127.4, 126.7, 126.4, 120.6 (q, *J* = 320.0 Hz), 91.5, 90.5, 68.3, 65.9, 61.6, 53.5, 20.9, 20.1. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{28}H_{26}N_6OI_3$: 842.9302; found: 846.9306.

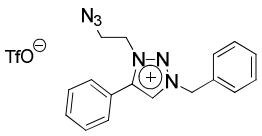
**(*S*)-4-{3-[*N*,*N*'-di(*tert*-butoxycarbonyl)guanidyl]propyl}-3-[2-(2,4,6-triiodophenoxy)ethyl]-1-{*N*-[1-phenyl-2-(methoxycarbonyl)ethyl]carbamoylmethyl}-5-iodo-1*H*-1,2,3-triazolium trifluoromethanesulfonate**



The general procedure 6.3.3 was followed starting from (*S*)-4-{3-[*N*,*N*'-di(*tert*-butoxycarbonyl)guanidyl]propyl}-5-iodo-1-{*N*-[1-phenyl-2-(methoxycarbonyl)ethyl]carbamoylmethyl}-1*H*-1,2,3-triazole (0.03 mmol, 24 mg) and 2-(2,4,6-triiodophenoxy)ethyl trifluoromethanesulfonate (0.04 mmol, 25 mg). Yield: 32 mg (77 %).

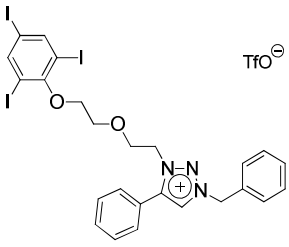
White solid (mp = 108-110 ºC). $[\alpha]_D^{20}$ = -28.35º (c. 0.96, $CH_2Cl_2$). IR ($cm^{-1}$): 1638 (C=O), 1276, 1245, 1155, 1028 ($SO_2$), 637. $^1$H NMR (400 MHz, $CDCl_3$) δ 11.48 (s, 1H, N*H*Boc), 8.88 (d, *J* = 8.3 Hz, 1H, N*H*CO), 8.47 (s, 1H, N*H*$CH_2CH_2CH_2$), 8.00 (s, 2H, Ar), 7.50 – 7.25 (m, 5H, Ar), 5.58 (s, 2H, C$H_2$CONH), 5.39 (q, *J* = 7.6 Hz, 1H, C*H*Ph), 5.17 – 5.02 (m, 2H, C$H_2N_{trz}$), 4.45 – 4.28 (m, 2H, C$H_2$Ar), 3.65 (s, 3H, COOC$H_3$), 3.60 – 3.46 (m, 2H, NHC$H_2CH_2CH_2$), 3.16 – 2.80 (m, 4H, $NHCH_2CH_2CH_2$, $CH_2CO_2Me$), 2.17 – 2.00 (m, 2H, $NHCH_2CH_2CH_2$), 1.51 (s, 18H, Boc). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.9, 163.3, 161.2, 156.5, 155.4, 153.1, 148.9, 147.2, 140.3, 128.7, 127.7, 127.0, 92.0, 90.9, 83.5, 79.5, 69.0, 56.3, 51.9, 51.8, 51.1, 40.2, 39.7, 28.3, 28.1, 27.2, 22.3. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{36}H_{46}N_7O_8I_4$: 1211.9587; found: 1211.9615.

**3-(2-Azidoethyl)-1-benzyl-4-phenyl-1*H*-1,2,3-triazolium trifluoromethanesulfonate**




The general procedure 6.3.3 was followed starting from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (0.14 mmol, 34 mg) and 2-azidoethyl trifluoromethanesulfonate (0.16 mmol, 35 mg). Yield: 30 mg (46 %). Colorless oil. IR ($cm^{-1}$): 2104 (N≡N), 1457 (triazole), 1255, 1224, 1151, 1029 ($SO_2$), 766, 739, 700, 636. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H, triazole), 7.70-7.50 (m, 7H, Ar), 7.50-7.41 (m, 3H, Ar), 5.86 (s, 2H, C$H_2$Ar), 4.68 (t, *J* = 5.7 Hz, 2H, C$H_2N_{trz}$), 3.97 (t, *J* = 5.7 Hz, 2H, C$H_2N_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 144.2, 132.0, 130.8, 130.1, 129.7, 129.6, 129.5, 128.5, 121.4, 58.0, 50.6, 48.7. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{17}H_{17}N_6$: 305.1515; found: 305.1524.

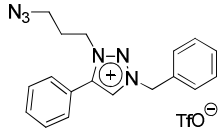
**1-Benzyl-4-phenyl-3-{2-[2-(2,4,6-triiodophenoxy)ethoxy]ethyl}-1*H*-1,2,3-triazolium trifluoromethanesulfonate**




The general procedure 6.3.3 was followed starting from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (0.04 mmol, 10 mg) and 2-[2-(2,4,6-triiodophenoxy)ethoxy]ethyl trifluoromethanesulfonate (0.05 mmol, 32 mg). Yield: 30 mg (77 %). Waxy solid. IR ($cm^{-1}$): 1452 (triazole), 1252, 1223, 1150, 1027 ($SO_2$), 765, 736, 697, 635. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H, triazole), 8.01 (s, 2H, Ar), 7.68 (d, *J* = 7.4 Hz, 2H, Ar), 7.64-7.47 (m,

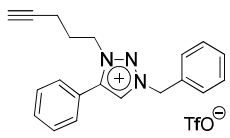
5H, Ar), 7.46-7.36 (m, 3H, Ar), 5.91 (s, 2H, C*H*$_2$Ar ), 4.77 (t, *J* = 5.2 Hz, 2H, C*H*$_2$N$_{trz}$), 4.19 (t, *J* = 5.2 Hz, 2H, C*H*$_2$CH$_2$N$_{trz}$), 4.04 (t, *J* = 4.4 Hz, 2H, C*H*$_2$CH$_2$OAr), 3.90 (t, *J* = 4.4 Hz, 2H, C*H*$_2$OAr). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 157.6, 147.3, 144.4, 131.8, 131.1, 130.0, 130.0, 129.7, 129.6, 129.5, 128.4, 121.8, 91.8, 89.5, 72.1, 70.5, 68.0, 57.9, 51.5. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{25}H_{23}N_3O_2I_3$: 777.8924; found: 777.8936.

**3-(3-Azidopropyl)-1-benzyl-4-phenyl-1*H*-1,2,3-triazolium trifluoromethanesulfonate**



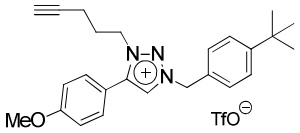

The general procedure 6.3.3 was followed starting from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (0.14 mmol, 34 mg) and 3-azidopropyl trifluoromethanesulfonate (0.16 mmol, 37 mg). Yield: 40 mg (59 %). Colorless oil. IR ($cm^{-1}$): 2100 (N≡N), 1457 (triazole), 1256, 1224, 1152, 1029 ($SO_2$), 766, 736, 700, 636. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H, triazole), 7.73-7.33 (m, 10H, Ar), 5.84 (s, 2H, C*H*$_2$Ar), 4.62 (t, *J* = 6.8 Hz, 2H, C*H*$_2$N$_{trz}$), 3.42 (t, *J* = 6.2 Hz, 2H, C*H*$_2$N$_3$), 2.32-2.07 (m, 3H, C*H*$_2$CH$_2$N$_{trz}$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 143.4, 131.9, 131.0, 130.0, 129.7, 129.5, 129.4, 128.6, 121.6, 57.8, 49.0, 47.7, 27.9. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{18}H_{19}N_6$: 319.1671; found: 319.1682.

**1-Benzyl-4-phenyl-3-(4-pentyn-1-yl)-1*H*-1,2,3-triazolium trifluoromethanesulfonate**



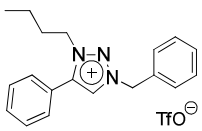

The general procedure 6.3.3 was followed starting from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (0.14 mmol, 34 mg) and hex-5-yn-1-yl triflate (0.16 mmol, 35 mg). Yield: 50 mg (76 %). Colorless oil. IR ($cm^{-1}$): 1458 (triazole), 1256, 1223, 1152, 1030 ($SO_2$), 700, 637. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H, triazole), 7.79 – 7.36 (m, 10H, Ar), 5.87 (s, 2H, C*H*$_2$), 4.68 (t, *J* = 6.9 Hz, 2H, CH$_2$CH$_2$C*H*$_2$N$_{trz}$), 2.34 – 2.25 (m, 2H, C*H*$_2$CH$_2$CH$_2$N$_{trz}$), 2.22 – 2.11 (m, 2H, CH$_2$C*H*$_2$CH$_2$N$_{trz}$), 1.85 (s, 1H, C*H*). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 143.6, 131.9, 131.2, 130.0, 129.8, 129.7, 129.5, 129.5, 128.8, 121.7, 80.7, 70.4, 57.8, 50.6, 27.1, 15.5. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{20}H_{20}N_3$: 302.1657; found: 302.1670.

**1-(4-*tert*-Butylbenzyl)-4-(4-methoxyphenyl)-3-(4-pentyn-1-yl)-1*H*-1,2,3-triazolium trifluoromethanesulfonate**



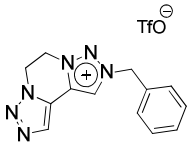
The general procedure 6.3.3 was followed starting from 1-(4-*tert*-buthylbenzyl)-4-(4-metoxyphenyl)-1*H*-1,2,3-triazole (0.16 mmol, 50 mg) and hex-5-yn-1-yl triflate (0.18 mmol, 38 mg). Yield: 70 mg (81 %). Colorless oil. IR ($cm^{-1}$): 1461 (triazole), 1254, 1223, 1180, 1029 ($SO_2$), 637. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H, triazole), 7.64 – 7.41 (m, 6H, Ar), 7.03 (d, *J* = 8.4 Hz, 2H, Ar), 5.79 (s, 2H, C*H*$_2$), 4.67 (t, *J* = 6.8 Hz, 2H, $CH_2CH_2CH_2N_{trz}$), 3.84 (s, 3H. OC*H*$_3$), 2.36 – 2.18 (m, 2H, C*H*$_2$$CH_2CH_2N_{trz}$), 2.21 – 2.08 (m, 2H, $CH_2CH_2CH_2N_{trz}$), 1.87 (s, 1H, C*H*), 1.31 (s, 9H, C*H*$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 162.5, 153.5, 143.8, 131.3, 129.8, 129.7, 128.5, 126.7, 120.4 (q, *J* = 320.0 Hz), 115.5, 113.8, 81.1, 70.6, 57.7, 55.8, 50.8, 35.0, 31.4, 27.3, 15.8. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{25}H_{30}N_3O$: 388.2389; found: 388.2399.

**1-Benzyl-3-butyl-4-phenyl-1*H*-1,2,3-triazolium trifluoromethanesulfonate**



The general procedure 6.3.3 was followed starting from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (0.14 mmol, 34 mg) and butyl trifluoromethanesulfonate (0.16 mmol, 33 mg). Yield: 33 mg (52 %). Colorless oil. IR ($cm^{-1}$): 1458 (triazole), 1256, 1223, 1152, 1029 ($SO_2$), 637. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H, triazole), 7.77-7.35 (m, 10H, Ar), 5.86 (s, 2H, C*H*$_2$Ar), 4.51 (t, *J* = 7.5 Hz, 2H, C*H*$_2$$N_{trz}$), 2.08-1.76 (m, 2H, C*H*$_2$$CH_2N_{trz}$), 1.44-1.11 (m, 2H, C*H*$_2$$CH_3$), 0.88 (t, *J* = 7.5 Hz, 3H, C*H*$_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 143.2, 132.0, 131.4, 130.0, 129.8, 129.6, 129.6, 129.5, 128.9, 122.0, 57.8, 51.7, 30.9, 19.4, 13.2. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{19}H_{22}N_3$: 292.1814; found: 292.1826.

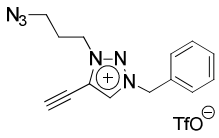
**2-Benzyl-4,5-dihydro-2,3,3a,5a,6,7-hexaaza-indacenium trifluoromethanesulfonate**



The general procedure 6.3.3 was followed starting from 1-benzyl-4-ethynyl-1*H*-1,2,3-triazole (1.09 mmol, 200 mg) and 2-azidoethyl trifluoromethanesulfonate (1.20 mmol, 263 mg) in $CH_3CN$ (4 mL). Yield: 320 mg (73 %). White solid (mp = 106-108 ºC). IR ($cm^{-1}$): 1458 (triazole), 1277,

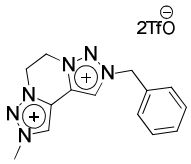
1223, 1130 ($SO_2$), 733, 634. $^1$H NMR (400 MHz, MeCN-$d_3$) δ 8.83 (s, 1H, triazole), 8.29 (s, 1H, triazole), 7.71-7.38 (m, 5H, Ar), 5.88 (s, 3H, C*H*$_3$), 5.20-4.97 (m, 4H, C*H*$_2$C*H*$_2$). $^{13}$C NMR (101 MHz, MeCN-$d_3$) δ 132.2, 131.3, 130.5, 129.6, 129.1, 129.0, 125.7, 121.4, 57.4, 47.4, 43.6. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{13}H_{13}N_6$: 253.1202; found: 253.1203.

**[3-(3-Azidopropyl)-1-benzyl-4-ethynyl-1*H*-1,2,3-triazolium trifluoromethanesulfonate**



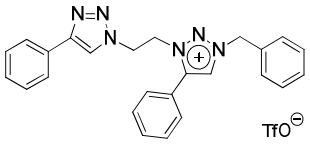

Yield: 75 mg (60 %). Colorless oil. IR ($cm^{-1}$): 3206 (≡CH), 2101 ($N_3$), 1458 (triazole), 1254, 1224, 1153, 1029, 737, 636. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H, triazole), 7.67 – 7.33 (m, 5H, Ar), 5.85 (s, 2H, C*H*$_2$), 4.72 (t, *J* = 6.9 Hz, 2H, C*H*$_2$CH$_2$CH$_2$N$_3$), 4.24 (s, 1H, C≡C*H*), 3.51 (t, *J* = 6.1 Hz, 2H, C*H*$_2$N$_3$), 2.28 (p, *J* = 6.6 Hz, 2H, C*H*$_2$CH$_2$N$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 133.3, 131.0, 130.4, 130.0, 129.8, 126.1, 95.1, 64.3, 58.6, 50.6, 48.0, 28.2.].

**2-Benzyl-3'-methyl-4,5-dihydro-2,3,3a,5a,6,7-hexaaza-indacenium ditrifluoromethanesulfonate**



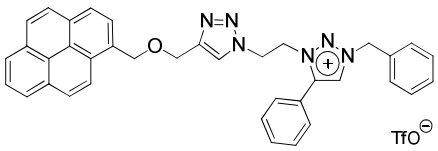

The general procedure 6.1.6 was followed starting from 2-benzyl-4,5-dihydro-2,3,3a,5a,6,7-hexaaza-indacenium trifluoromethanesulfonate (0.08 mmol, 34 mg) and methyl trifluoromethanesulfonate (0.09 mmol, 10 µL) in $CH_2Cl_2$ (0.5 mL). Yield: 40 mg (84 %). White solid (mp = 186-187 ºC). IR ($cm^{-1}$): 1459 (triazole), 1245, 1225, 1161, 1028 ($SO_2$), 709, 637. $^1$H NMR (400 MHz, MeCN-$d_3$) δ 9.15 (s, 1H, triazole), 9.06 (s, 1H, triazole), 7.66 – 7.46 (m, 5H, Ar), 5.94 (s, 2H, C*H*$_2$), 5.30 (s, 4H, C*H*$_2$C*H*$_2$), 4.43 (s, 3H, C*H*$_3$). $^{13}$C NMR (101 MHz, MeCN-$d_3$) δ 130.9, 129.7, 129.7, 129.3, 129.0, 128.8, 126.8, 126.5, 120.4 (q, *J* = 320.0 Hz), 57.9, 46.9, 46.7, 40.9. HRMS (ESI+): *m/z* $[M-H]^+$ calcd for $C_{14}H_{15}N_6$: 267.1358; found: 267.1354.

**1-Benzyl-4-phenyl-3-[2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethyl]-1*H*-1,2,3-triazolium trifluoromethanesulfonate**



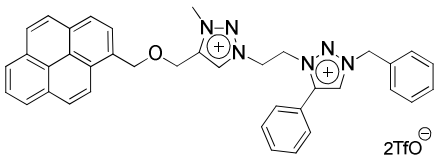
The general procedure 6.1.4 B was followed starting from 3-(2-azidoethyl)-1-benzyl-4-phenyl-1*H*-1,2,3-triazolium trifluoromethanesulfonate (0.06 mmol, 26 mg), phenylacetylene (0.06 mmol, 7 µL), CuOAc (0.01 mmol, 1 mg), NaOAc (0.06 mmol, 5 mg) in $H_2O/CH_3CN$ 1:1 (2 mL). Yield: 22 mg (71 %). Waxy solid. IR ($cm^{-1}$): 1458, 1444 (triazole), 1255, 1223, 1152, 1028 ($SO_2$), 764, 695, 635. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H, triazole), 8.09 (s, 1H, triazole), 7.77 (d, *J* = 7.5 Hz, 2H, Ar), 7.54-7.31 (m, 13H, Ar), 5.75 (s, 2H, C*H*$_2$Ar), 5.18 (t, *J* = 4.8 Hz, 2H, C*H*$_2$N$_{trz}$), 5.01 (t, *J* = 4.8 Hz, 2H, C*H*$_2$N$_{trz}$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 148.4, 144.5, 132.3, 130.6, 130.5, 130.3, 129.9, 129.7, 129.2, 128.6, 128.2, 126.0, 121.9, 121.3, 58.3, 51.6, 48.2. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{25}H_{23}N_6$: 407.1984; found: 407.1996.

**1-Benzyl-4-phenyl-3-{2-[4-(1-pyrenemethylmethylether)-1*H*-1,2,3-triazol-1-yl]ethyl}-1*H*-1,2,3-triazolium trifluoromethanesulfonate**



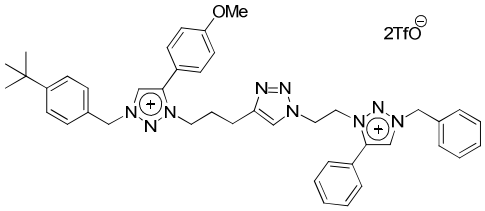
The general procedure 6.1.4 B was followed starting from 3-(2-azidoethyl)-1-benzyl-4-phenyl-1*H*-1,2,3-triazolium trifluoromethanesulfonate (0.10 mmol, 45 mg), 1-((prop-2-yn-1-yloxy)methyl)pyrene (0.11 mmol, 30 mg), CuOAc (0.02 mmol, 2 mg) and NaOAc (0.1 mmol, 9 mg) in $CH_3CN$/THF 2:1 (1.5 mL). Yield: 55 mg (95 %). White solid (mp = 52-54 ºC). IR ($cm^{-1}$): 1457, 1223, 1071, 1223, 1048, 1028, 848, 700, 636. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 9.2 Hz, 1H), 8.20 – 8.12 (m, 2H), 8.12 – 8.05 (m, 2H), 8.05 – 7.94 (m, 5H), 7.74 (s, 1H), 7.40 – 7.17 (m, 10H), 5.52 (s, 2H), 5.23 (s, 2H), 4.98 (t, *J* = 5.5 Hz, 2H), 4.86 (t, *J* = 5.5 Hz, 2H), 4.67 (s, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 145.2, 144.0, 131.8, 131.3, 131.1, 130.7, 130.6, 130.2, 129.9, 129.5, 129.4, 129.3, 129.2, 127.8, 127.4, 127.3, 127.2, 125.9, 125.2, 124.7, 124.6, 124.5, 124.4, 123.3, 120.9, 71.1, 63.2, 57.7, 51.0, 47.6. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{37}H_{31}N_6O$: 575.2559; found: 575.2564.

**1-Benzyl-4-phenyl-3-{2-[3-methyl-4-(1-pyrenemethylmethylether)-1*H*-1,2,3-triazol-1-ium]ethyl}-1*H*-1,2,3-triazolium ditrifluoromethanesulfonate**



The general procedure 6.1.6 was followed starting from 1-benzyl-4-phenyl-3-{2-[4-(1-pyrenemethylmethylether)-1*H*-1,2,3-triazol-1-yl]ethyl}-1*H*-1,2,3-triazolium trifluoromethanesulfonate (0.09 mmol, 51 mg) and methyl trifluoromethanesulfonate (0.1 mmol, 11 µL) in $CH_2Cl_2$ (0.7 mL). Yield: 40 mg (77 %). Waxy solid. IR ($cm^{-1}$): 1462 (triazole), 1257, 1153, 1027 ($SO_2$), 738, 635. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.33 (s, 1H, triazole), 8.79 (s, 1H, triazole), 7.81 – 7.40 (m, 19H, Ar), 5.93 (s, 2H, C*H*$_2$Ph), 5.38 – 5.14 (m, 4H, C*H*$_2$C*H*$_2$), 4.73 (s, 2H, C*H*$_2$OCH$_2$Pyr), 4.14 (s, 3H, C*H*$_3$), 3.18 (s, 2H, CH$_2$OC*H*$_2$Pyr). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 143.9, 143.2, 132.5, 131.8, 129.7, 129.6, 129.5, 129.4, 129.1, 129.1, 127.9, 125.2, 121.8, 120.7 (d, *J* = 320.0 Hz), 56.7, 52.0, 50.9, 49.7, 48.6, 38.0. HRMS (ESI+)/MALDI-MS: *m/z* found: 262.1334, 285.1452, 525.1518.

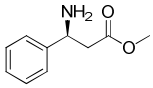
**1-[2-(1-Benzyl-4-phenyl-1*H*-1,2,3-triazol-3-ium)ethyl]-4-{3-[1-(4-*tert*-butylbenzyl)-4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-3-ium]propyl}-1*H*-1,2,3-triazolium ditrifluoromethanesulfonate**



The general procedure 6.1.4 B was followed starting from 3-(2-azidoethyl)-1-benzyl-4-phenyl-1*H*-1,2,3-triazolium trifluoromethanesulfonate (0.06 mmol, 27 mg), 1-(4-*tert*-butylbenzyl)-4-(4-methoxyphenyl)-3-(4-pentyn-1-yl)-1*H*-1,2,3-triazolium trifluoromethanesulfonate (0.06 mmol, 32 mg), CuOAc (0.01 mmol, 1 mg) and NaOAc (0.12 mmol, 11 mg) in $CH_3CN/^tBuOH/H_2O$ 1:1:0.1 (1.7 mL). Yield: 32 mg (77 %). Colorless oil. IR ($cm^{-1}$): 1459 (triazole), 1254, 1223, 1150, 1028 ($SO_2$), 636. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H, triazole), 8.32 (s, 1H, triazole), 7.65 (s, 1H, triazole), 7.63 – 7.33 (m, 16H), 6.99 (d, *J* = 8.2 Hz, 2H, Ar), 5.81 (s, 2H, C*H*$_2$Ar), 5.77 (s, 2H, C*H*$_2$Ar), 5.09 (t, *J* = 4.9 Hz, 2H, C*H*$_2$CH$_2$N$_{trz}$), 4.90 (t, *J* = 4.9 Hz, 2H, CH$_2$C*H*$_2$N$_{trz}$), 4.53 (t, *J* = 7.0 Hz, 2H, C*H*$_2$CH$_2$CH$_2$N$_{trz}$), 3.81 (s, 3H, OC*H*$_3$), 2.68 (t, *J* = 7.0 Hz, 2H, CH$_2$CH$_2$C*H*$_2$N$_{trz}$), 2.40 – 2.22 (m, 2H, CH$_2$C*H*$_2$CH$_2$N$_{trz}$), 1.31 (s, 9H, C*H*$_3$). $^{13}$C NMR (101

MHz, $CDCl_3$) δ 162.5, 153.7, 145.8, 144.3, 143.6, 132.2, 131.2, 131.0, 130.3, 130.0, 129.9, 129.8, 129.8, 129.6, 128.7, 128.2, 128.0, 126.8, 123.8, 121.4, 120.4 (q, *J* = 320.0 Hz), 115.5, 113.8, 58.2, 57.7, 55.8, 51.6, 51.1, 48.2, 35.0, 31.4, 28.2, 22.1. HRMS (ESI+): *m/z* $[M]^{2+}$ calcd for $C_{42}H_{47}N_9O$: 346.6952; found: 346.6960.

**(*S*)-Methyl 3-amino-3-phenylpropanoate**[164]

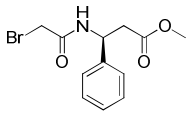



To a solution of benzaldehyde (47.30 mmol, 4.81 mL) in EtOH (50 mL), $NH_4OAc$ (94.60 mmol, 7.29 g) was added and the mixture was stirred at 45 ºC for 12 hours. Then, a solution of malonic acid (47.30 mmol, 4.92 g) in EtOH (25 mL) was added, the mixture was stirred at 60 ºC for 18 hours and followed by a reflux for 6 hours. Upon completion, the reaction mixture was slowly cooled at 5 ºC to give a precipitate which was collected by filtration, washed with cold EtOH and dried in vacuo to afford the intermediate 3-amino-3-phenylpropionic acid. To a solution of the later acid in MeOH (25 mL) cooled at 5 ºC, $SOCl_2$ (34.29 mmol, 2.50 mL) was added dropwise and the mixture was stirred at room temperature for 18 h. Then, the solution was refluxed for 2 hours and concentrated to dryness. To the white residue 2 M $Na_2CO_3$ (20 mL) was added and the product was extracted with EtOAc (20 mL x 3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, to afford the racemic (±)-methyl 3-amino-3-phenylpropanoate. Yield: 4.00 g (47 %).

To a refluxing solution of (+)-L-tartaric acid (5.60 mmol, 0.84 g) in MeOH (6 mL) a solution of (±)-methyl 3-amino-3-phenylpropanoate (5.60 mmol, 1.00 g) in MeOH (5 mL) was added. The (*S*)-amine L-tartrate salt was crystallized at -20 ºC for 18 hours and was filtered off. To liberate the amine, the tartrate was dissolved in 1M NaOH and extracted with $CH_2Cl_2$ (20 mL x 3). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Yield: 250 mg (50 %). $[\alpha]^{25}_D$ = -15.6 (*c* = 1, $CH_2Cl_2$) (Lit.[164] $[\alpha]^{22}_D$ = -20.3 (*c* = 1.53, $CHCl_3$)). IR ($cm^{-1}$): 3377, 1436, 1729 (C=O). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.25 (m, 5H, Ar), 4.46 (t, *J* = 6.9 Hz, 1H, $NH_2CH$), 3.71 (s, 3H, $COOCH_3$), 2.72 (d, *J* = 6.9 Hz, 2H, $CH_2$), 2.19 (s, 2H, $NH_2$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.3, 144.8, 128.6, 127.4, 126.2, 52.6, 51.5, 43.9.

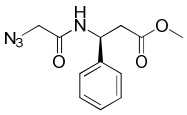
[164] Kuehne, P.; Linden, A.; Hesse, M. *Helv. Chim. Acta* **1996**, *79*, 1085-1094. "Asymmetric synthesis of the alkaloids mayfoline and *N*(1)-acetyl-*N*(1)-dexymayfoline".

**(*S*)-(3-Bromoacetamido)-3-phenylpropionic acid methyl ester**[165]



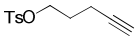
To a solution of (*S*)-β-phenylalanine (0.92 mmol, 165 mg) and $Et_3N$ (0.92 mmol, 128 µL) in anhydrous $CH_2Cl_2$ (1 mL) at -10 ºC, bromoacetyl chloride (0.92 mmol, 77 µL) was added. The mixture was stirred at -10 ºC for 15 min and then warmed up to room temperature for 30 min. Then, the mixture was washed successively with 5 % HCl and brine. The organic layer was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Yield: 272 mg (98 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 6.2 Hz, 1H, Ar), 7.41 – 7.26 (m, 4H, Ar), 5.51 - 5.37 (m, 1H, $NH_2CH$), 3.94 (d, *J* = 6.0 Hz, 2H, $BrCH_2$), 3.67 (s, 3H, $COOCH_3$), 3.02 - 2.85 (m, 2H, $CH_2$).

**(*S*)-3-(Azidoacetamido)-3-phenylpropionic acid methyl ester**[165]



To a solution of **X** (0.91 mmol, 273 mg) in DMF (4.5 mL), $NaN_3$ (2.73 mmol, 177 mg) was added and the mixture was stirred at 80 ºC for 16 hours. Then, $H_2O$ was added and the solution was extracted with $Et_2O$. The organic layer was dried over $MgSO_4$, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel, Hex/EtOAc 1:1). Yield: 197 mg (83 %). $[\alpha]^{22}_D$ = -15.3 (c = 0.38, $CH_2Cl_2$). IR ($cm^{-1}$): 3291, 2102 ($N_3$), 1733 (C=O), 1656 (C=O). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.6 Hz, 1H, Ar), 7.43 – 7.18 (m, 4H, Ar), 5.43 (q, *J* = 6.7 Hz, 1H, $NH_2CH$), 4.03 – 3.86 (m, 2H, $N_3CH_2$), 3.63 (s, 3H, $COOCH_3$), 3.01 – 2.76 (m, 2H, $CH_2$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 171.1, 165.9, 139.8, 128.6, 127.7, 126.1, 52.4, 51.7, 49.5, 39.6.

**4-Pentyn-1-yl *p*-toluenesulfonate**[166]



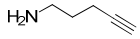
To a solution of 4-pentyn-1-ol (59.44 mmol, 5.53 mL) and $Et_3N$ (89.16 mmol, 12.42 mL) in anhydrous $CH_2Cl_2$ (60 mL) at 0 ºC, *p*-toluenesulfonyl chloride (59.44 mmol, 11.33 g) was added dropwise. The mixture was stirred at ambient temperature for 16 hours. Then, the mixture was washed with a saturated aqueous solution of $NH_4Cl$. The

[165] Trabocchi, A.; Menchi, G.; Cini, N.; Bianchini F.; Raspanti, S.; Bottoncetti, A.; Pupi, A.; Calorini, L.; Guarna, A. *J. Med. Chem.* **2010**, *53*, 7119-7128. "Click-chemistry-derived triazole ligands of arginine-glycine-aspartate (RGD) integrins with a broad capacity to inhibit adhesion of melanoma cells and both in vitro and in vivo angiogenesis".

[166] Hayashi, K.; Tanimoto, H.; Zhang, H.; Morimoto, T.; Nishiyama, Y.; Kakiuchi, K. *Org. Lett.* **2012**, *14*, 5728-5731. "Efficient synthesis of α,β-unsaturated alkylimines performed with allyl cations and azides: application to the synthesis of an ant venom alkaloid".

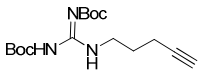
organic layer was dried over $MgSO_4$, the solvent was evaporated and the crude product was purified by column chromatography (silica gel, Hex/EtOAc 10:1). Yield: 12.30 g (87 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 2H, Ar), 7.37 (d, *J* = 8.0 Hz, 2H, Ar), 4.17 (t, *J* = 6.1 Hz, 2H, TsOC*H*$_2$), 2.47 (s, 3H, C*H*$_3$), 2.39 – 2.20 (m, 2H, C*H*$_2$C≡CH), 1.99 – 1.79 (m, 3H, C*H*$_2$CH$_2$C≡CH, C≡C*H* ). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 144.7, 132.7, 129.7, 127.7, 81.9, 69.3, 68.6, 27.5, 21.4, 14.4.

**4-Pentyn-1-amine**[167]



4-Pentyn-1-yl *p*-toluenesulfonate (25.12 mmol, 6.00 g) was dissolved in a 7N ammonia solution in methanol (100 mL). The mixture was stirred at 60 ºC for 24 hours in an Ace pressure tube. Then, volatiles were evaporated under reduced pressure, the crude was dissolved in $CH_2Cl_2$ and KOH (25.12 mmol, 1.41 g) was added until basic pH to obtain the free amine. The suspension was filtered trough a celite:silica (1:1) pad and the solvent was carefully removed under vacuo avoiding complete dryness to prevent the evaporation of the amine. The product was used in the next reaction without further purification. $^1$H NMR (500 MHz, $CDCl_3$) δ 2.80 (t, *J* = 6.8 Hz, 2H, NH$_2$C*H*$_2$), 2.25 (td, *J* = 6.8 Hz, *J* = 2.4 Hz, 2H, C*H*$_2$C≡CH), 1.94 (t, *J* = 2.4 Hz, 1H, CH$_2$C≡C*H*), 1.65 (p, *J* = 6.8 Hz, 2H, NH$_2$CH$_2$C*H*$_2$).

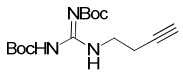
***N*,*N*'-Di(*tert*-butoxycarbonyl)-*N*''-(4-pentyn-1-yl)-guanidine**[165]



A solution of 4-pentyn-1-amine (25.18 mmol, 2.01 g), DMAP (2.52 mmol, 308 mg) and 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (25.18 mmol, 7.31 g) in anhydrous $CH_2Cl_2$ (100 mL) was stirred at 60 ºC for 18 hours in an Ace pressure tube. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel, Hex/EtOAc 10:1). Yield: 6.80 g (83 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 11.50 (s, 1H, N*H*Boc), 8.39 (s, 1H, N*H*), 3.52 (q, *J* = 7.1 Hz, 2H, NHC*H*$_2$), 2.26 (td, *J* = 7.1, 2.5 Hz, 2H, C*H*$_2$C≡CH), 1.98 (t, *J* = 2.5 Hz, 1H, CH$_2$C≡C*H*), 1.81 (p, *J* = 7.1 Hz, 2H, NHCH$_2$C*H*$_2$), 1.50 (s, 9H, Boc), 1.49 (s, 9H, Boc). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.5, 156.2, 153.2, 83.0, 79.2, 69.2, 39.7, 28.2, 28.0, 27.8, 16.0.

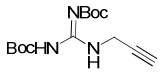
[167] Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295-9306. "Organolanthanide-catalyzed intramolecular hydroamination/cyclization of aminoalkynes".

***N,N'*-Di(*tert*-butoxycarbonyl)-*N''*-(3-butyn-1-yl)-guanidine**[165]



A solution of 3-butyn-1-amine (14.47 mmol, 1.18 mL), DMAP (1.45 mmol, 177 mg) and 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (14.47 mmol, 4.20 g) in anhydrous $CH_2Cl_2$ (58 mL) was stirred at 35 ºC for 72 hours in an Ace pressure tube and then at 40 ºC for 18 hours. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel, Hex/EtOAc 10:1). Yield: 2.88 g (64 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 11.47 (s, 1H, N*H*Boc), 8.58 (s, 1H, N*H*), 3.58 (q, *J* = 6.3 Hz, 2H, NHC$H_2$CH$_2$), 2.45 (td, *J* = 6.3, 2.9 Hz, 2H, NHCH$_2$C$H_2$), 2.04 (t, *J* = 2.9 Hz, 1H, C*H*), 1.48 (s, 18H, Boc). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.3, 156.0, 152.9, 83.0, 80.9, 79.2, 70.2, 39.3, 28.2, 27.9, 19.0.

***N,N'*-Di(*tert*-butoxycarbonyl)-*N''*-propargyl-guanidine**[165]



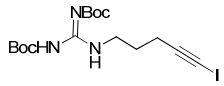
A solution of propargylamine (32.73 mmol, 2.24 mL), DMAP (2.52 mmol, 308 mg) and 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (25.18 mmol, 7.31 g) in anhydrous $CH_2Cl_2$ (100 mL) was stirred at 35 ºC for 72 hours and then at 40 ºC for 18 hours in an Ace pressure tube. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel, Hex/EtOAc 10:1). Yield: 6.67 g (89 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 11.44 (s, 1H, N*H*Boc), 8.45 (s, 1H, N*H*), 4.36 – 4.08 (m, 2H, C$H_2$), 2.27 (s, 1H, C*H*), 1.49 (s, 18H, Boc). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.1, 155.5, 152.9, 83.3, 79.5, 78.7, 72.2, 30.6, 28.1, 27.9.

### 6.3.4 General procedure for the synthesis of iodoalkynes from *N*-alkynylguanidines

A suspension of the corresponding alkyne (1.00 mmol), *N*-iodomorpholine[168] (1.30 mmol) and CuI (0.05 mmol) in anhydrous THF (6 mL) was stirred at room temperature for 1 hour. The organic solvent was evaporated under reduced pressure, $CH_2Cl_2$ was added and the mixture was washed with a saturated aqueous solution of $NH_4Cl$ (4 mL x 3). Evaporation of the solvent yielded a product which was further used without additional purification.

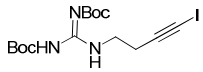
[168] Rice, R. V.; Beal, G. D. *US Patent 2.290.710*, **1943**.

***N,N'*-Di(*tert*-butoxycarbonyl)-*N''*-(5-iodo-4-pentyn-1-yl)-guanidine**



The general procedure 6.3.4 was followed starting from *N,N'*-di(*tert*-butoxycarbonyl)-*N''*-(4-pentyn-1-yl)-guanidine (2.46 mmol, 800 mg), *N*-iodomorpholine (3.20 mmol, 1.09 g) and CuI (0.12 mol, 23 mg) in THF (14 mL). Yield: quantitative. Yellow solid (mp = 162-163 ºC). IR ($cm^{-1}$): 3327 (NH), 2976, 1723 (C=O), 642, 553 (C-I). $^1$H NMR (500 MHz, $CDCl_3$) δ 11.47 (s, 1H, N*H*Boc), 8.37 (s, 1H, N*H*), 3.50 (t, *J* = 6.8 Hz, 2H, NHC$H_2$), 2.44 (t, *J* = 7.0 Hz, 2H, C$H_2$C≡CI), 1.84 – 1.75 (m, 2H, $CH_2CH_2CH_2$), 1.49 (s, 18H, Boc). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.6, 156.3, 153.3, 93.1, 83.2, 79.4, 40.0, 28.4, 28.2, 28.0, 18.6, -5.1. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{27}N_3O_4I$: 452.1046; found: 452.1025.

***N,N'*-Di(*tert*-butoxycarbonyl)-*N''*-(4-iodo-3-butyn-1-yl)-guanidine**

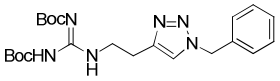


The general procedure 6.3.4 was followed starting from *N,N'*-di(*tert*-butoxycarbonyl)-*N''*-(3-butyn-1-yl)-guanidine (0.16 mmol, 50 mg), *N*-iodomorpholine (0.21 mmol, 72 mg) and CuI (8 µmol, 1.5 mg) in THF (1 mL). Yield: 62 mg (86 %). Yellow solid (mp = 142-143 ºC). IR ($cm^{-1}$): 3327 (NH), 2978, 1718 (C=O), 644, 625, 550 (C-I). $^1$H NMR (400 MHz, $CDCl_3$) δ 11.48 (s, 1H, N*H*Boc), 8.62 (s, 1H, N*H*), 3.59 (q, *J* = 6.5 Hz, 2H, NHC$H_2$), 2.66 (t, *J* = 6.5 Hz, 2H, C$H_2$C≡CI), 1.52 (s, 9H, Boc), 1.51 (s, 9H, Boc). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 163.4, 156.1, 153.0, 91.1, 83.1, 79.3, 39.4, 28.2, 28.0, 21.4, -3.9. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{15}H_{25}N_3O_4I$: 438.0890; found: 438.0895.

### 6.3.5 General procedure for the synthesis of 1-substituted-4-{ω-[4-*N,N'*-di(*tert*-butoxycarbonyl)-guanidyl]-alkyl}-1*H*-1,2,3-triazoles

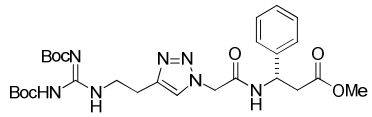
A suspension of the corresponding alkyne (1.00 mmol), the selected azide (1.00 mmol), CuI (1.00 mmol) and DIPEA (1.00 mmol) in anhydrous MeCN (6 mL) was stirred under $N_2$ for 24 hours at ambient temperature. The solvent was evaporated under reduced pressure, $CH_2Cl_2$ was added and the product was washed with a saturated aqueous solution of $NH_4Cl$. The organic layer was dried over $MgSO_4$, the solvent was evaporated and the resulting mixture product was purified by column chromatography.

**1-Benzyl-4-{2-[*N*,*N*'-di(*tert*-butoxycarbonyl)-guanidyl]-ethyl}-1*H*-1,2,3-triazole**



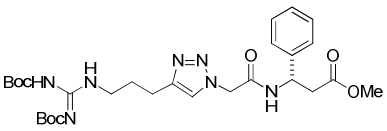
The general procedure 6.3.5 was followed starting from *N*,*N*'-di(*tert*-butoxycarbonyl)-*N*''-(4-butyn-1-yl)-guanidine (1.61 mmol, 500 mg), benzyl azide (1.61 mmol, 214 mg), CuI (1.61 mol, 306 mg) and DIPEA (1.61 mmol, 281 µL) in MeCN (10 mL) to afford the crude product, which was purified by column chromatography (silica gel, Hex/EtOAc 1:1). Yield: 633 mg (89 %). White solid (mp = 139-140 ºC). IR ($cm^{-1}$): 3328 (NH), 1714 (C=O), 1153, 1130. $^1$H NMR (400 MHz, $CDCl_3$) δ 11.48 (s, 1H, N*H*Boc), 8.59 (s, 1H, N*H*), 7.49-7.22 (m, 6H, triazole, Ar), 5.53 (s, 2H, C$H_2$Ar), 3.79 (q, *J* = 6.5 Hz, 2H, NHC$H_2$CH$_2$), 3.01 (t, *J* = 6.9 Hz, 2H, NHCH$_2$C$H_2$), 1.52 (s, 9H, Boc), 1.51 (s, 9H, Boc). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 163.0, 155.6, 152.4, 144.5, 134.5, 128.4, 128.0, 127.3, 121.2, 82.4, 78.4, 53.3, 39.5, 27.7, 27.4, 25.0. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{22}H_{33}N_6O_4$: 445.2563; found: 445.2570.

**(*S*)-4-{2-[*N*,*N*'-Di(*tert*-butoxycarbonyl)-guanidyl]-ethyl}-1-{*N*-[1-phenyl-2-(methoxycarbonyl)ethyl]carbamoylmethyl}-1*H*-1,2,3-triazole**[165]



The general procedure 6.3.5 was followed starting from *N*,*N*'-di(*tert*-butoxycarbonyl)-*N*''-(3-butyn-1-yl)-guanidine (0.42 mmol, 130 mg), the azide **X** (0.42 mmol, 110 mg), CuI (0.46 mmol, 88 mg) and DIPEA (1.05 mmol, 184 µL) in MeCN (18 mL) to afford the crude product, which was purified by column chromatography (silica gel, Hex/EtOAc 1:4). Yield: 117 mg (49 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 11.47 (s, 1H, N*H*Boc), 8.52 (s, 1H, N*H*), 7.61 (s, 1H, triazole), 7.56 (d, *J* = 8.2 Hz, 1H, N*H*CO), 7.32 – 7.18 (m, 5H, Ar), 5.42 – 5.30 (m, 1H, C*H*Ph), 5.05 (dd, *J* = 25.4, 16.2 Hz, 2H, C$H_2$CONH), 3.82 – 3.65 (m, 2H, NHC$H_2$CH$_2$), 3.56 (s, 3H, CO$_2$C$H_3$), 3.01 (t, *J* = 6.9 Hz, 2H, NHCH$_2$C$H_2$), 2.86, 2.78 (dd, dd, *J* = 15.7, 6.1 Hz, 2H, C$H_2$CO$_2$Me), 1.49 (s, 9H, Boc), 1.47 (s, 9H, Boc). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 171.2, 164.7, 163.4, 156.2, 153.1, 145.4, 139.9, 128.8, 127.9, 126.3, 123.4, 83.2, 79.5, 52.9, 52.0, 50.3, 40.2, 39.9, 28.4, 28.1, 25.6.

**(*S*)-4-{3-[*N*,*N'*-Di(*tert*-butoxycarbonyl)-guanidyl]-propyl}-1-{*N*-[1-phenyl-2-(methoxycarbonyl)ethyl]carbamoylmethyl}-1*H*-1,2,3-triazole**[165]



The general procedure 6.3.5 was followed starting from *N*,*N'*-di(*tert*-butoxycarbonyl)-*N''*-(4-pentyn-1-yl)-guanidine (0.31 mmol, 100 mg), the azide **X** (0.31 mmol, 80 mg), CuI (0.31 mmol, 59 mg) and DIPEA (0.31 mmol, 54 µL) in MeCN (2.50 mL) to afford the crude product, which was purified by column chromatography (silica gel, Hex/EtOAc 1:4). Yield: 90 mg (50 %). $^{1}$H NMR (500 MHz, $CDCl_3$) δ 11.50 (s, 1H, N*H*Boc), 8.43 (s, 1H, N*H*), 7.71 (s, 1H, triazole), 7.34 – 7.18 (m, 5H, Ar), 5.39 (dd, *J* = 13.7, 6.4 Hz, 1H, C*H*Ph), 5.06 (s, 2H, C$H_2$CONH), 3.58 (s, 3H, COOC$H_3$), 3.47 (d, *J* = 5.9 Hz, 2H, NHC$H_2$C$H_2$C$H_2$), 2.91 – 2.77 (m, 4H, NHC$H_2$C$H_2$C$H_2$, C$H_2$CO$_2$Me), 1.98 (p, *J* = 7.0 Hz, 2H, NHC$H_2$C$H_2$C$H_2$), 1.51 (s, 9H, Boc), 1.50 (s, 9H, Boc). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 171.2, 164.9, 163.6, 156.5, 153.4, 147.9, 140.0, 129.0, 128.0, 126.4, 123.4, 83.4, 79.6, 53.2, 52.1, 50.2, 40.0, 39.9, 29.0, 28.5, 28.3, 22.9.

### 6.3.6 General procedure for the synthesis of 5-iodo-1,4,5-trisubstituted-1,2,3-triazoles

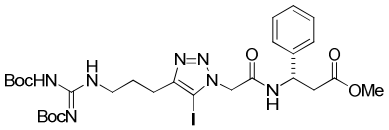
**Method A:**

A suspension of the corresponding alkyne (1.00 mmol), the selected azide (1.00 mmol), CuI (1.10 mmol), *N*-bromosuccinimide (1.20 mmol) and DIPEA (1.10 mmol) in anhydrous MeCN (6 mL) was stirred under $N_2$ for 4 hours at ambient temperature. The solvent was evaporated under reduced pressure and the resulting product was purified by column chromatography (silica gel, Hex/EtOAc).

**Method B:**

A suspension of the corresponding iodoalkyne (1.20 mmol), the selected azide (1.00 mmol), CuI (1.50 mmol) and $Et_3N$ (5.00 mmol) in anhydrous THF (11 mL) was stirred under $N_2$ for 18 hours at ambient temperature. The solvent was evaporated under reduced pressure and the resulting product was purified by column chromatography (silica gel, Hex/EtOAc).

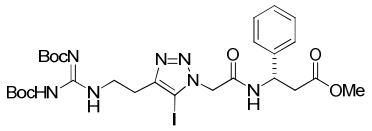
**(*S*)-4-{3-[*N*,*N*'-Di(*tert*-butoxycarbonyl)-guanidyl]-propyl}-5-iodo-1-{*N*-[1-phenyl-2-(methoxycarbonyl)ethyl]carbamoylmethyl}-1*H*-1,2,3-triazole**



The general procedure 6.3.6 (method A) was followed starting from alkyne **6** (0.15 mmol, 50 mg), the azide **7** (0.15 mmol, 40 mg), DIPEA (0.17 mmol, 30 µL), CuI (0.17 mmol, 32 mg) and *N*-bromosuccinimide (0.18 mmol, 33 mg) in MeCN (0.40 mL). Purification by chromatography (silica gel, Hex/EtOAc 1:4). Yield: 65 mg (58 %). Brown solid (mp = 68-70 ºC) $^{1}$H NMR (500 MHz, $CDCl_3$) δ 11.50 (s, 1H, N*H*Boc), 8.44 (s, 1H, N*H*), 7.34 – 7.18 (m, 5H, Ar), 7.06 (d, *J* = 8.3 Hz, 1H, N*H*CO), 5.40 (m, 1H, C*H*Ph), 5.11 (s, 2H, C$H_2$CONH), 3.58 (s, 3H, COOC$H_3$), 3.55-3.46 (m, 2H, NHC$H_2$CH$_2$CH$_2$), 2.90 – 2.71 (m, 4H, NHCH$_2$CH$_2$C$H_2$, C$H_2$CO$_2$Me), 2.08 – 2.00 (m, 2H, NHCH$_2$C$H_2$CH$_2$), 1.51 (s, 9H, Boc), 1.50 (s, 9H, Boc). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 177.4, 171.2, 163.9, 163.4, 156.1, 153.2, 151.6, 139.6, 128.7, 127.8, 126.1, 83.1, 80.1, 79.3, 53.2, 51.9, 49.8, 40.0, 39.4, 29.5, 28.2, 28.0, 23.5.

[The general procedure 6.3.6 (method B) was followed starting from alkyne **6** (2.46 mmol, 1.11 g), azide **7** (2.00 mmol, 524 mg), CuI (3.00 mmol, 571 mg) and $Et_3N$ (10.00 mmol, 1.40 mL) in THF (23 mL). Purification by chromatography (silica gel, Hex/EtOAc 1:4). Yield: 935 mg (65 %).]

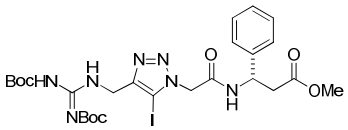
**(*S*)-4-{2-[*N*,*N*'-Di(*tert*-butoxycarbonyl)-guanidyl]-ethyl}-5-iodo-1-{*N*-[1-phenyl-2-(methoxycarbonyl)ethyl]carbamoylmethyl}-1*H*-1,2,3-triazole**



The general procedure 6.3.6 (method A) was followed starting from alkyne **6** (0.16 mmol, 50 mg), the azide **7** (0.16 mmol, 42 mg), DIPEA (0.18 mmol, 32 µL), CuI (0.18 mmol, 34 mg) and *N*-bromosuccinimide (0.19 mmol, 34 mg) in MeCN (0.7 mL). Yield: 60 mg (53 %). Yellow solid (mp = 51-53 ºC). $[\alpha]^{24}_{D}$ = -3.85 (c = 1.06 in $CH_2Cl_2$). IR (cm$^{-1}$): 3323 (NH), 2955, 1722 (C=O), 616, 556 (C-I). $^{1}$H NMR (500 MHz, $CDCl_3$) δ 11.49 (s, 1H, N*H*Boc), 8.52 (t, *J* = 5.5, 1H, N*H*), 7.39 – 7.15 (m, 5H, Ar), 7.09 (d, *J* = 8.3 Hz, 1H,

N*H*CO), 5.45 – 5.33 (m, 1H, C*H*Ph), 5.11 (dd, *J* = 27.7, 16.7 Hz, 2H, C$H_2$CONH), 3.83, 3.77 (q, *J* = 13.1, 6.5 Hz, 2H, NHC$H_2$CH$_2$), 3.57 (s, 3H, COOC$H_3$), 2.99 (t, *J* = 6.5 Hz, 2H NHCH$_2$C$H_2$), 2.85, 2.80 (dd, *J* = 15.7, 5.9 Hz, 2H, C$H_2$CO$_2$Me), 1.51 (s, 9H, Boc), 1.47 (s, 19H, Boc). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 171.3, 163.8, 163.5, 156.1, 152.9, 150.1, 139.5, 128.7, 127.8, 126.0, 82.9, 80.8, 79.2, 53.2, 51.9, 49.8, 39.7, 39.4, 28.2, 28.0, 26.0. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{27}H_{39}IN_7O_7$: 700.1956; found: 700.1959.

**(*S*)-4-[*N*,*N*'-Di(*tert*-butoxycarbonyl)-guanidylmethyl]-5-iodo-1-{*N*-[1-phenyl-2-(methoxycarbonyl)ethyl]carbamoylmethyl}-1*H*-1,2,3-triazole**

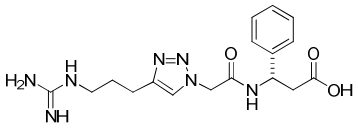



The general procedure 6.3.6 (method A) was followed starting from alkyne **6** (0.17 mmol, 50 mg), the azide **7** (0.13 mmol, 34 mg), DIPEA (0.14 mmol, 25 µL), CuI (0.14 mmol, 27 mg) and *N*-bromosuccinimide (0.16 mmol, 28 mg) in MeCN (5.6 mL). Yield: 35 mg (40 %). Yellow solid (mp = 76-80 ºC). $[\alpha]^{24}_D$ = -3.41 (c = 1.19 in $CH_2Cl_2$). IR ($cm^{-1}$): 3315 (NH), 2853, 1724 (C=O), 615, 551 (C-I). $^1$H NMR (500 MHz, $CDCl_3$) δ 11.50 (s, 1H, N*H*Boc), 8.87 (s, 1H, N*H*), 7.45 – 7.15 (m, 5H, Ar), 7.06 (d, *J* = 8.3 Hz, 1H, N*H*CO), 5.50 – 5.32 (m, 1H, C*H*Ph), 5.15 (dd, *J* = 20.0, 17.0 Hz, 2H, C$H_2$CONH), 4.73 (d, *J* = 4.8 Hz, 2H, NHC$H_2$), 3.60 (s, 3H, COOC$H_3$), 2.88, 2.81 (dd, *J* = 15.7, 5.7 Hz, 2H, C$H_2$CO$_2$Me), 1.54 (s, 9H, Boc), 1.50 (s, 9H, Boc). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 171.2, 163.6, 163.3, 156.0, 152.9, 148.3, 139.5, 128.8, 127.8, 126.1, 83.2, 80.3, 79.5, 53.2, 52.0, 49.9, 39.5, 37.2, 28.2, 28.0. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{26}H_{37}IN_7O_7$: 686.1799; found: 686.1818.

### 6.3.7 General procedure for Boc and ester groups deprotection

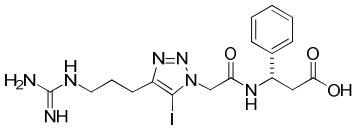
The corresponding triazole **X** (1.00 mmol) was dissolved in a 4.0 M solution of hydrogen chloride in dioxane (4 mL) and $H_2O$ (2 mL). The mixture was stirred at ambient temperature for 16 hours. Then, the volatiles were evaporated under vacuo yielding the corresponding clorohydrate derivative.

**(*S*)-4-(3-Guanidyl-propyl)-1-{*N*-[1-phenyl-2-(carboxy)ethyl]carbamoylmethyl}-1*H*-1,2,3-triazole**[165]



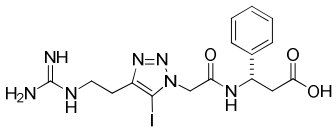
The general procedure 6.3.7 was followed starting from **X** (0.11 mmol, 65 mg), 4.0 M hydrogen chloride solution in dioxane (2 mL) and $H_2O$ (0.5 mL). Yield: 37 mg (89 %). $[\alpha]^{24}_D$ = -62.01 (c = 0.6 en $H_2O$) (Lit.[165] $[\alpha]^{24}_D$ = -63.5 (c = 0.57 in $H_2O$)). IR ($cm^{-1}$): 3324 (NH), 3179, 2451, 1655(C=O). $^1$H NMR (500 MHz, $D_2O$) δ 7.92 (s, 1H, triazole), 7.35-7.22 (m, 5H, Ar), 5.34 (t, *J* = 6.8 Hz, 1H, C*H*Ph), 5.27 (d, *J* = 4.3 Hz, 2H, C$H_2$CONH), 3.23 (t, *J* = 6.4 Hz, 2H, NHC$H_2$CH$_2$CH$_2$), 3.01 (d, *J* = 7.3 Hz, 2H, C$H_2$CO$_2$H), 2.83 (t, *J* = 7.2 Hz, 2H, NHCH$_2$CH$_2$C$H_2$), 2.04-1.93 (m, 2H, NHCH$_2$C$H_2$CH$_2$). $^{13}$C NMR (101 MHz, $H_2O$+$D_2O$) δ 177.0, 168.9, 168.8, 159.4, 142.5, 142.4, 131.6, 130.8, 130.7, 128.9, 55.4, 55.1, 53.5, 53.4, 43.0, 42.9, 42.5, 29.7, 23.9.

**(*S*)-4-(3-Guanidyl-propyl)-5-iodo-1-{*N*-[1-phenyl-2-(carboxy)ethyl]carbamoylmethyl}-1*H*-1,2,3-triazole**



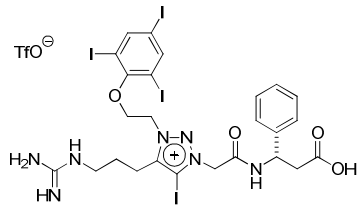
The general procedure 6.3.7 was followed starting from **X** (0.06 mmol, 40 mg), 4.0 M hydrogen chloride solution in dioxane (2 mL) and $H_2O$ (0.5 mL). Yield: 26 mg (91 %). White solid (at pH = 7.0). $[\alpha]^{24}_D$ = -27.04 (c = 1.10 in $H_2O$). IR ($cm^{-1}$): 3337 (NH), 3181, 1662 (C=O). $^1$H NMR (500 MHz, $D_2O$) δ 7.53 – 7.34 (m, 5H, Ar), 5.39 – 5.23 (m, 3H, C*H*Ph, C$H_2$CONH), 3.17 (t, *J* = 5.9 Hz, 2H, NHC$H_2$CH$_2$CH$_2$), 3.01 (d, *J* = 7.3 Hz, 2H, C$H_2$CO$_2$H), 2.76 (t, *J* = 6.9 Hz, 2H, NHCH$_2$CH$_2$C$H_2$), 2.02 – 1.93 (m, 2H, NHCH$_2$C$H_2$CH$_2$). $^{13}$C NMR (101 MHz, $D_2O$) δ 174.5, 173.3, 166.4, 156.8, 151.4, 139.9, 139.8, 129.0, 128.2, 128.1, 126.5, 126.3, 82.8, 52.8, 52.8, 50.9, 50.81 40.2, 40.1, 39.9, 26.7, 22.4. HRMS (TOF MS $Cl^+$, [M+H]): caldc for $C_{17}H_{23}N_7O_3I$: 500.0907; found: 500.0913.

**(*S*)-4-(2-Guanidyl-ethyl)-5-iodo-1-{*N*-[1-phenyl-2-(carboxy)ethyl]carbamoylmethyl}-1*H*-1,2,3-triazole**



The general procedure 6.3.7 was followed starting from **X** (1.00 mmol, 700 mg), 4.0 M hydrogen chloride solution in dioxane (4 mL) and $H_2O$ (2 mL). Yield: 250 mg (52 %).White solid (at pH = 7.0) (mp = 187-188 ºC). $[\alpha]^{24}_D$ = -28.52 (c = 1.30 in $H_2O$). IR ($cm^{-1}$): 3339 (NH), 3196, 1659 (C=O). $^1$H NMR (500 MHz, $D_2O$) δ 7.13 – 6.79 (m, 5H, Ar), 4.99 – 4.60 (m, 3H, C*H*$_2$CO, C*H*Ph), 3.05 (t, *J* = 5.5 Hz, 2H, NHC*H*$_2$CH$_2$), 2.64 – 2.37 (m, 4H, NHCH$_2$C*H*$_2$, C*H*$_2$CO$_2$H). $^{13}$C NMR (126 MHz, $D_2O$) δ 174.27, 165.84, 156.46, 139.62, 128.81, 127.95, 126.34, 85.67, 53.23, 50.75, 39.79, 39.70, 24.76. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{21}IN_7O_3$: 486.0751; found: 486.0755.

**(*S*)-4-(3-Guanidyl-propyl)-5-iodo-1-{*N*-[1-phenyl-2-(carboxy)ethyl]carbamoylmethyl}-3-[2-(2,4,6-triiodophenoxy)ethyl]-1*H*-1,2,3-triazolium trifluoromethanesulfonate**



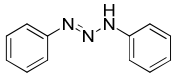
To a solution of (*S*)-4-{3-[*N*,*N*'-di(*tert*-butoxycarbonyl)guanidyl]propyl}-3-[2-(2,4,6-triiodophenoxy)ethyl]-1-{*N*-[1-phenyl-2-(methoxycarbonyl)ethyl]carbamoylmethyl}-5-iodo-1*H*-1,2,3-triazolium trifluoromethanesulfonate (0.03 mmol, 40 mg) in $CH_2Cl_2$ (0.4 mL) at 0 ºC, trifluoroacetic acid (5.22 mmol, 0.40 mL) was added and the mixture was stirred at ambient temperature for 1 hour. Then, the volatiles were evaporated under vacuo yielding the corresponding ester. To a solution of the later ester in DMSO/$H_2O$ 2:1 (1 mL), 12 M HCl (0.1 mL) was added and the mixture was stirred at room temperature for 24 h. The solvents were removed under reduced pressure and the crude product was purified by precipitation with $CH_2Cl_2$. Yield: quantitative. White solid (mp = 70-72 ºC). $[\alpha]^{22}_D$ = -5.99 (c = 1.84 in DMSO). IR ($cm^{-1}$): 3331 (NH), 1647 (C=O), 1425 (triazole), 1232, 1164, 1028 ($SO_2$). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.33 (s, 1H, N*H*), 7.69 (s, 2H, Ar), 7.06 – 6.80 (m, 5H, Ar), 5.19 (q, *J* = 18.6 Hz, 1H, C*H*Ph), 5.01 – 4.66 (m, 4H, C*H*$_2$N$_{trz}$, C*H*$_2$CONH), 3.86 (s, 2H, C*H*$_2$Ar), 2.98 (s, 2H, NHC*H*$_2$CH$_2$CH$_2$), 2.79 – 2.60 (m, 2H, NHCH$_2$CH$_2$C*H*$_2$), 2.46 (s, 2H, C*H*$_2$CO$_2$H), 1.48 (s, 2H, NHCH$_2$C*H*$_2$CH$_2$). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 171.6, 162.3, 157.4, 155.8, 147.4, 146.6, 141.4, 128.9, 127.8, 127.0,

100.3, 95.0, 94.0, 70.0, 55.8, 51.7, 50.6, 41.0, 27.4, 21.8. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{25}H_{28}I_4N_7O_4$: 997.8382; found: 997.8395.

## 6.4 Experimental section of chapter 4

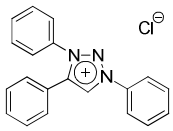
### 6.4.1 Preparation of 1,3,4-triphenyl-1*H*-1,2,3-triazolium chloride

**(Phenyliminio)-2-phenylhydrazine**[169]



To a stirred solution of 12 M HCl (5 mL), aniline was added (5 mmol, 456 µL). The resulting stirring mixture was cooled to 0 ºC and treated dropwise with a 0 ºC cooled $NaNO_2$ solution (2.75 mmol, 190 mg in 0.7 mL of water) for 15 min followed by 0 ºC cooled $CH_3COONa$ solution (7.49 mmol, 614 mg in 1.7 mL of water) for 15 min. The stirring was continued at 0 ºC for 1 h and the resultant yellow precipitate was filtered and washed with cold water. The product was used without further purification due to it unstability. Yield: 386 mg (78 %).

**1,3,4-Triphenyl-1*H*-1,2,3-triazolium chloride**[170]



To a solution of (phenyliminio)-2-phenylhydrazine (1.27 mmol, 250 mg) in dry $CH_2Cl_2$ (8.5 mL) at -78ºC, phenylacetylene (2.54 mmol, 278 mg) was added and the reaction mixture was stirred in the dark at -78 ºC. Then, *tert*-butyl hypochloride (1.86 mmol, 211 µL) was added and the reaction mixture was stirred at -78 ºC for 16 hours. The product was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH 95:5). Yield: 180 mg (43 %). $^1$H NMR (400 MHz,$CDCl_3$) δ 11.26 (s, 1H, triazole), 8.46 (d, *J* = 7.6 Hz, 2H, Ar), 7.61 (d, *J* = 7.7 Hz, 2H, Ar), 7.56 (s, 3H, Ar), 7.51 (d, *J* = 8.4 Hz, 2H, Ar), 7.36 (s, 1H, Ar), 7.33 (d, *J* = 7.4 Hz, 2H, Ar), 7.28 (d, *J* = 7.7 Hz, 2H, Ar), 7.25 (s, 1H, Ar). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 143.9, 134.9, 134.1, 132.4, 132.0, 131.7, 130.5, 130.4, 129.6, 129.4, 128.8, 125.8, 121.8, 121.7.

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[169] Kumar, R. K.; Ali, M. A.; Punniyamurthy, T. *Org. Lett.* **2011**, *13*, 2102-2105. "Pd-Catalyzed C-H activation/C-N bond formation: a new route to 1-Aryl-1H-benzotriazoles".

[170] Bouffard, J.; Keitz, B. K.; Tonner, R.; Lavallo, V.; Guisado-Barrios, G.; Frenking, G.; Grubbs, R. H.; Bertrand, G. *Organometallics* **2011**, *30*, 2617-2627. "Synthesis of highly stable 1,3-diaryl-1H-1,2,3-triazol-5-ylidenes and their applications in ruthenium-catalyzed olefin metathesis".

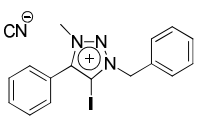
### 6.4.2 General procedure for the synthesis of iodinated compounds by using the $Ag_2O$/ICN system

A suspension of the corresponding 1,2,3-triazolium salt (1.00 mmol) in $CH_2Cl_2$/MeCN 1:1 (17 mL), was added $Ag_2O$ (0.60 mmol) followed by cyanogen iodide (1.20 mmol) and the suspension was stirred at room temperature for 6 hours. The mixture was filtered through a celite/silice 1:1 pad which was successively washed with $CH_2Cl_2$ and MeCN.

**Cyanogen iodide**[171]

I–C≡N To a solution of NaCN (0.035 mol, 1.72 g) in $H_2O$ (6.4 mL) cooled at 0 ºC, $I_2$ (0.039 mol, 10.00 g) was slowly added over a period of 30-40 min and the mixture was stirred at room temperature for 10 min. Then, $Et_2O$ (6 mL) was added and the mixture was stirred at room temperature for a few min until the precipitated cyanogen iodide was dissolved in the ethereal layer and after that, the product was extracted with $Et_2O$ (6 mL x 3) and the solvent was evaporated under reduced pressure. $H_2O$ was added (6 mL) and the mixture was heated at 50 ºC for 15 min under slightly diminished pressure (1/2 atm.) with vigorous shaking. The mixture is then cooled at 0 ºC, the crystalline cyanogen iodide is separated from the light yellow mother liquor by suction on a filter plate, washed with ice water and air dried. Yield: 1.7 g (32 %). $^{13}$C NMR (126 MHz, MeCN-$d_3$) δ 44.33.

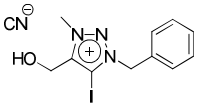
**1-Benzyl-5-iodo-3-methyl-4-phenyl-1*H*-1,2,3-triazolium cyanide**



The general procedure 6.4.2 was followed starting from 1-benzyl-3-methyl-4-phenyl-1*H*-1,2,3-triazolium iodide (0.15 mmol, 56 mg), $Ag_2O$ (0.09 mmol, 21 mg) and cyanogen iodide (0.30 mmol, 45 mg) in MeCN/$CH_2Cl_2$ 1:1 (2 mL). Yield: 59 mg (99 %). Colorless oil. IR ($cm^{-1}$): 2131 (C≡N), 1454 (triazole). $^1$H NMR (400 MHz, MeCN-$d_3$) δ 7.69 – 7.47 (m, 10H, Ar), 5.83 (s, 2H, C$H_2$), 4.11 (s, 3H, C$H_3$). $^{13}$C NMR (101 MHz, MeCN-$d_3$) δ 148.1, 133.0, 132.6, 131.1, 130.53, 130.4, 130.1, 129.9, 123.7, 58.8, 40.1. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{16}H_{15}N_3I$: 376.0311; found: 376.0316.

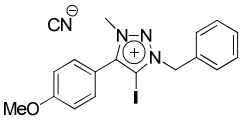
[171] Prepare according to procedure: Bak, B.; Hillebert, A. *Org. Synth.* **1952**, *32*, 29-31. "Cyanogen iodide".

**1-Benzyl-4-hydroxymethyl-5-iodo-3-methyl-4-phenyl-1*H*-1,2,3-triazolium cyanide**



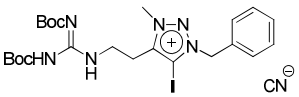
The general procedure 6.4.2 was followed starting from 1-benzyl-4-hydroxymethyl-3-methyl-1*H*-1,2,3-triazolium iodide (0.24 mmol, 81 mg), $Ag_2O$ (0.15 mmol, 34 mg) and cyanogen iodide (0.49 mmol, 74 mg) in $MeCN/CH_2Cl_2$ 1:1 (2 mL). Yield: 83 mg (96 %). Yellow oil. IR ($cm^{-1}$): 2135 (C≡N), 1455 (triazole). $^1$H NMR (400 MHz, MeCN-$d_3$) δ 7.46 (m, 5H, Ar), 5.77 (s, 2H, C$H_2$Ar), 5.25 (m, 2H, C$H_2$OH), 4.31 (m, 3H, C$H_3$). $^{13}$C NMR (101 MHz, MeCN-$d_3$) δ 155.7, 132.3, 130.5, 130.1, 129.8, 129.5, 94.7, 59.0, 58.7, 40.4. IR ($cm^{-1}$): 3340 (OH), 2129 (CN), 1742, 1685 (C-O). HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{16}H_{15}N_3I$: 376.0311; found: 376.0316.

**1-Benzyl-5-iodo-4-(4-methoxyphenyl)-3-methyl-1*H*-1,2,3-triazolium cyanide**



The general procedure 6.4.2 was followed starting from 1-benzyl-4-(4-methoxyphenyl)-3-methyl-1*H*-1,2,3-triazolium iodide (0.15 mmol, 27 mg), $Ag_2O$ (0.09 mmol, 21 mg) and cyanogen iodide (0.30 mmol, 46 mg) in $MeCN/CH_2Cl_2$ 1:1 (2 mL). Yield: 57 mg (89 %). Colorless oil. IR ($cm^{-1}$): 2131 (C≡N), 1455 (triazole), 702 (C-I). $^1$H NMR (400 MHz, MeCN-$d_3$) δ 7.46 (m, 6H, Ar), 7.15 (m, 2H, Ar), 5.79(s, 2H, C$H_2$), 4.09 (s, 3H, C$H_3$), 3.87 (s, 3H, OC$H_3$). $^{13}$C NMR (101 MHz, MeCN-$d_3$) δ 161.9, 146.7, 131.4, 129.1, 128.7, 128.6, 114.6, 114.0, 92.6, 57.4, 55.1, 38.6. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{17}H_{17}N_3OI$: 406.0416; found: 406.0417.

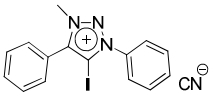
**1-Benzyl-4-{2-[*N*,*N*'-di(*tert*-butoxycarbonyl)-guanidyl]ethyl}-5-iodo-3-methyl-1*H*-1,2,3-triazolium cyanide**



The general procedure 6.4.2 was followed starting from 1-benzyl-4-{2-[*N*,*N*'-di(*tert*-butoxycarbonyl)-guanidyl]ethyl}-3-methyl-1*H*-1,2,3-triazolium iodide (0.06 mmol, 38 mg), $Ag_2O$ (0.04 mmol, 9 mg) and cyanogen iodide (0.08 mmol, 12 mg) in $MeCN/CH_2Cl_2$ 1:1 (1 mL). Yield: quantitative. Yellow solid (mp = 65-66 ºC). IR ($cm^{-1}$): 3318 (NH), 2133 (C≡N), 1723 (C=O), 1611, 1293, 1126. $^1$H NMR (400 MHz, $CDCl_3$) δ 11.01 (s, 1H, N*H*Boc), 8.63 (s, 1H, N*H*), 7.61-7.16 (m, 5H, Ar), 5.76 (s, 2H, C$H_2$Ar), 4.59 (s, 3H, C$H_3$), 3.77 (q, *J* = 6.6 Hz, 2H,

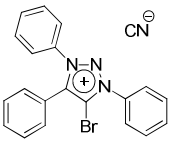
NHC*H*$_2$CH$_2$), 3.26 (t, *J* = 6.6 Hz, 2H, NHCH$_2$C*H*$_2$), 1.49 (s, 9H, Boc), 1.45 (s, 9H, Boc). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 162.2, 156.3, 152.4, 146.0, 130.6, 129.7, 129.6, 128.0, 93.4, 84.0, 79.4, 58.1, 39.3, 36.9, 28.1, 28.0, 25.4. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{23}H_{34}N_6O_4I$: 585.1686; found: 585.1697.

**1,4-Diphenyl-5-iodo-3-methyl-1*H*-1,2,3-triazolium cyanide**



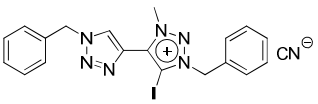
The general procedure 6.4.2 was followed starting from 1,4-diphenyl-3-methyl-1*H*-1,2,3-triazolium iodide (0.11 mmol, 40 mg), $Ag_2O$ (0.07 mmol, 15 mg) and cyanogen iodide (0.13 mmol, 20 mg) in MeCN/$CH_2Cl_2$ 1:1 (2 mL). Yield: 41 mg (96 %). Yellow solid (mp = 190-191 ºC). IR ($cm^{-1}$): 3053, 2921 (Ar), 2140 (C≡N), 1444 (triazole), 605, 514 (C-I). $^1$H NMR (400 MHz, MeCN-$d_3$) δ 8.13 – 7.36 (m, 10H, Ar), 4.25 (s, 3H, C*H*$_3$). $^{13}$C NMR (101 MHz, MeCN-$d_3$) δ 132.4, 131.9, 130.0, 129.8, 129.4, 125.9, 116.9, 38.8. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{15}H_{13}N_3I$: 362.0154; found: 362.0145.

**5-Bromo-1,3,4-triphenyl-1*H*-1,2,3-triazolium cyanide**



The general procedure 6.4.2 was followed starting from 1,3,4-triphenyl-1*H*-1,2,3-triazolium chloride (0.13 mmol, 45 mg), $Ag_2O$ (0.08 mmol, 19 mg) and cyanogen bromide (0.27 mmol, 28 mg) in MeCN/$CH_2Cl_2$ 1:1 (2 mL). Yield: 52 mg (96 %). Colorless oil. IR ($cm^{-1}$): 2129 (C≡N), 1488 (triazole), 761, 689. $^1$H NMR (400 MHz, MeCN-$d_3$) δ 7.98 – 7.76 (m, 5H, Ar), 7.76 – 7.48 (m, 10H, Ar). $^{13}$C NMR (101 MHz, MeCN-$d_3$) δ 132.6, 132.1, 131.8, 130.1, 129.8, 129.8, 129.2, 125.6, 125.4, 119.1, 116.9. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{20}H_{15}N_3I$: 376.0449; found: 376.0450.

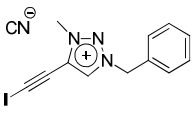
**4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1-benzyl-5-iodo-3-methyl-1H-1,2,3-triazolium cyanide**



The general procedure 6.4.2 was followed starting from 4-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-1-benzyl-3-methyl-1H-1,2,3-

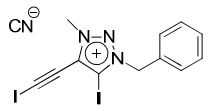
triazolium iodide (0.06 mmol, 30 mg), $Ag_2O$ (0.04 mmol, 9 mg) and cyanogen bromide (0.13 mmol, 20 mg) in $MeCN/CH_2Cl_2$ 1:1 (2 mL). Yield: 29 mg (92 %). Yellow solid (mp = 46-48 ºC). IR ($cm^{-1}$): 2131 (C≡N), 1454 (triazole). $^1H$ NMR (400 MHz, MeCN-$d_3$) δ 8.7 (s, 1H, triazole), 7.5 (m, 10H, Ar), 5.9 (s, 2H, C$H_2$), 5.7 (s, 2H, C$H_2$), 4.5 (s, 3H, C$H_3$). $^{13}C$ NMR (101 MHz, MeCN-$d_3$) δ 138.9, 134.6, 131.2, 131.1, 129.2, 128.8, 128.7, 128.5, 128.4, 127.9, 126.2, 90.1, 57.6, 53.8, 40.4. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{19}H_{18}N_6I$: 457.0638; found: 457.0642.

**1-Benzyl-4-iodoethynyl-3-methyl-1*H*-1,2,3-triazolium iodide**



The general procedure 6.4.2 was followed starting from 1-benzyl-4-ethynyl-3-methyl-1*H*-1,2,3-triazolium iodide (0.09 mmol, 29 mg), $Ag_2O$ (0.05 mmol, 12 mg) and cyanogen iodide (0.18 mmol, 28 mg) in $MeCN/CH_2Cl_2$ 1:1 (2 mL). The product was used in the next step without further purification. $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H, triazole), 7.61 – 7.51 (m, 2H, Ar), 7.52 – 7.38 (m, 3H, Ar), 5.87 (s, 2H, C$H_2$), 4.34 (s, 3H, C$H_3$).

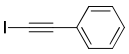
**1-Benzyl-5-iodo-4-iodoethynyl-3-methyl-1*H*-1,2,3-triazolium iodide**



The general procedure 6.4.2 was followed starting from 1-benzyl-4-iodoethynyl-3-methyl-1*H*-1,2,3-triazolium iodide (0.09 mmol, 32 mg), $Ag_2O$ (0.05 mmol, 12 mg) and cyanogen iodide (0.18 mmol, 28 mg) in $MeCN/CH_2Cl_2$ 1:1 (2 mL). Yield: 34 mg (80 %). IR ($cm^{-1}$): 2176 (C≡C), 2133 (C≡N), 1455 (triazole). $^1H$ NMR (400 MHz, MeCN-$d_3$) δ 7.69 – 7.37 (m, 5H, Ar), 5.76 (s, 2H, C$H_2$), 4.27 (s, 3H, C$H_3$). $^{13}C$ NMR (101 MHz, MeCN-$d_3$) δ 130.8, 129.3, 128.8, 128.6, 117.0, 92.5, 74.7, 57.9, 39.2, 36.6. IR ($cm^{-1}$): 2955, 2176, 1538, 1497, 1026, 696. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{12}H_{10}N_3I_2$: 449.8964; found: 449.8969.

### 6.4.3 Preparation of 1-iodoalkynes and 5-iodo-1,2,3-triazoles

**2-Iodoethynylbenzene**[172]



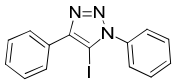
To a solution of phenylacetylene (3.92 mmol, 0.43 mL) in THF (22 mL), copper iodide (0.20 mmol, 37 mg) and *N*-iodomorpholine (5.10 mmol, 1.74 g) were added. The mixture was stirred vigorously at ambient temperature for 4 hours. After this time, the solvent was evaporated under reduced pressure, the mixture was filtered through a celite:silice 1:1 pad and washed with $CH_2Cl_2$. The resulting solution was washed with a saturated aqueous solution of $NH_4Cl$ (15 mL x 1) and the organic layer was dried over $MgSO_4$. Yield: 398 mg (89 %). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.42 (m, 2H, Ar), 7.41 – 7.30 (m, 3H, Ar). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 132.11, 128.63, 128.08, 123.08, 94.05, 7.11.

**1,4-Diiodo-1,3-butadiyne**[173]



A solution of 1,4-bis(trimethylsilyl)-1,3-butadiyne (0.26 mmol, 50 mg), cessium fluoride (0.52 mmol, 79 mg), copper iodide (0.03 mmol, 5 mg) and *N*-iodomorpholine (0.68 mmol, 230 mg) in THF (4 mL) was stirred vigorously at room temperature for 18 hours. After this time, the product was purified by column chromatography (silica gel, Hex/EtOAc 1:1). Yield: 30 mg (40 %). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 80.0, -3.1.

**1,4-Diphenyl-5-iodo-1*H*-1,2,3-triazole**



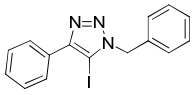

A solution of phenylacetylene (3.22 mmol, 354 µL) and phenylazide (3.22 mmol, 383 mg) in anhrydrous MeCN (7 mL), was added to a solution of CuI (3.54 mmol, 674 mg) and *N*-bromosuccinimide (3.86 mmol, 687 mg) in anhydrous MeCN (7 mL). DIPEA (3.54 mmol, 617 µL) was added and the mixture was stirred for 18 hours at 10ºC. After this time, the product was purified by column chromatography (silica gel, Hex/EtOAc 4:1). Yield: 100 mg (9 %). Orange solid (mp = 191-

[172] Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2009**, *48*, 8018-8021. "Copper(I)-catalyzed cycloaddition of organic azides and 1-iodoalkynes".

[173] Homsi, F.; Rousseau, G. *Tetrahedron Lett.* **1999**, *40*, 1495-1498. "Halodecarboxylation of α,β-acetylenic and α,β-ethylenic acids".

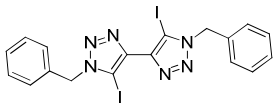
193 ºC). IR ($cm^{-1}$): 3057, 1596 (Ar), 1445 (triazole), 574, 525 (C-I). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.5 Hz, 2H, Ar), 7.62 (s, 5H, Ar), 7.54 (t, *J* = 7.5 Hz, 2H, Ar), 7.48 (t, *J* = 7.3 Hz, 1H, Ar). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 150.4, 137.0, 130.2, 130.1, 129.3, 128.7, 128.6, 127.7, 126.5, 77.7. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{14}H_{11}IN_3$: 347.9998; found: 348.0001.

**1-Benzyl-5-iodo-4-phenyl-1*H*-1,2,3-triazole**[174]



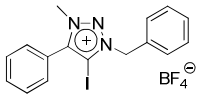
A solution of iodoethynylbenzene (3.92 mmol, 894 mg), benzyl azide (3.19 mmol, 425 mg), copper iodide (4.78 mmol, 910 mg) and $Et_3N$ (15.95 mmol, 2.22 mL) in THF (35 mL) was stirred at ambient temperature for 18 hours. After this time, the solvent was evaporated under reduced pressure, the product was extracted with $CH_2Cl_2$/$NH_4OH$ aq. sat. and the organic layers were combined and dried over $MgSO_4$. The product was purified by column chromatography (silica gel, Hex:EtOAc 1:1). Yield: 1.26 g (89 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.89 (m, 2H, Ar), 7.53 – 7.31 (m, 8H, Ar), 5.71 (s, 2H, C*H*$_2$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 150.2, 134.4, 130.3, 129.0, 128.7, 128.6, 128.5, 127.9, 127.5, 76.8, 54.4.

**1,1'-Dibenzyl-5,5'-diiodo-4,4'-bis(1*H*-1,2,3-triazole)**



A solution of 1,4-diiodo-1,3-butadiine (0.10 mmol, 30 mg), benzyl azide (0.20 mmol, 27 mg), copper iodide (0.005 mmol, 1 mg) and TBTA (0.005 mmol, 3 mg) in THF (1 mL) was stirred at ambient temperature for 18 hours. After this time, the solvent was evaporated under reduced pressure and the product was used without further purification. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.32 (m, 10H, Ar), 5.71 (s, 4H, *CH*$_2$).

**1-Benzyl-5-iodo-3-methyl-4-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate**

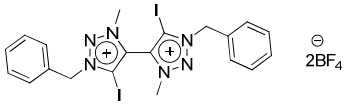


The general procedure 6.1.6 was followed starting from 1-benzyl-5-iodo-4-phenyl-1*H*-1,2,3-triazole (0.55 mmol, 200 mg) and

[174] Wu, Y.-M.; Deng, J.; Li, Y.; ChenKey, Q.-Y. *Synthesis* **2005**, 1314-1318. "Regiospecific synthesis of 1,4,5-trisubstituted-1,2,3-triazole via one-pot reaction promoted by copper(I) salt".

trimethyloxonium tetrafluoroborate (1.10 mmol, 209 mg) in $CH_2Cl_2$ (5 mL). Yield: 246 mg (96 %). White solid (mp = 165-166 ºC). IR ($cm^{-1}$): 1455 (triazole), 1030 ($BF_4$). $^1H$ NMR (400 MHz, MeOH-$d_4$) δ 7.79 – 7.62 (m, 5H, Ar), 7.60 – 7.43 (m, 5H, Ar), 5.96 (s, 2H, C*H*$_2$), 4.26 (s, 3H, C*H*$_3$). $^{13}C$ NMR (101 MHz, MeOH-$d_4$) δ 148.8, 133.2, 133.1, 131.3, 130.6, 130.5, 130.3, 130.0, 124.3, 91.2, 59.0, 39.6. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{16}H_{15}IN_3$: 376.0311; found: 376.0318.

**1,1'-Dibenzyl-5,5'-diiodo-3,3'-dimethyl-4,4'-bis(1*H*-1,2,3-triazolium) ditetrafluoroborate**



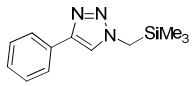

A solution of 1,1'-dibenzyl-5,5'-diiodo-4,4'-bis(1*H*-1,2,3-triazole) (0.09 mmol, 50 mg) and trimethyloxonium tetrafluoroborate (0.35 mmol, 67 mg) in $CH_2Cl_2$ (8 mL) was stirred vigorously at room temperature for 18 hours and the solvent was evaporated under reduced pressure. Yield: 39 mg (57 %). Yellow solid (mp = 194 ºC dec). IR ($cm^{-1}$): 1456 (triazole), 1052 ($BF_4$), 712, 693, 497 (C-I). $^1H$ NMR (500 MHz, MeOH-$d_4$) δ 7.65 – 7.41 (m, 10H, Ar), 6.03 (dd, *J* = 25.4, 15.2 Hz, 4H, C*H*$_2$), 4.42 (s, 6H, C*H*$_3$). $^{13}C$ NMR (126 MHz, MeOH-$d_4$) δ 133.3, 132.3, 130.9, 130.6, 130.4, 98.7, 60.3, 41.2. HRMS (ESI+): *m/z* $[M]^{2+}$ calcd for $C_{20}H_{20}I_2N_6$: 299.9998; found: 300.0013.

### 6.4.4 Preparation of 1-[1-(trimethylsilyl)-alkyl]-1*H*-1,2,3-triazoles

#### 6.4.4.1 General procedure for the synthesis of 1-trimethylsilylmethyl- and 1-bis(trimethylsilyl)methyl-1*H*-1,2,3-triazoles

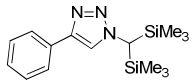
To a solution of the corresponding chloromethylsilane (1.00 mmol) in HMPA (0.5 mL) $NaN_3$ (1.10 mmol) was added, and the mixture was stirred for 2 hours at ambient temperature. Then, phenylacetylene (1.00 mmol), CuI (0.20 mmol) and DIPEA (5.00 mmol) were added and the resulting mixture was stirred for 18 hours. After this time, 1M HCl was added and the crude was extracted with $CH_2Cl_2$. The organic layer was dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The product was filtered through a celite/silica 1:1 pad and washed with Hex/EtOAc 4:1.

**4-Phenyl-1-(trimethylsilylmethyl)-1*H*-1,2,3-triazole**[175]



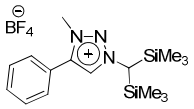
The general procedure 6.4.4.1 was followed starting from trimethylsilylchloromethane (4.00 mmol, 558 µL), $NaN_3$ (4.40 mmol, 286 mg), phenylacetylene (4.00 mmol, 439 µL), CuI (0.80 mmol, 152 mg) and DIPEA (20.00 mmol, 3.50 mL) in HMPA (2.20 mL). Yield: 858 mg (93%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.6 Hz, 2H, Ar), 7.66 (s, 1H, triazole), 7.42 (t, *J* = 7.6 Hz, 2H, Ar), 7.33 (t, *J* = 7.6 Hz, 1H, Ar), 3.95 (s, 2H, C*H*$_2$), 0.18 (s, 9H, SiC*H*$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 147.2, 130.7, 128.7, 127.8, 125.5, 120.2, 42.0, -2.6.

**1-[Bis(trimethylsilyl)methyl]-4-phenyl-1*H*-1,2,3-triazole**



The general procedure 6.4.4.1 was followed starting from bis(trimethylsilyl)chloromethane (4.58 mmol, 1.00 mL), $NaN_3$ (5.04 mmol, 328 mg), phenylacetylene (4.58 mmol, 0.50 mL), CuI (0.92 mmol, 174 mg) and DIPEA (22.90 mmol, 4.01 mL) in HMPA (2.30 mL). Yield: 793 mg (86 %). White solid (mp = 80-81 ºC). IR (cm$^{-1}$): 1459 (triazole), 842 ($SiCH_3$), 767 ($SiCH_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.6 Hz, 2H, Ar), 7.59 (s, 1H, triazole), 7.41 (t, *J* = 7.6 Hz, 2H, Ar), 7.30 (t, *J* = 7.5 Hz, 1H, Ar), 3.65 (s, 1H, C*H*), 0.14 (s, 18H, SiC*H*$_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 146.7, 130.9, 128.6, 127.7, 125.4, 120.1, 46.5, -1.2. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{15}H_{26}N_3Si_2$: 304.1565; found: 304.1663.

**1-[Bis(trimethylsilyl)methyl]-3-methyl-4-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate**

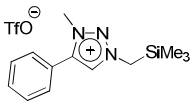


The general procedure 6.1.6 was followed starting from 1-[bis(trimethylsilyl)methyl]-4-phenyl-1*H*-1,2,3-triazole (0.42 mmol, 128 mg) and trimethyloxonium tetrafluoroborate (0.55 mmol, 104 mg) in anhydrous $CH_2Cl_2$ (3.2 mL). Yield: 144 mg (73 %). White solid (mp = 146-147 ºC). IR (cm$^{-1}$): 1490 (triazole), 1055 ($BF_4$), 851 ($SiCH_3$), 770 ($SiCH_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H, triazole), 7.63 (m, 5H, Ar), 4.47 (s, 1H, C*H*), 4.31 (s, 3H, C*H*$_3$), 0.21 (s, 18H,

[175] Nulwala, H. B.; Tang, C. N.; Kail, B. W.; Damodaran, K.; Kaur, P.; Wickramanayake, S.; Shi, W.; Luebke, D. R. *Green Chem.* **2011**, *13*, 3345-3349. "Probing the structure-property relationship of regioisomeric ionic liquids with click chemistry".

SiC*H*$_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 142.9, 131.8, 129.8, 129.5, 129.2, 121.8, 51.0, 38.6, -1.6. HRMS (ESI+): *m/z* $[M\text{-}CH_2]^+$ calcd for $C_{15}H_{26}N_3Si_2$: 304.1565; found: 304.1655.

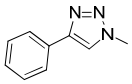
**3-Methyl-4-phenyl-1-(trimethylsilylmethyl)-1*H*-1,2,3-triazolium trifluoromethanesulfonate**




The general procedure 6.1.6 was followed starting from 4-phenyl-1-(trimethylsilylmethyl)-1*H*-1,2,3-triazole (0.86 mmol, 200 mg) and methyl trifluoromethanesulfonate (0.95 mmol, 108 µL) in anhydrous $CH_2Cl_2$ (4.8 mL). Yield: quantitative. White solid (mp = 94-96 ºC). IR ($cm^{-1}$): 1495 (triazole), 1308, 1278, 1251, 1163, 1149, 1078 ($SO_2$), 852, 767 ($SiCH_3$), 629. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H, triazole), 7.71 – 7.50 (m, 5H, Ar), 4.30 (s, 2H, C*H*$_2$), 4.26 (s, 3H, C*H*$_3$), 0.21 (s, 9H, SiC*H*$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 143.2, 131.8, 129.6, 129.3, 129.2, 121.8, 45.9, 38.4, -2.9. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{13}H_{20}N_3Si$: 246.1426; found: 246.1440.

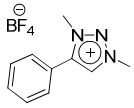
### 6.4.5 General procedure for the desilylation of 1-trimethylsilylmethyl-1*H*-1,2,3-triazoles

**1-Methyl-4-phenyl-1*H*-1,2,3-triazole**




To a solution of 1-[bis(trimethylsilyl)methyl]-4-phenyl-1*H*-1,2,3-triazole (0.13 mmol, 40 mg) in $CH_3CN$ (2 mL), cessium fluoride (0.13 mmol, 20 mg) was added and the resulting mixture was stirred at ambient temperature for 4 hours. The solution was filtered through a silica and celite pad, washed with $CH_2Cl_2$ (5 mL x 3) and the filtrate was evaporated under reduced pressure. Yield: 20 mg (95 %). White solid (mp = 114-119 ºC). IR ($cm^{-1}$): 1454 (triazole). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.3 Hz, 2H, Ar), 7.76 (s, 1H, triazole), 7.44 (t, *J* = 7.6 Hz, 2H, Ar), 7.35 (t, *J* = 7.3 Hz, 1H, Ar), 4.15 (s, 3H, C*H*$_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 148.0, 130.5, 128.8, 128.1, 125.6, 120.6, 36.7. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_9H_{10}N_3$: 160.0875; found: 160.0882.

**1,3-Dimethyl-4-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate**

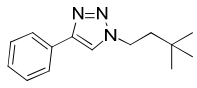


To a solution of 1-[bis(trimethylsilyl)methyl]-3-methyl-4-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.10 mmol, 40 mg) in $CH_3CN$ (0.2 mL), cessium fluoride (0.10 mmol, 27 mg) was added and the resulting mixture was stirred at ambient temperature for 4 hours. The solution was filtered through a silica and celite pad, washed with MeOH (5 mL x 3) and the filtrate was evaporated under reduced pressure. The crude product was purified by precipitation from $Et_2O$. Yield: 19 mg (73 %). White solid (mp = 111-113 ºC). IR ($cm^{-1}$): 1450 (triazole), 1044 ($BF_4$). $^1$H NMR (500 MHz, $CDCl_3$) δ 9.28 (s, 1H, triazole), 7.60 (m, 5H, Ar), 4.46 (s, 3H, C*H*$_3$), 4.26 (s, 3H, C*H*$_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 143.2, 131.9, 130.4, 129.7, 129.4, 122.0, 40.4, 38.3. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{10}H_{12}N_3$: 174.1031; found: 174.1035.

### 6.4.6 General procedure for the Peterson homologation of 1-bis(trimethylsilyl)methyl-1*H*-1,2,3-triazoles with aldehydes

To a solution of 1-[bis(trimethylsilyl)methyl]-4-phenyl-1*H*-1,2,3-triazole (1.00 mmol) and the corresponding aldehyde (1.50 mmol) in THF (15 mL) under nitrogen atmosphere, TASF (0.50 mmol) was added. The mixture was stirred at ambient temperature for 4 hours. After this time, the organic solvents were evaporated under reduced pressure and the crude was extracted with aqueous solution of NaCl (3 x 10 mL). The organic layer was dried over $MgSO_4$ to afford the corresponding intermediate 1-alkenyl 4-bis-1*H*-1,2,3-triazole. The latter product was used in the next reaction without further purification. To a solution of the corresponding alkene (1.00 mmol) in MeOH (35 mL), was added Pd/C (10% in mass). The suspension was stirred for 1hour under $H_2$ atmosphere. After this time, the suspension was filtered through a celite pad and the solvent was evaporated under reduced pressure.

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

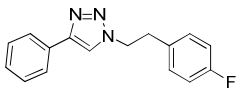


The general procedure 6.4.6 was followed starting from 1-[bis(trimethylsilyl)methyl]-4-phenyl-1*H*-1,2,3-triazole (0.33 mmol, 100 mg), pivaldehyde (0.50 mmol, 54 µL) and TASF (0.16 mmol, 45 mg) in THF (5 mL) to

afford 1-(3,3´-dimethyl-1-buten-1-yl)-4-phenyl-1*H*-1,2,3-triazole as a 61:39 mixture of *Z:E* isomers. The mixture of isomers was purified by column chromatography (silica gel, Hex/EtOAc 1:1). Yield: 58 mg (97 %). $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.99, 7.79 (s, s, 1H, triazole), 7.93 – 7.83 (m, m, 2H, Ar), 7.51 – 7.41 (m, m, 2H, Ar), 7.39-7.36 (m, m, 1H, Ar), 7.13, 6.69 (d, d, *J* = 14.6 Hz, *J* = 9.3 Hz, 1H, C*H*), 6.33, 5.85 (d, d, *J* = 14.6 Hz, *J* = 9.3 Hz, 1H, C*H*), 1.21, 1.06 (s, s, 3H, C$H_3$). After that, the product was purified by slow vapor diffusion of pentane into a solution of crude into $CH_2Cl_2$ at room temperature to afford *E* isomer. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H, triazole), 7.88 (d, *J* = 7.1 Hz, 2H, Ar), 7.46 (t, *J* = 7.6 Hz, 2H, Ar), 7.37 (t, *J* = 7.4 Hz, 1H, Ar), 7.14 (d, *J* = 14.6 Hz, 1H, *CH*), 6.33 (d, *J* = 14.6 Hz, 1H, *CH*), 1.22 (s, 9H, *CH*$_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 148.0, 134.1, 130.6, 129.1, 128.6, 126.0, 121.7, 116.6, 32.8, 29.6.

1-(3,3-Dimethyl-1-buten-1-yl)-4-phenyl-1*H*-1,2,3-triazole (0.07 mmol, 15 mg) and Pd/C (0.01 mmol, 7 mg) in MeOH (3 mL). Yield: quantitative. White solid (mp = 98-102 ºC). IR (cm$^{-1}$): 2956 (CH), 2923 (CH), 1468 (triazole), 765, 692. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.4 Hz, 2H, Ar), 7.78 (s, 1H, triazole), 7.45 (t, *J* = 7.6 Hz, 2H, Ar), 7.35 (t, *J* = 7.3 Hz, 1H, Ar), 4.55 – 4.34 (m, 2H, C$H_2$), 2.01 – 1.81 (m, 2H, C$H_2$), 1.04 (s, 9H, C$H_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 147.8, 130.7, 128.8, 128.0, 125.7, 119.2, 47.3, 44.0, 30.0, 29.2. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{14}H_{20}N_3$: 230.1657; found: 230.1659.

**1-[2-(4-Fluorophenyl)ethyl]-4-phenyl-1*H*-1,2,3-triazole**

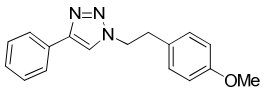



The general procedure 6.4.6 was followed starting from 1-[bis(trimethylsilyl)methyl]-4-phenyl-1*H*-1,2,3-triazole (0.33 mmol, 100 mg), 4-fluorobenzaldehyde (0.50 mmol, 53 µL) and TASF (0.16 mmol, 45 mg) in THF (5 mL) to afford 1-(4-fluorostyryl)-4-phenyl-1*H*-1,2,3-triazole as a mixture of *Z*:*E* isomers. The mixture of isomers was partially separated by slow vapor diffusion of pentane into a solution of crude into $CH_2Cl_2$ at room temperature to afford *E* isomer. Yield: 32 mg (36 %). White solid (mp = 202-204 ºC). IR (cm$^{-1}$): 1457 (triazole), 1226, 1160 (F-Ar). $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H, triazole), 7.91 (d, *J* = 7.2 Hz, 2H, Ar), 7.76 (d, *J* = 14.7 Hz, 1H, C*H*), 7.52-7.47 (m, 4H, Ar), 7.40 (t, *J* = 7.4 Hz, 1H, Ar), 7.20 (d, *J* = 14.7 Hz, 1H, C*H*), 7.14 (t, *J* = 8.5 Hz, 2H, Ar). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 163.0 (d, *J* = 249.4 Hz), 148.1, 130.0,

129.8, 129.0, 128.6, 128.42 (d, *J* = 8.2 Hz), 125.9, 122.9, 120.6, 116.5, 116.2 (d, *J* = 21.9 Hz). HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{13}FN_3^+$: 266.1094; found: 266.1102.

1-(4-Fluorostyryl)-4-phenyl-1*H*-1,2,3-triazole (0.05 mmol, 13 mg) and Pd/C (0.03 mmol, 39 mg) in MeOH (5 mL). Yield: quantitative. White solid (mp = 166-168 ºC). IR ($cm^{-1}$): 1441 (triazole), 1219 (F-Ar). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.2 Hz, 2H, Ar), 7.50 (s, 1H, triazole), 7.44 (t, *J* = 7.6 Hz, 2H, Ar), 7.35 (t, *J* = 7.4 Hz, 1H, Ar), 7.10 (m, 2H, Ar), 7.01 (t, *J* = 8.6 Hz, 2H, Ar), 4.63 (t, *J* = 7.1 Hz, 2H, C$H_2$), 3.26 (t, *J* = 7.1 Hz, 2H, C$H_2$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 162.0 (d, *J* = 245.8 Hz), 147.6, 132.8, 130.6, 130.3 (d, *J* = 8.0 Hz), 128.8, 128.2, 125.7, 119.9, 115.7 (d, *J* = 21.4 Hz), 51.8, 36.0. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}FN_3$: 268.1250; found: 268.1263.

**1-[2-(4-Methoxyphenyl)ethyl]-4-phenyl-1*H*-1,2,3-triazole**




The general procedure 6.4.6 was followed starting from 1-[bis(trimethylsilyl)methyl]-4-phenyl-1*H*-1,2,3-triazole (0.20 mmol, 60 mg), 4-methoxybenzaldehyde (0.22 mmol, 27 µL) and TASF (0.10 mmol, 27 mg) in THF (3 mL) to afford 1-(4-methoxystyryl)-4-phenyl-1*H*-1,2,3-triazole as a mixture of *Z*:*E* isomers. Yield: 44 mg (81 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H, triazole), 7.95 – 7.87 (m, 2H, Ar), 7.84 – 7.67 (m, 4H, triazole, C*H*, Ar), 7.52 – 7.31 (m, 8H, Ar), 7.23 – 7.08 (m, 4H, C*H*, C*H*, Ar), 6.96 (d, *J* = 8.7 Hz, 2H, Ar), 6.87 (d, *J* = 8.7 Hz, 2H, Ar), 6.54 (d, *J* = 9.5 Hz, 1H, C*H*), 3.87 (s, 3H, C$H_3$), 3.83 (s, 3H, C$H_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 160.4, 160.2, 148.1, 147.6, 130.3, 130.3, 129.1, 129.0, 128.6, 128.5, 128.3, 126.4, 126.0, 125.4, 124.7, 122.0, 121.6, 121.6, 119.5, 116.7, 114.7, 114.5, 55.56, 55.5.

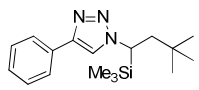
1-(4-Methoxystyryl)-4-phenyl-1*H*-1,2,3-triazole (0.1 mmol, 26 mg) and Pd/C (0.01 mmol, 10 mg) in MeOH (3.5 mL). Yield: quantitative. White solid (mp = 137-139 ºC). IR ($cm^{-1}$): 1462 (triazole), 1248, 1237 (MeO-Ar). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.2 Hz, 2H, Ar), 7.50 (s, 1H, triazole), 7.43 (t, *J* = 7.6 Hz, 2H, Ar), 7.34 (t, *J* = 7.3 Hz, 1H, Ar), 7.06 (d, *J* = 8.4 Hz, 2H, Ar), 6.86 (d, *J* = 8.5 Hz, 2H, Ar), 4.61 (t, *J* = 7.2 Hz, 2H, C$H_2$), 3.81(s, 3H, C$H_3$), 3.21 (t, *J* = 7.1 Hz, 2H, C$H_2$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 158.9, 147.6, 130.9,

130.0, 129.2, 129.0, 128.3, 125.9, 120.1, 114.4, 55.5, 52.2, 36.1. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{17}H_{18}N_3O$: 280.1450; found: 280.1461.

### 6.4.7 General procedure for the synthesis of 1-(1-trimethylsilylalkyl)-1*H*-1,2,3-triazoles by Peterson homologation of 1-bis(trimethylsilyl)methyl-1*H*-1,2,3-triazoles with aldehydes

To a solution of 1-[bis(trimethylsilyl)methyl]-4-phenyl-1*H*-1,2,3-triazole (1.00 mmol) and *n*-BuLi 1.6 M in hexanes (1.20 mmol) in THF (15 mL), the corresponding aldehyde (1.10 mmol) was added. The mixture was stirred for 1 hour at -78 ºC. After this time, chlorotrimethylsilane (5.00 mmol) was added, the organic solvents were evaporated under reduced pressure and the crude was extracted with aqueous solution of NaCl (3 x 10 mL). The organic layer was dried over $MgSO_4$ to afford the corresponding intermediate 1-[(trimethylsilyl)vinyl]-1*H*-1,2,3-triazole. The product was used in the next reaction without further purification. To a solution of the corresponding alkene (1.00 mmol) in MeOH (35 mL), was added Pd/C (10 % in mass). The suspension was stirred for 1 hour under $H_2$ atmosphere. After this time, the suspension was filtered through a celite pad and the solvent was evaporated under reduced pressure.

**1-[3,3-Dimethyl-1-(trimethylsilyl)butyl]-4-phenyl-1*H*-1,2,3-triazole**

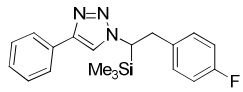



The general procedure 6.4.7 was followed starting from 1-[bis(trimethylsilyl)methyl]-4-phenyl-1*H*-1,2,3-triazole (0.33 mmol, 100 mg), *n*-BuLi 1.6 M in hexanes (0.40 mmol, 247 µL), pivaldehyde (0.66 mmol, 72 µL) and chlorotrimethylsilane (1.65 mmol, 143 µL) in THF (5 mL). The product was purified by slow vapor diffusion of pentane into a solution of crude into $CH_2Cl_2$ at room temperature to afford *E* isomer. Yield: 30 mg (30 %). White solid (mp = 169-170 ºC). IR ($cm^{-1}$): 1457 (triazole), 830 ($SiCH_3$), 764 ($SiCH_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.2 Hz, 2H, Ar), 7.64 (s, 1H, triazole), 7.46 (t, *J* = 7.6 Hz, 2H, Ar), 7.36 (t, *J* = 7.4 Hz, 1H, Ar), 6.07 (s, 1H, C*H*), 0.96 (s, 9H, C$H_3$), 0.15 (s, 9H, C$H_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ

152.9, 147.1, 137.8, 130.7, 128.8, 128.0, 125.6, 121.0, 35.3, 29.8, -2.1. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{17}H_{26}N_3Si$: 300.1896; found: 300.1908

1-[2-(*tert*-Butyl)-1-(trimethylsilyl)vinyl]-4-phenyl-1*H*-1,2,3-triazole (0.08 mmol, 25 mg) and Pd/C (0.01 mmol, 9 mg) in MeOH (3 mL). Yield: quantitative. White solid (mp = 145-147 ºC). IR ($cm^{-1}$): 1466 (triazole), 838 (Si-C), 762 ($SiCH_3$). $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.2 Hz, 2H, Ar), 7.68 (s, 1H, triazole), 7.45 (t, *J* = 7.7 Hz, 2H, Ar), 7.34 (t, *J* = 7.4 Hz, 1H, Ar), 4.32 (d, *J* = 10.6 Hz, 1H, C*H*), 2.17 (dd, *J* = 15.2, 11.5 Hz, 1H, C$H_2$), 1.70 (d, *J* = 15.3 Hz, 1H, C$H_2$), 0.83 (s, 6H, C$H_3$), 0.08 (s, 6H, C$H_3$). $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 147.3, 131.0, 128.8, 127.9, 125.6, 118.7, 50.8, 43.6, 31.6, 29.0, -3.8. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{17}H_{28}N_3Si$: 302.2052; found: 302.2059.

**1-[2-(4-Fluorophenyl)-1-(trimethylsilyl)ethyl)]-4-phenyl-1*H*-1,2,3-triazole**

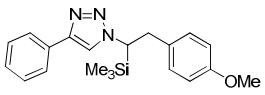



The general procedure 6.4.7 was followed starting from 1-[bis(trimethylsilyl)methyl]-4-phenyl-1*H*-1,2,3-triazole (0.16 mmol, 50 mg), *n*-BuLi 1.6 M in hexanes (0.20 mmol, 124 µL), 4-fluorobenzaldehyde (0.18 mmol, 20 µL) and chlorotrimethylsilane (0.82 mmol, 71 µL) in THF (2.5 mL). The product was purified by slow vapor diffusion of pentane into a solution of crude into $CH_2Cl_2$ at room temperature to afford *E* isomer. Yield: 20 mg (36 %). White solid (mp = 153-154 ºC). IR ($cm^{-1}$): 1454 (triazole), 1220 (F-Ar), 834 (Si-C), 765 ($SiCH_3$). $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H, triazole), 7.92 (d, *J* = 7.4 Hz, 2H, Ar), 7.61 (s, 1H, C*H*), 7.48 (t, *J* = 7.6 Hz, 2H, Ar), 7.42 – 7.33 (m, 3H, Ar), 7.13 (t, *J* = 8.5 Hz, 2H, Ar), 0.10 (s, 9H, C$H_3$). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 162.9 (d, *J* = 248.6 Hz), 147.3, 142.8, 140.4, 131.4, 131.3, 130.6 (d, *J* = 8.1 Hz), 128.9, 128.2, 125.7, 118.4, 115.4 (d, *J* = 21.7 Hz), -0.3. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{19}H_{21}FN_3Si$: 338.1489; found: 338.1491.

1-[2-(4-Fluorophenyl)-1-(trimethylsilyl)vinyl]-4-phenyl-1*H*-1,2,3-triazole (0.1 mmol, 27 mg) and Pd/C (0.01 mmol, 8 mg) in MeOH (3 mL). Yield: quantitative. White solid (mp = 82-83 ºC). IR ($cm^{-1}$): 1458 (triazole), 1251, 1216, 1154 (Ar-F), 841 (Si-C), 759 ($SiMe_3$). $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.1 Hz, 2H, Ar), 7.41 (t, *J* = 7.6 Hz, 2H, Ar), 7.32 (t, *J* = 7.4 Hz, 1H, Ar), 7.24 (s, 1H, triazole), 6.95-6.89 (m, 4H, Ar), 4.03 (dd, *J* = 11.9, 3.7 Hz, 1H, C*H*), 3.30 (dd, *J* = 14.3, 12.0 Hz, 1H, C*H*), 3.17 (dd, *J* = 14.4, 3.6 Hz, 1H, C*H*), 0.21 (s, 9H,

C*H*$_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 161.7 (d, *J* = 245.0 Hz), 146.6, 134.6, 130.8, 130.0 (d, *J* = 7.8 Hz), 128.8, 127.9, 125.5, 120.5, 115.4 (d, *J* = 21.3 Hz), 56.5, 36.8, -3.1. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{19}H_{23}FN_3Si$: 340.1645; found: 340.1649.

**1-[2-(4-Methoxyphenyl)-1-(trimethylsilyl)ethyl]-4-phenyl-1*H*-1,2,3-triazole**



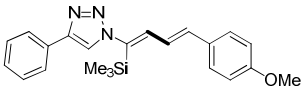

The general procedure 6.4.7 was followed starting from 1-[bis(trimethylsilyl)methyl]-4-phenyl-1*H*-1,2,3-triazole (0.20 mmol, 60 mg), *n*-BuLi 1.6 M in hexanes (0.24 mmol, 148 µL), 4-methoxybenzaldehyde (0.22 mmol, 27 µL) and chlorotrimethylsilane (0.99 mmol, 86 µL) in THF (3 mL). The product was purified by column chromatography (silica gel, Hex: EtOAc 1:1) to afford the desire product as a 44:56 mixture of *Z*:*E* isomers. Yield: 53 mg (77 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H, C*H*), 7.93 (d, *J* = 7.3 Hz, 2H, Ar), 7.85 (d, *J* = 7.2 Hz, 2H, Ar), 7.59 (s, 1H, C*H*), 7.58 (s, 1H, C*H*), 7.48 - 7.42 (m, 4H, Ar), 7.40 – 7.25 (m, 4H, Ar), 6.95 (d, *J* = 8.6 Hz, 2H, Ar), 6.86 (s, 1H, C*H*), 6.85 (d, *J* = 9.0 Hz, 2H, Ar), 6.74 (d, *J* = 8.8 Hz, 2H, Ar), 3.87 (s, 3H, C*H*$_3$), 3.76 (s, 3H, C*H*$_3$), 0.28 (s, 9H, C*H*$_3$), 0.12 (s, 9H, C*H*$_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 160.0, 151.9, 147.4, 147.1, 141.9, 141.1, 138.5, 137.4, 130.7, 130.6, 130.4, 130.2, 128.8, 128.8, 128.0, 127.5, 125.9, 125.6, 126.6, 119.8, 118.6, 114.0, 113.7, 55.2, 55.1, -0.4, -1.9.

1-[2-(4-Methoxyphenyl)-1-(trimethylsilyl)vinyl]-4-phenyl-1*H*-1,2,3-triazole (0.1 mmol, 30 mg) and Pd/C (0.01 mmol, 9 mg) in MeOH (4 mL). Yield: quantitative. White solid (mp = 115-116 ºC). IR ($cm^{-1}$): 1458 (triazole), 829 (Si-C), 764 ($SiMe_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.2 Hz, 2H, Ar), 7.41 (t, *J* = 7.6 Hz, 2H, Ar), 7.31 (t, *J* = 7.4 Hz, 1H, Ar), 7.26 (s, 1H, triazole), 6.90 (d, *J* = 8.5 Hz, 2H, Ar), 6.76 (d, *J* = 8.6 Hz, 2H, Ar), 4.05 (dd, *J* = 11.6, 3.9 Hz, 1H, C*H*), 3.75 (s, 3H, C*H*$_3$), 3.24 (dd, *J* = 14.3, 11.7 Hz, 1H, C*H*), 3.15 (dd, *J* = 14.4, 3.8 Hz, 1H, C*H*), 0.20 (s, 9H, C*H*$_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 158.3, 146.5, 130.9, 130.8, 129.5, 128.7, 127.8, 125.5, 120.5, 113.9, 56.5, 55.1, 36.8, -3.1. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{20}H_{26}N_3OSi$: 352.1845; found: 352.1842.

### 6.4.8 General procedure for the synthesis of *N*-α-(silyl-vinyl)-1*H*-1,2,3-triazoles

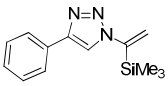
To a solution of 1-[bis(trimethylsilyl)methyl]-4-phenyl-1*H*-1,2,3-triazole (1.00 mmol) and *n*-BuLi 1.6 M in hexanes (1.20 mmol) in THF, was added the corresponding aldehyde (1.10 mmol). The mixture was stirred for 1 h at -78 ºC. After this time, chlorotrimethylsilane (5.00 mmol) was added, the organic solvents were evaporated under reduced pressure and the crude was extracted with aqueous solution of NaCl. The organic layer was dried over $MgSO_4$.

**1-[4-(4-Methoxyphenyl)-1-(trimethylsiyl)]-1,3-butadienyl-4-phenyl-1*H*-1,2,3-triazole**




The general procedure 6.4.8 was followed starting from 1-[bis(trimethylsilyl)methyl]-4-phenyl-1*H*-1,2,3-triazole (0.16 mmol, 50 mg), *n*-BuLi 1.6 M in hexanes (0.20 mmol, 124 µL), *trans-p*-methoxycinnamaldehyde (0.18 mmol, 30 mg) and chlorotrimethylsilane (0.82 mmol, 100 µL) in THF (2.5 mL). Both diastereoisomers were purified by column chromatography (silica gel, Hex:EtOAc 4:1). Yield: 40 mg (64 %). *E-E isomer*: White solid (mp= 101-103 ºC). IR ($cm^{-1}$): 1455 (triazole), 831 (Si-C), 756 ($SiMe_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.2 Hz, 2H, Ar), 7.81 (s, 1H, triazole), 7.49 (t, *J* = 7.6 Hz, 2H, Ar), 7.38 (t, *J* = 7.4 Hz, 1H, Ar), 7.31 (d, *J* = 8.7 Hz, 2H, Ar), 6.86 – 6.82 (m, 3H, Ar, C*H*), 6.74 (d, *J* = 10.8 Hz, 1H, C*H*), 6.62 (dd, *J* = 15.4, 10.8 Hz, 1H, C*H*), 3.82 (s, 3H, C$H_3$), 0.27 (s, 9H, C$H_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 160.3, 147.2, 138.8, 138.4, 138.3, 130.7, 129.0, 128.6, 128.2, 125.8, 120.7, 119.6, 114.3, 55.4, -1.7. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{22}H_{26}N_3OSi$: 376.1845; found: 376.1856. *Z-E isomer*: IR ($cm^{-1}$): 1455 (triazole), 832 (Si-C), 759 ($SiMe_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.3 Hz, 2H, Ar), 7.87 (s, 1H, triazole), 7.47 (t, *J* = 7.6 Hz, 2H, Ar), 7.41 (d, *J* = 8.6 Hz, 2H, Ar), 7.37 (t, *J* = 7.4 Hz, 1H, Ar), 7.13 – 7.06 (m, 2H, C*H*), 6.94 (d, *J* = 8.7 Hz, 2H, Ar), 6.75 (d, *J* = 13.7 Hz, 1H, C*H*), 3.87 (s, 3H, C$H_3$), 0.42 (s, 9H, C$H_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 160.2, 147.1, 140.6, 140.0, 138.5, 130.8, 129.3, 128.9, 128.3, 128.2, 125.8, 121.6, 118.5, 114.4, 55.4, 0.4. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{22}H_{26}N_3OSi$: 376.1845; found: 376.1851.

**4-Phenyl-1-[1-(trimethylsilyl)vinyl]-1*H*-1,2,3-triazole**

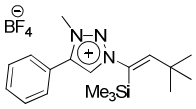


The general procedure 6.4.8 was followed starting from 1-[bis(trimethylsilyl)methyl]-4-phenyl-1*H*-1,2,3-triazole (0.10 mmol, 30 mg), *n*-BuLi 1.6 M in hexanes (0.12 mmol, 75 µL), formaldehyde (0.12 mmol, 4 mg) and chlorotrimethylsilane (0.50 mmol, 60 µL) in THF (1.5 mL). The product was purified by column chromatography (silica gel Hex:AcOEt 4:1). Yield: 20 mg (83 %). Colorless oil. IR ($cm^{-1}$): 1455 (triazole), 842 (Si-C), 762 ($SiMe_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H, triazole), 7.91 (d, *J* = 7.3 Hz, 2H, Ar), 7.46 (t, *J* = 7.6 Hz, 2H, Ar), 7.37 (t, *J* = 7.4 Hz, 1H, Ar), 5.98 (s, 1H, C*H*), 5.43 (s, 1H, C*H*), 0.38 (s, 9H, C$H_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 147.8, 147.1, 130.3, 128.8, 128.2, 125.7, 115.4, 115.3, -1.2. HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{13}H_{18}N_3Si$: 244.1270; found: 244.1275.

### 6.4.9 General procedure for the synthesis of 1,2,3-triazolium tetrafluoroborates

To a solution of the corresponding 1,2,3-triazole (1.0 mmol) in anhydrous $CH_2Cl_2$, trimethyloxonium tetrafluoroborate (1.3 mmol) was added. The mixture was stirred at room temperature for 5 hours. The volatiles were evaporated in vacuo, the residue was redissolved in anhydrous MeOH, and the resulting mixture was stirred overnight and evaporated. The crude product was purified by precipitation from $Et_2O$ or by column chromatography (silica gel, $CH_2Cl_2$/MeOH 9:1).

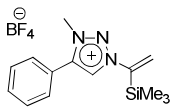
**1-[2-(*tert*-Butyl)-1-(trimethylsilyl)vinyl]-3-methyl-4-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate**



The general procedure 6.1.6 was followed starting from 1-[2-(*tert*-butyl)-1-(trimethylsilyl)vinyl]-4-phenyl-1*H*-1,2,3-triazole (0.04 mmol, 12 mg) and trimethyloxonium tetrafluoroborate (0.05 mmol, 10 mg) in $CH_2Cl_2$ (0.3 mL). The product was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH 9:1). Yield: 12 mg (75 %). Colorless oil. IR ($cm^{-1}$): 1446 (triazole), 1078 ($BF_4$), 840 (Si-C), 769 ($SiCH_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H, triazole), 7.78 – 7.68 (m, 2H, Ar), 7.60 (m, 3H, Ar), 6.22 (s, 1H, C*H*), 4.39 (s, 3H, C$H_3$), 1.00 (s, 9H, C$H_3$), 0.23 (s, 9H, C$H_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 155.9, 144.0, 136.9, 132.3, 130.0, 129.8,

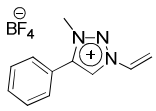
139.7, 121.7, 39.2, 36.4, 29.6, -2.2. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{18}H_{28}N_3Si$: 314.2053; found: 314.2060.

**3-Methyl-4-phenyl-1-[1-(trimethylsilyl)vinyl]-1*H*-1,2,3-triazolium tetrafluoroborate**



The general procedure 6.1.6 was followed starting from 4-phenyl-1-[1-(trimethylsilyl)vinyl]-1*H*-1,2,3-triazole (0.08 mmol, 20 mg) and trimethyloxonium tetrafluoroborate (0.11 mmol, 20 mg) in $CH_2Cl_2$ (0.6 mL). The product was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH 9:1). Yield: 19 mg (67 %). White solid (mp = 155-165 ºC). IR ($cm^{-1}$): 1462 (triazole), 1076 ($BF_4$), 854 (Si-C), 767 ($SiCH_3$). $^1$H NMR (500 MHz, MeCN-$d_3$) δ 8.73 (s, 1H, triazole), 7.72-7.69 (m, 5H, Ar), 6.51 (d, *J* = 2.0 Hz, 1H, C*H*), 6.03 (d, *J* = 1.6 Hz, 1H, C*H*), 4.25 (s, 3H, C$H_3$), 0.40 (s, 9H, C$H_3$). $^{13}$C NMR (126 MHz, MeCN-$d_3$) δ 146.8, 142.9, 131.5, 129.3, 129.0, 125.4, 124.8, 122.0, 38.3, -3.1. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{14}H_{20}N_3Si$: 258.1427; found: 258.1426.

**3-Methyl-4-phenyl-1-vinyl-1*H*-1,2,3-triazolium tetrafluoroborate**

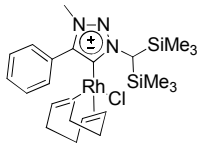


To a solution of 3-methyl-4-phenyl-1-[1-(trimethylsilyl)vinyl]-1*H*-1,2,3-triazolium tetrafluoroborate (0.12 mmol, 40 mg) in toluene (0.60 mL), furan (1.20 mmol, 88 µL) was added and the resulting mixture was stirred for 18 hours at 150 ºC. After this time, the solvent was evaporated under reduced pressure. The product was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH 9:1). Yield: 24 mg (73 %). White solid (mp = 156-161 ºC). IR ($cm^{-1}$): 1460 (triazole), 1051 ($BF_4$), 841 (Si-C), 754 ($SiCH_3$). $^1$H NMR (400 MHz, MeCN-$d_3$) δ 8.77 (s, 1H, triazole), 7.89 – 7.61 (m, 5H, Ar), 7.52 (dd, *J* = 15.5, 8.7 Hz, 1H, C*H*), 6.30 (dd, *J* = 15.5, 2.2 Hz, 1H, C*H*), 5.83 (dd, *J* = 8.2, 1.8 Hz, 1H, C*H*), 4.26 (s, 3H, C$H_3$). $^{13}$C NMR (101 MHz, MeCN-$d_3$) δ 144.4, 132.6, 130.3, 130.0, 126.5, 122.8, 114.5, 39.4. HRMS (ESI+): *m/z* $[M]^+$ calcd for $C_{11}H_{12}N_3$: 189.1031; found: 186.1031.

### 6.4.10 Preparation of mesoionic carbenes by direct metalation of 3-alkyl-1,2,3-triazolium salts

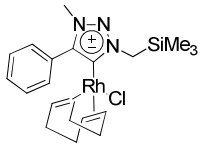
To a solution of the corresponding 1,2,3-triazolium salt (1.00 mmol) and metal salt (1.20 mmol) in anhydrous THF (6 mL) at -78 ºC, $LiN(SiMe_3)_2$ in THF 1 M (1.50 mmol) was added. The mixture was stirred at -78 ºC for 4 hours. The volatiles were evaporated in vacuo, the crude was filtered through a celite: silica pad and washed with $CH_2Cl_2$. In some cases, the product was purified by column chromatography (silica gel; $CH_2Cl_2$:MeOH, 95:5).

**1-[Bis(trimethylsilyl)]-3-methyl-4-phenyl-1*H*-1,2,3-triazol-5-ylidene[chloro(cyclooctadiene)rhodium(I)]**




The general procedure 6.4.10 was followed starting from 1-[bis(trimethylsilyl)methyl]-3-methyl-4-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.06 mmol, 25 mg), $[Rh(cod)Cl]_2$ (0.06 mmol, 31 mg) and $LiN(SiMe_3)_2$ in THF 1 M (0.09 mmol, 93 µL) in THF (0.40 mL). Yield: 34 mg (93 %). Yellow solid (mp = 135-136 ºC). IR ($cm^{-1}$): 2951 (cod), 823, 733 ($Si(CH_3)_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.4 Hz, 2H, Ar), 7.68 – 7.44 (m, 3H, Ar), 5.05 (s, 1H, C*H*), 5.00 – 4.81 (m, 2H, cod), 3.99 (s, 3H, C$H_3$), 3.20 (s, 1H, cod), 2.70 (s, 1H, cod), 2.61 – 1.51 (m, 8H, cod), 0.25 (s, 9H, SiC$H_3$), 0.23 (s, 9H, SiC$H_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 169.1 (d, *J* = 48.1 Hz, $C_{carbene}$), 143.6, 130.3, 129.0, 128.6, 128.2, 96.0, 95.6, 70.7 (d, *J* = 15.3 Hz, $C_{cod}$), 65.7 (d, *J* = 15.1 Hz, $C_{cod}$), 50.6, 36.8, 32.9, 32.0, 29.7, 28.0, -0.3, -0.4. HRMS (ESI+): *m/z* $[M\text{-}Cl]^+$ calcd for $C_{24}H_{39}N_3Si_2Rh$: 528.1738; found: 528.1749.

**3-Methyl-4-phenyl-1-trimethylsilylmethyl-1*H*-1,2,3-triazol-5-ilydene[chloro(cyclooctadiene)rhodium(I)]**

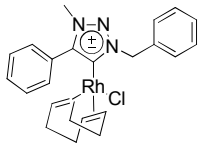



The general procedure 6.4.10 was followed starting from 3-methyl-4-phenyl-1-trimethylsilyl-1*H*-1,2,3-triazolium triflate (0.06 mmol, 24 mg), $[Rh(cod)Cl]_2$ (0.06 mmol, 31 mg) and $LiN(SiMe_3)_2$ in THF 1 M (0.09 mmol, 93 µL) in THF (0.40 mL). Yield: 26 mg (85 %). Yellow solid (mp = 163-165 ºC). IR ($cm^{-1}$): 2952 (cod), 1445 (triazole), 847, 765 ($Si(CH_3)_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.4 Hz, 2H, Ar), 7.70 – 7.46 (m, 3H, Ar), 5.14 – 4.96 (m, 1H, cod), 4.90 (s, 1H, cod), 4.71, 4.47 (d, *J* = 15.7 Hz, 1H, C$H_2$SiMe$_3$), 4.01 (s, 3H,

C*H*$_3$), 3.17 (s, 1H, cod), 2.66 – 2.26 (m, 4H, cod), 1.93 – 1.49 (m, 5H, cod), 0.27 (s, 9H, Si(C*H*$_3$)$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 171.4 (d, *J* = 46.6 Hz, $C_{carbene}$), 143.6, 130.1, 129.2, 128.2, 128.1, 96.2 (t, *J* = 9.4 Hz, $C_{cod}$), 69.1 (d, *J* = 14.5 Hz, $C_{cod}$), 66.7 (d, *J* = 14.9 Hz, $C_{cod}$), 47.1, 37.0, 33.2, 32.0, 29.0, 28.9, -1.7. HRMS (ESI+): *m/z* $[M\text{-}Cl]^+$ calcd for $C_{21}H_{31}N_3SiRh$: 456.1342; found: 456.1349.

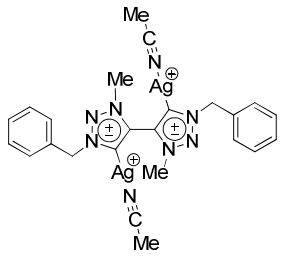
**1-Benzyl-3-methyl-4-phenyl-1*H*-1,2,3-triazol-5-ylidene**

**[chloro(cyclooctadiene)rhodium(I)]**




The general procedure 6.4.10 was followed starting from 1-benzyl-3-methyl-4-phenyl-1*H*-1,2,3-triazolium tetrafluoroborate (0.10 mmol, 33 mg), $[Rh(cod)Cl]_2$ (0.10 mmol, 49 mg) and $LiN(SiMe_3)_2$ in THF 1 M (0.15 mmol, 148 µL) in THF (0.60 mL). Yield: 26 mg (82 %). Yellow solid (mp = 91-92 ºC). IR ($cm^{-1}$): 2987 (cod), 1455 (triazole). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.03 (m, 2H, Ar), 7.75 – 7.64 (m, 2H, Ar), 7.62 – 7.48 (m, 3H, Ar), 7.48 – 7.35 (m, 3H, Ar), 6.41, 5.76 (d, *J* = 14.3 Hz, 1H, C*H*$_2$Ph), 5.07 – 4.89 (m, 2H, cod), 4.02 (s, 3H, C*H*$_3$), 2.78 – 2.60 (m, 1H, cod), 2.43 – 2.27 (m, 1H, cod), 2.19 – 1.43 (m, 8H, cod). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 171.0 (d, *J* = 46.6 Hz, $C_{carbene}$), 144.5 (d, *J* = 2.4 Hz), 135.4, 130.3, 129.4, 129.3, 128.7, 128.5, 128.4, 128.2, 96.7 (d, *J* = 7.3 Hz, $C_{cod}$), 96.1 (d, *J* = 7.3 Hz, $C_{cod}$), 70.7 (d, *J* = 14.7 Hz, $C_{cod}$), 67.5 (d, *J* = 14.7 Hz, $C_{cod}$), 58.4, 37.2, 32.6, 32.4, 29.3, 28.5. HRMS (ESI+): *m/z* $[M\text{-}Cl]^+$ calcd for $C_{24}H_{27}N_3Rh$: 460.1260; found: 460.1271.

### 6.4.11 Synthesis of 1,1'-dibenzyl-3,3'-dimethyl-4,4'-bis(1*H*-1,2,3-triazol-5,5'-diylidene)-silver(I)acetonitrile



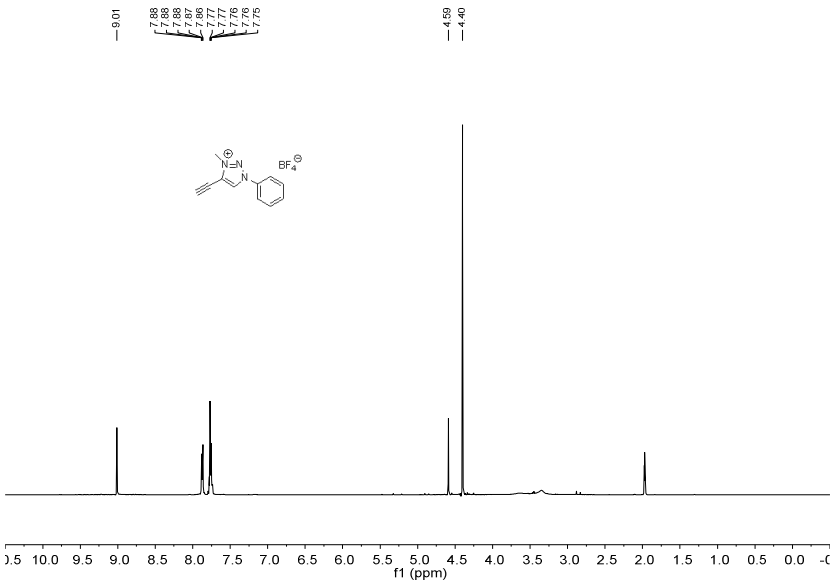

To a solution of the 1,1'-dibenzyl-3,3'-dimethyl-4,4'-bis(1*H*-1,2,3-triazolium) ditetrafluoroborate (0.31 mmol, 160 mg) in anhydrous MeCN (5.3 mL) was added $Ag_2O$ (1.23 mmol, 284 mg) and the mixture was refluxed for 24 hours at 80 ºC. The suspension was filtered through a celite pad, washed with anhydrous methanol (5 mL x 3) and the combined filtrate was evaporated under reduced pressure to afford the Ag(I) intermediate dicarbene complex. Yield: 187 mg (94 %). Yellowish oil. $^1$H NMR (400 MHz,

MeCN-$d_4$) δ 7.27 – 7.09 (m, 10H, Ar), 5.57 (d, *J* = 14.2, 2H, C$H_2$), 5.41 (d, *J* = 14.3, 2H, C$H_2$), 4.22 (s, 6H, C$H_3$). $^{13}$C NMR (101 MHz, MeCN-$d_4$) δ 169.8 ($C_{carbene}$), 137.4, 134.1, 128.8, 128.4, 128.2, 117.1, 58.1, 37.7.].

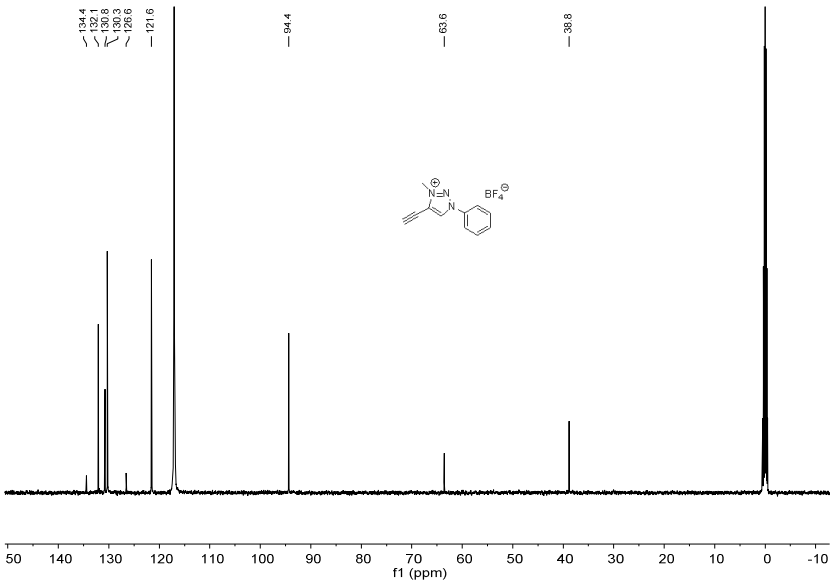
# 7

*Appendix*

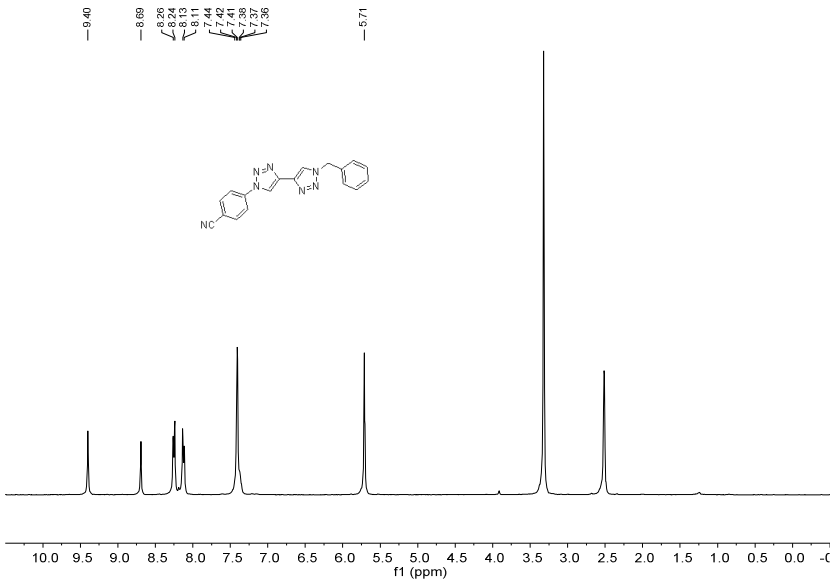
## APPENDIX 1: $^{1}$H NMR and $^{13}$C NMR Spectra



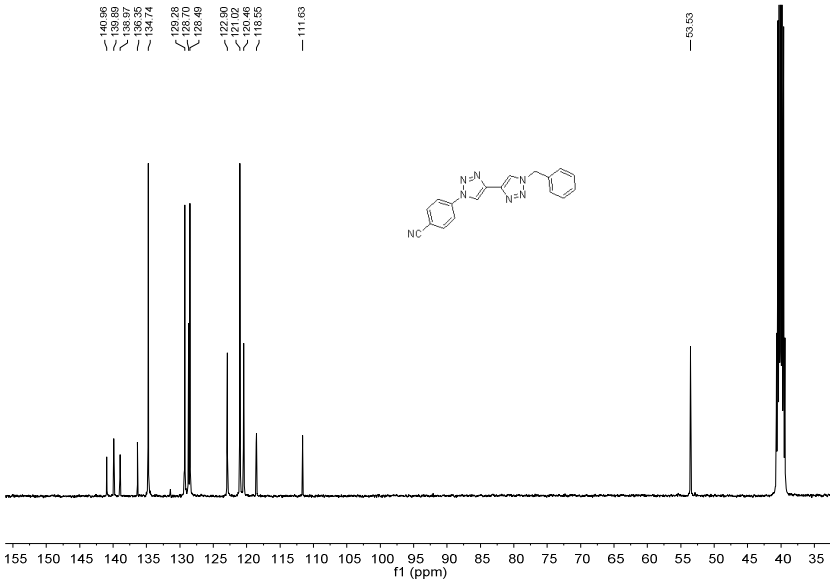

**Spectrum 1.** $^{1}$H NMR (500 MHz, MeCN-$d_3$) spectra of compound **2e**.



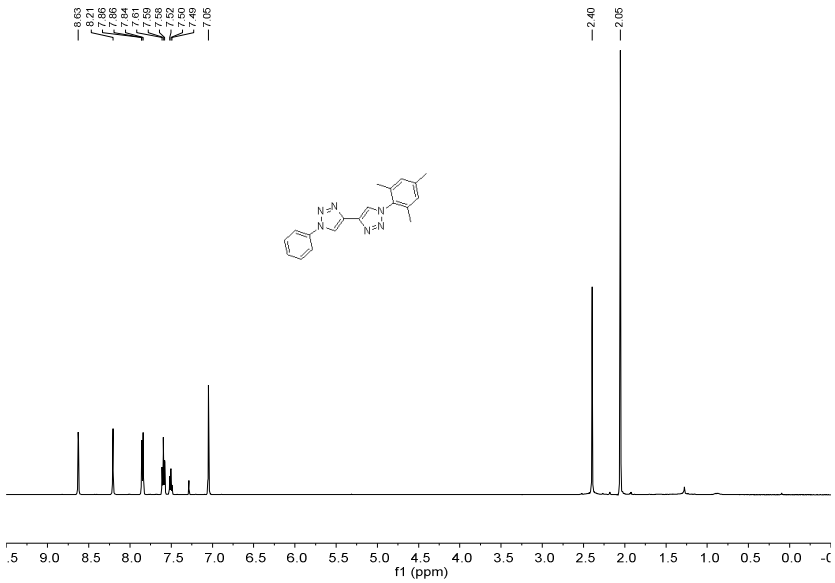

**Spectrum 2.** $^{13}$C NMR (126 MHz, MeCN-$d_3$) spectra of compound **2e**.



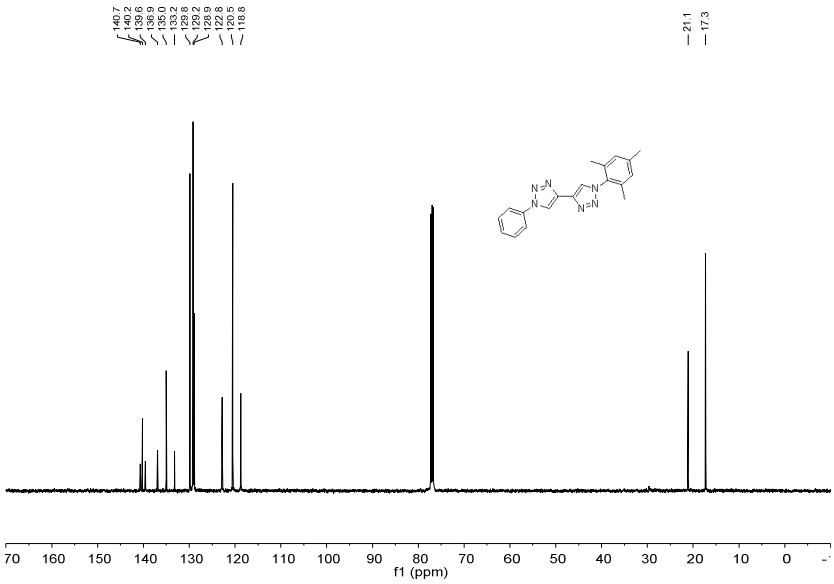

**Spectrum 3.** $^{1}$H NMR (400 MHz, DMSO-$d_6$) spectra of compound $\mathbf{8_{1,4}}$.



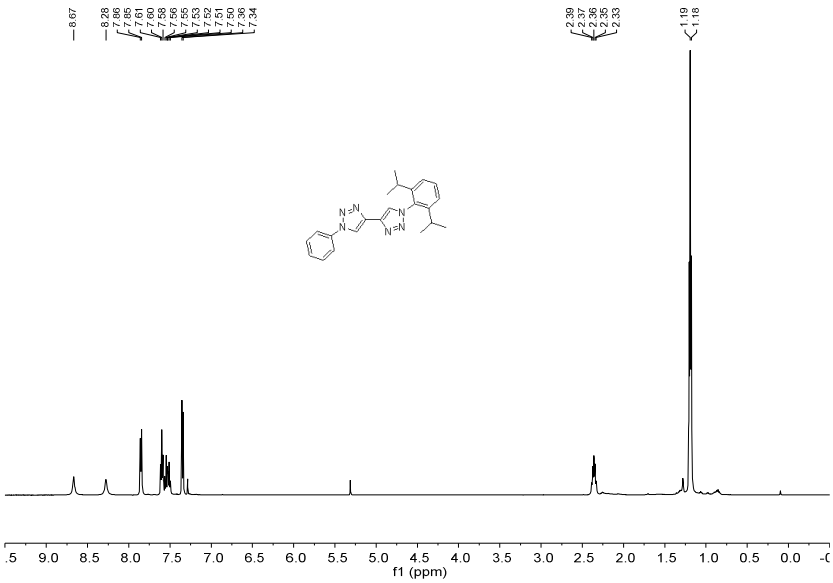

**Spectrum 4.** $^{13}$C NMR (101 MHz, DMSO-$d_6$) spectra of compound $\mathbf{8_{1,4}}$.



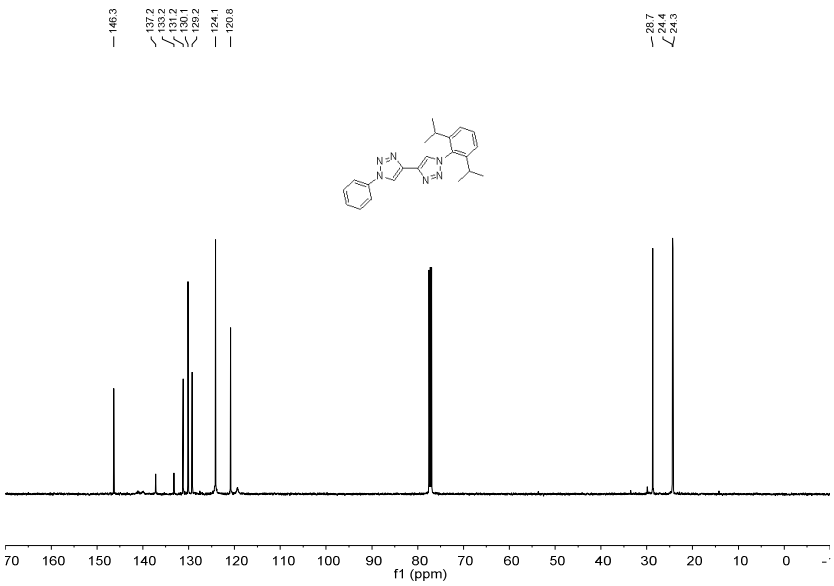

**Spectrum 5.** $^{1}H$ NMR (500 MHz, $CDCl_3$) spectra of compound **21**.



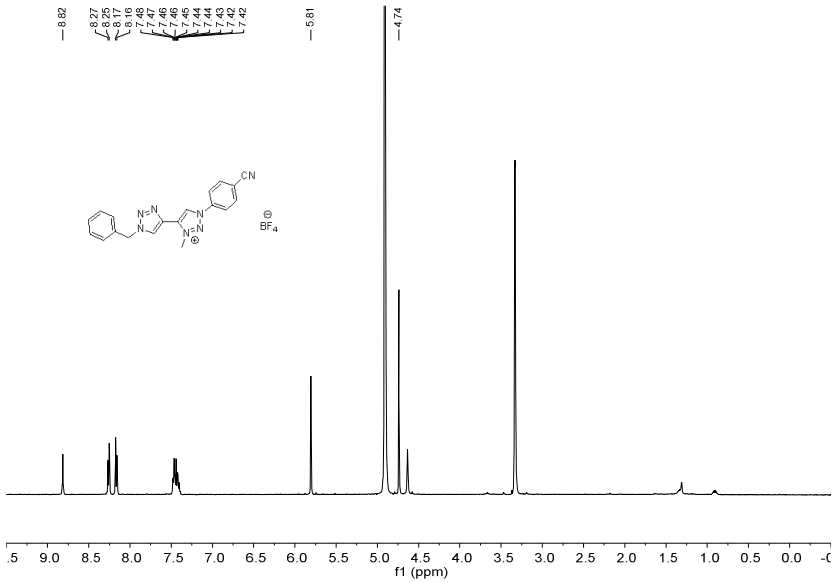

**Spectrum 6.** $^{13}C$ NMR (126 MHz, $CDCl_3$) spectra of compound **21**.



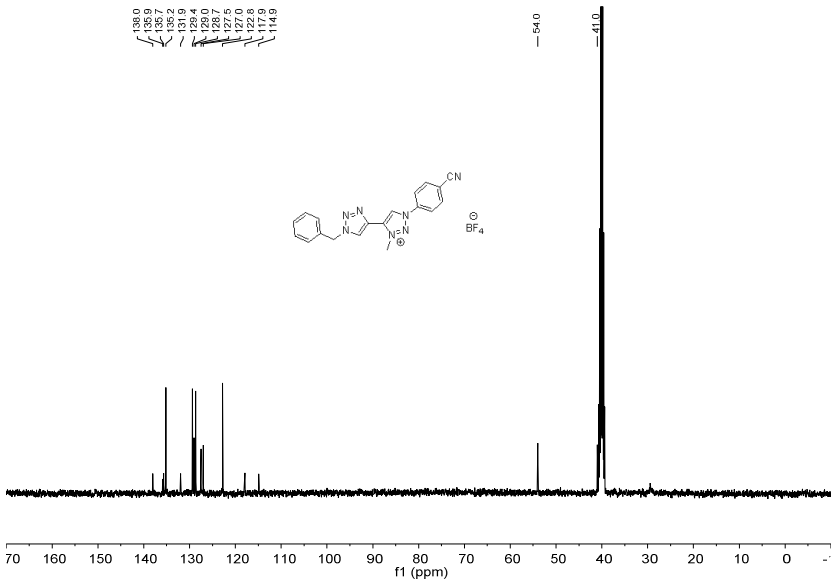

**Spectrum 7.** $^{1}$H NMR (500 MHz, $CDCl_3$) spectra of compound **22**.



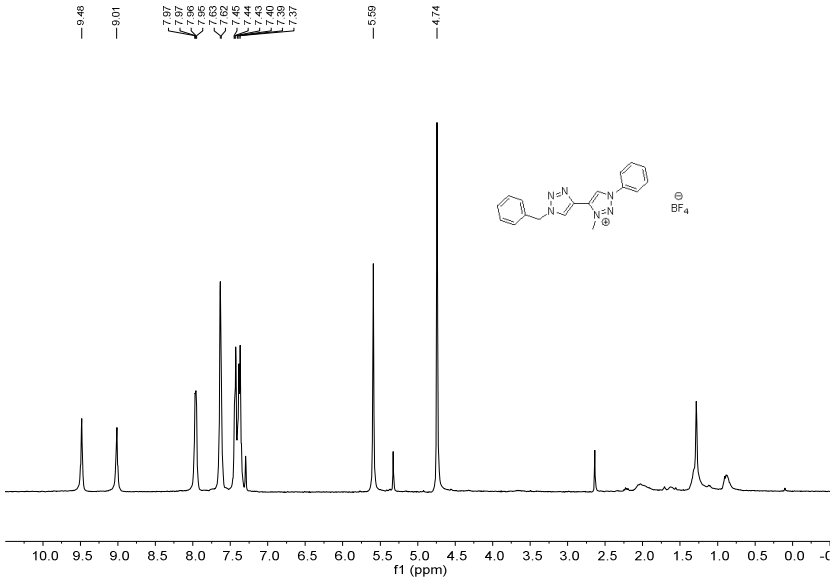

**Spectrum 8.** $^{13}$C NMR (126 MHz, $CDCl_3$) spectra of compound **22**.



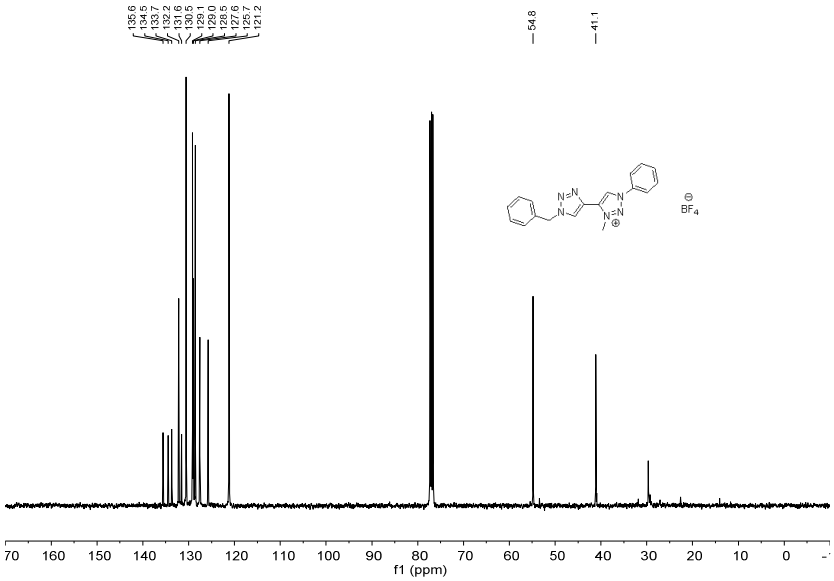

**Spectrum 9.** $^{1}$H NMR (500 MHz, MeOH-$d_4$) spectra of compound $\mathbf{9_{1,4}}$.



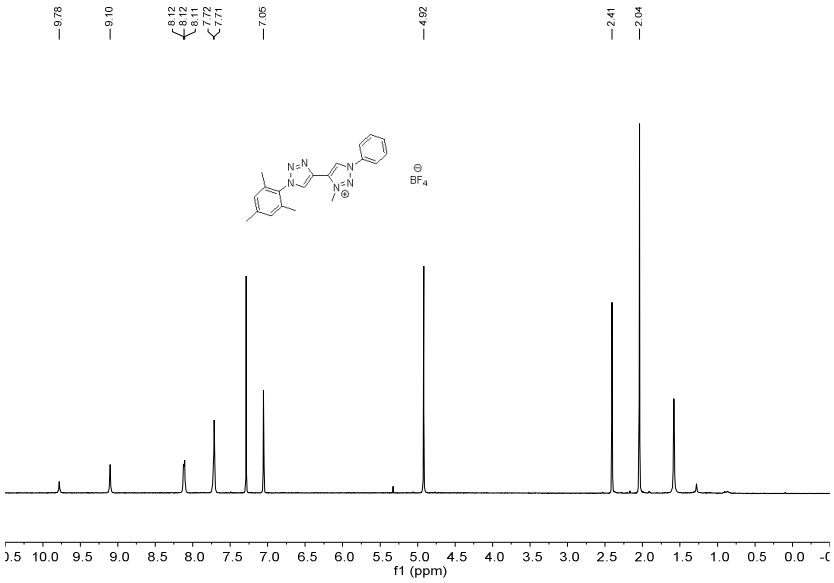

**Spectrum 10.** $^{13}$C NMR (101 MHz, DMSO-$d_6$) spectra of compound $\mathbf{9_{1,4}}$.



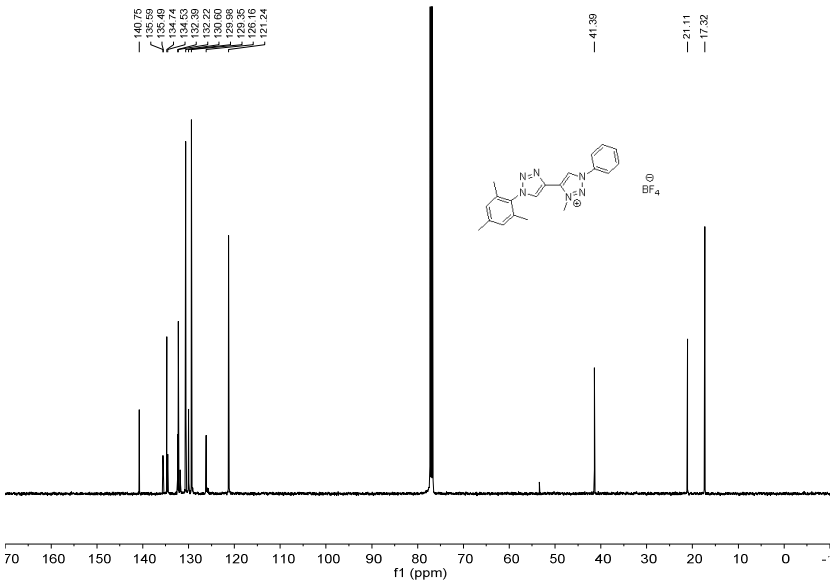

**Spectrum 11.** $^{1}H$ NMR (400 MHz, $CDCl_3$) spectra of compound **11**.



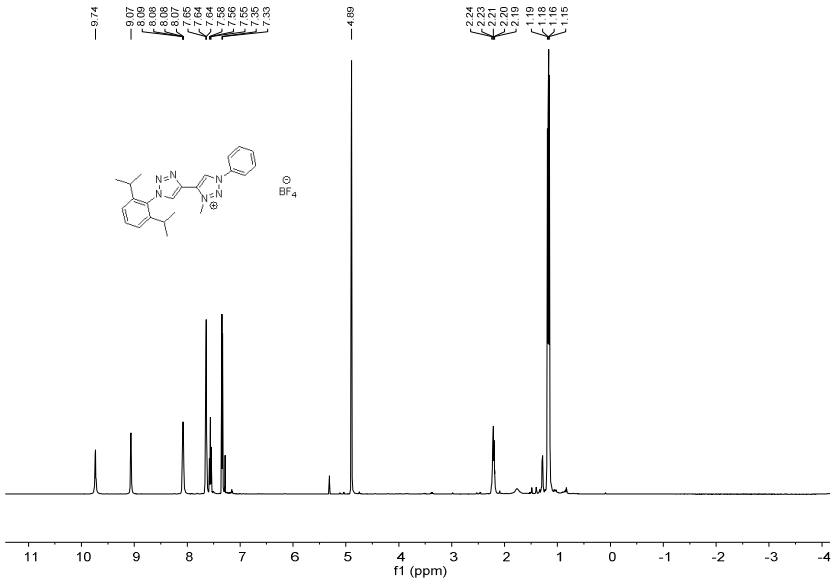

**Spectrum 12.** $^{13}C$ NMR (101 MHz, $CDCl_3$) spectra of compound **11**.



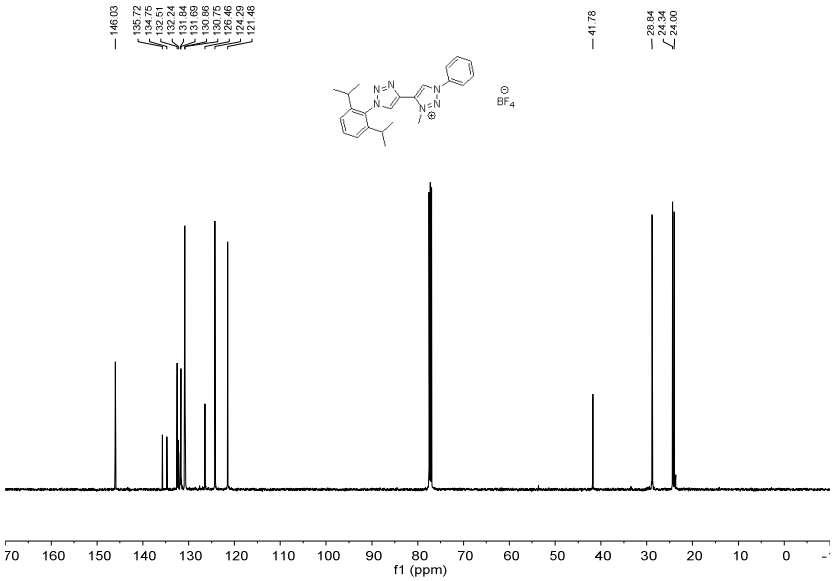

**Spectrum 13.** $^{1}$H NMR (500 MHz, $CDCl_3$) spectra of compound **17**.



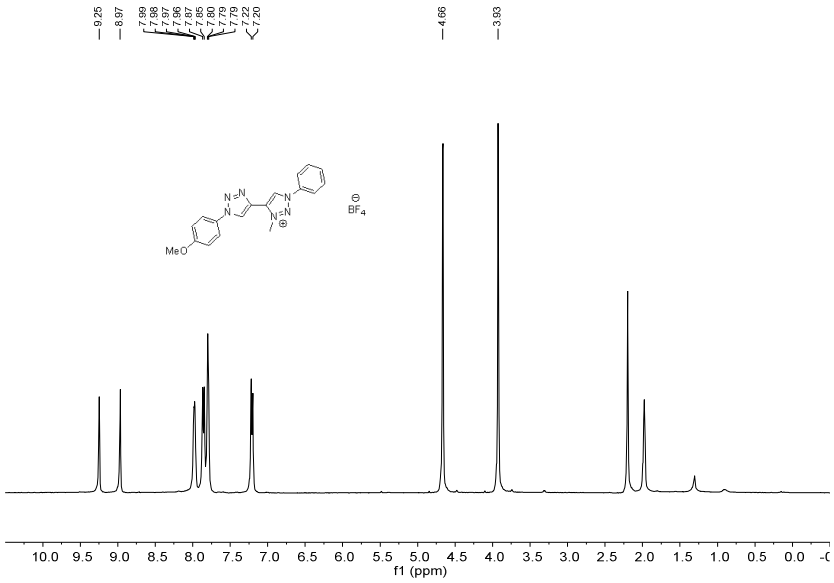

**Spectrum 14.** $^{13}$C NMR (126 MHz, $CDCl_3$) spectra of compound **17**.



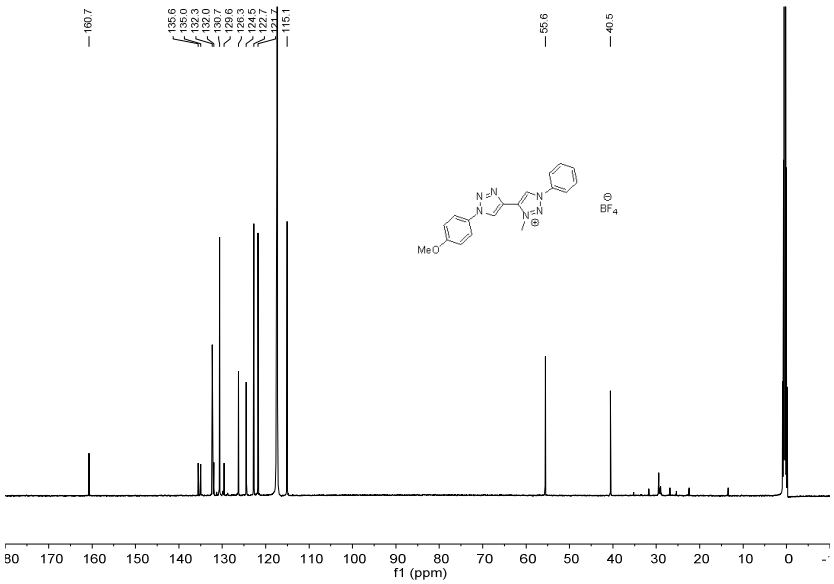

**Spectrum 15.** $^{1}$H NMR (500 MHz, $CDCl_3$) spectra of compound **16**.



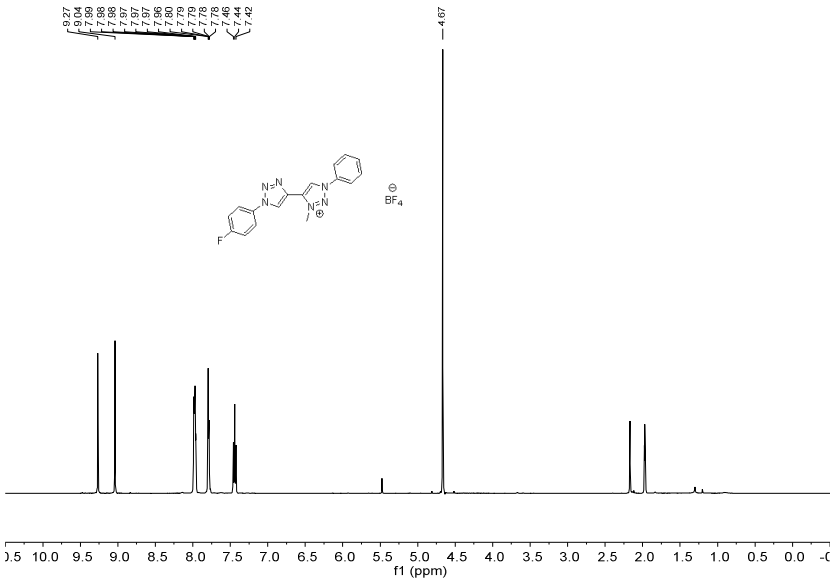

**Spectrum 16.** $^{13}$C NMR (126 MHz, $CDCl_3$) spectra of compound **16**.



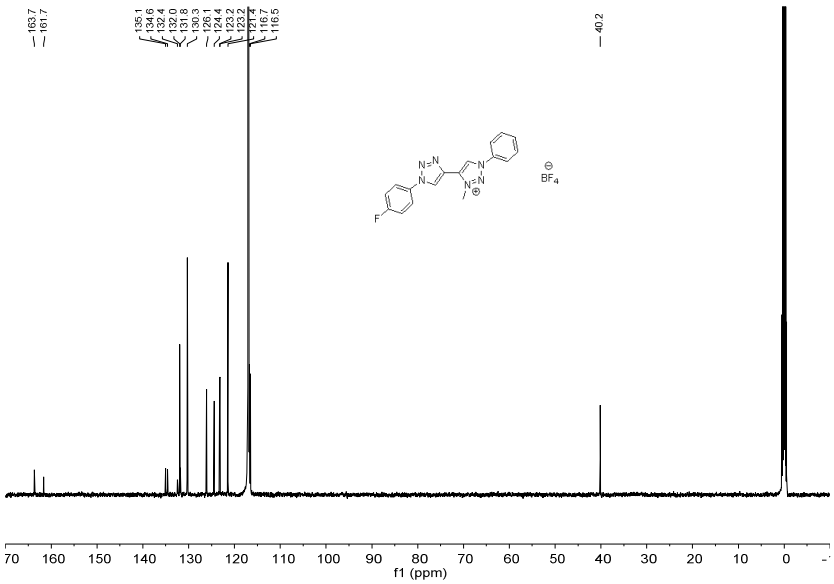

**Spectrum 17.** $^{1}$H NMR (400 MHz, MeCN-$d_3$) spectra of compound **14**.



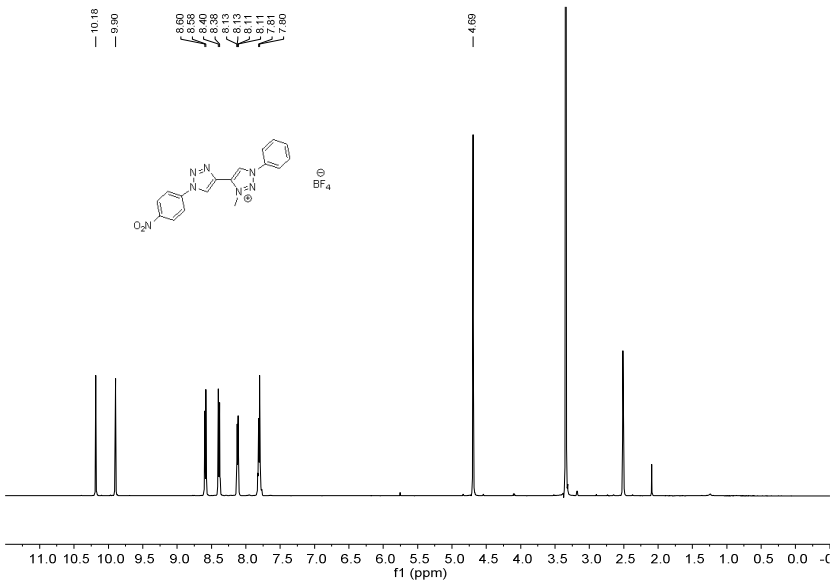

**Spectrum 18.** $^{13}$C NMR (126 MHz, MeCN-$d_3$) spectra of compound **14**.



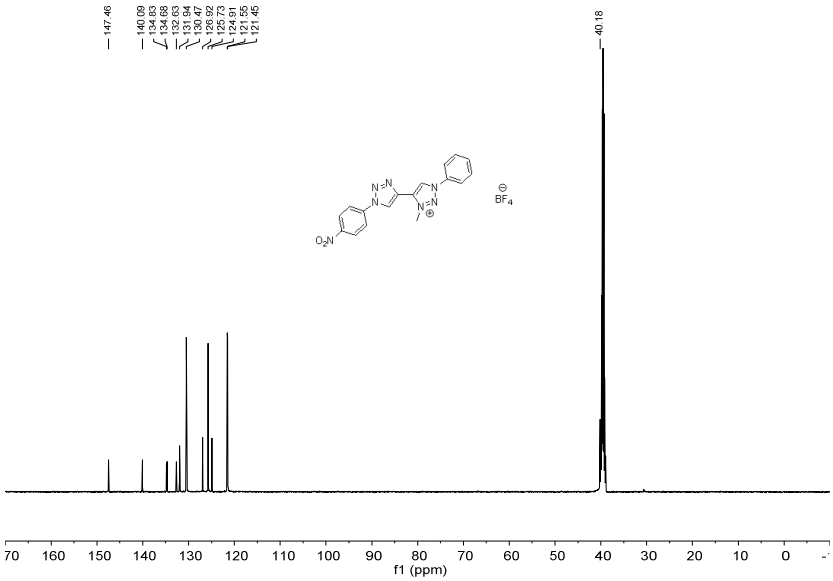

**Spectrum 19.** $^{1}$H NMR (500 MHz, MeCN-$d_3$) spectra of compound **15**.



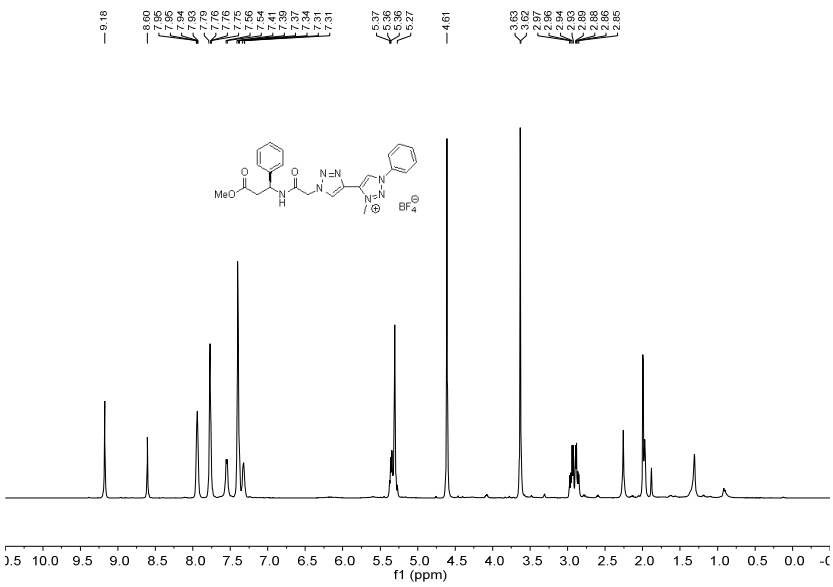

**Spectrum 20.** $^{13}$C NMR (126 MHz, MeCN-$d_3$) spectra of compound **15**.



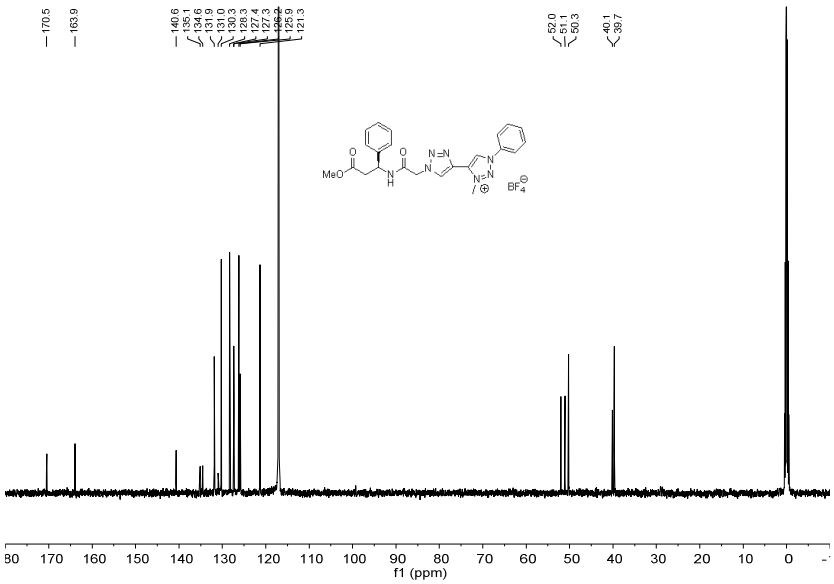

**Spectrum 21.** $^{1}$H NMR (500 MHz, DMSO-$d_6$) spectra of compound **13**.



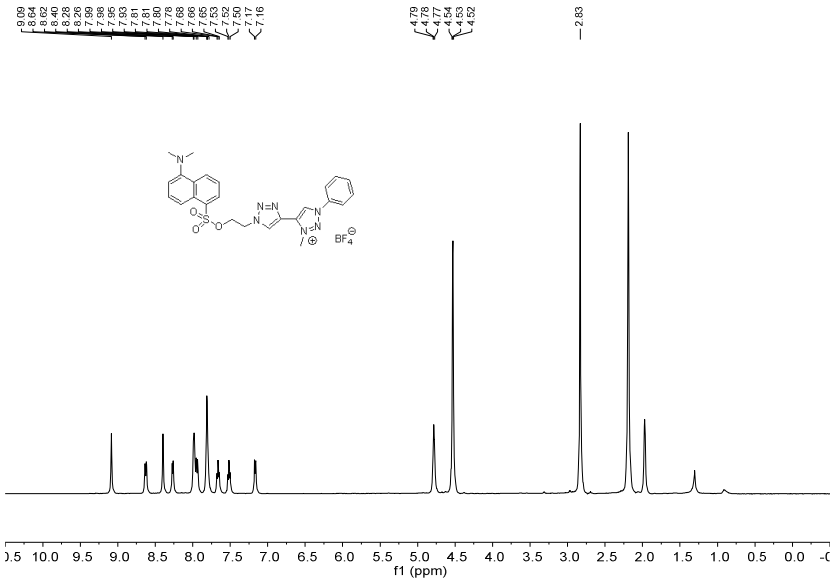

**Spectrum 22.** $^{13}$C NMR (126 MHz, DMSO-$d_6$) spectra of compound **13**.



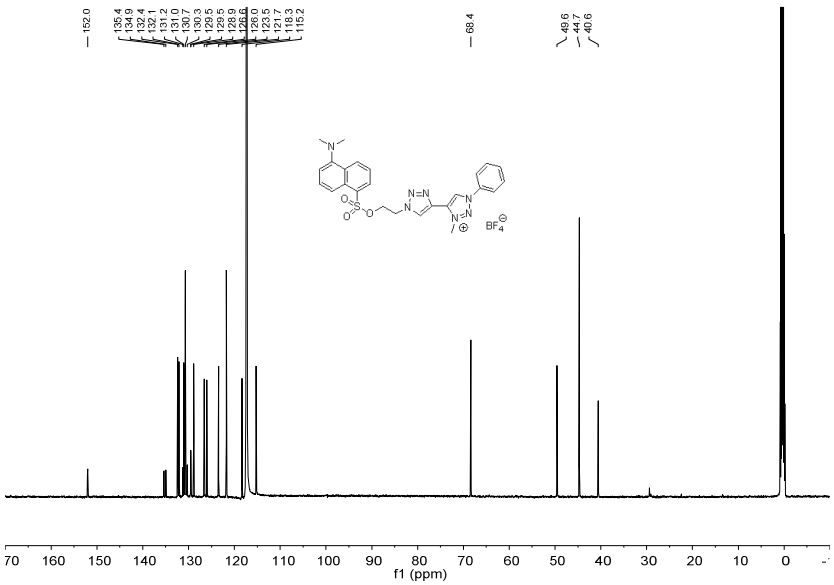

**Spectrum 23.** $^{1}$H NMR (500 MHz, MeCN-$d_3$) spectra of compound **18**.



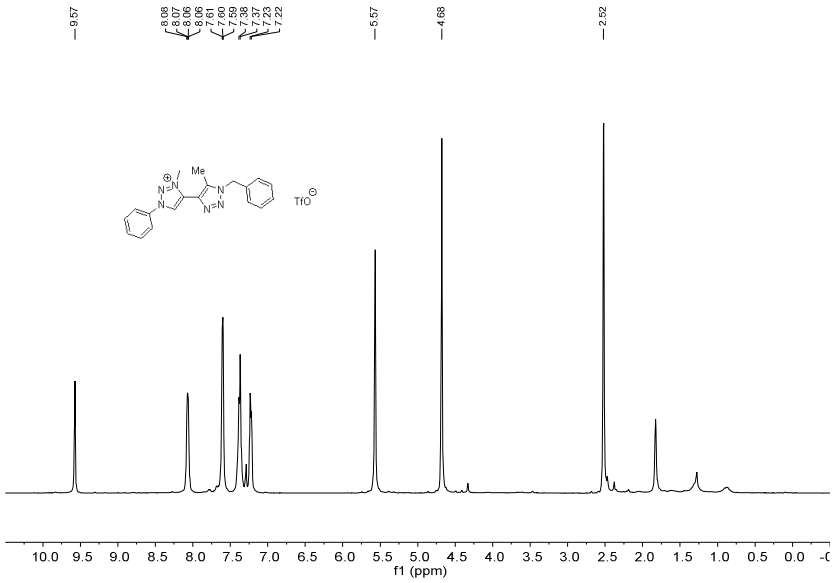

**Spectrum 24.** $^{13}$C NMR (126 MHz, MeCN-$d_3$) spectra of compound **18**.



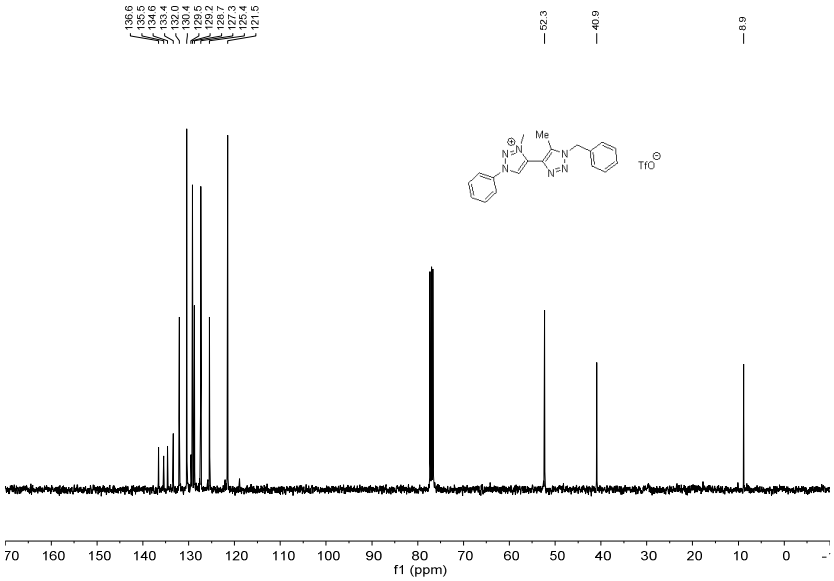

**Spectrum 25.** $^{1}$H NMR (500 MHz, MeCN-$d_3$) spectra of compound **19**.



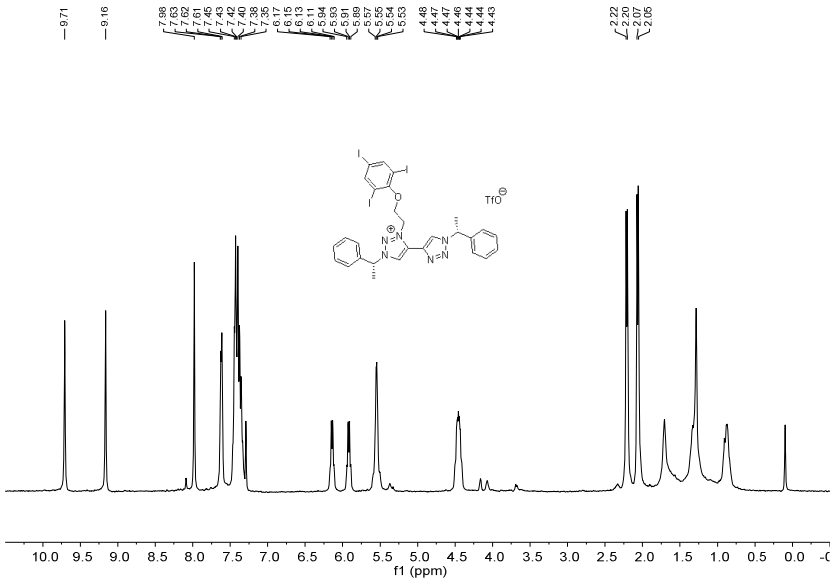

**Spectrum 26.** $^{13}$C NMR (126 MHz, MeCN-$d_3$) spectra of compound **19**.



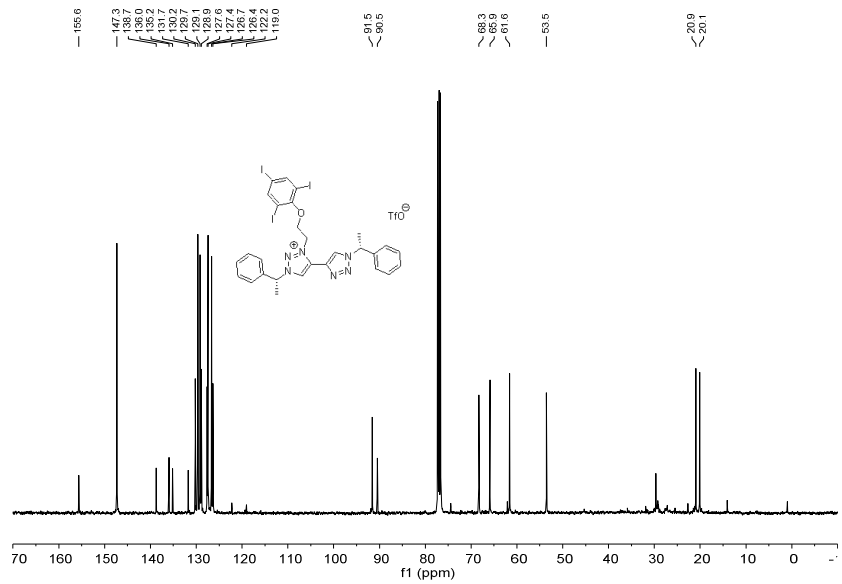

**Spectrum 27.** $^{1}$H NMR (400 MHz, $CDCl_3$) spectra of compound **10**.



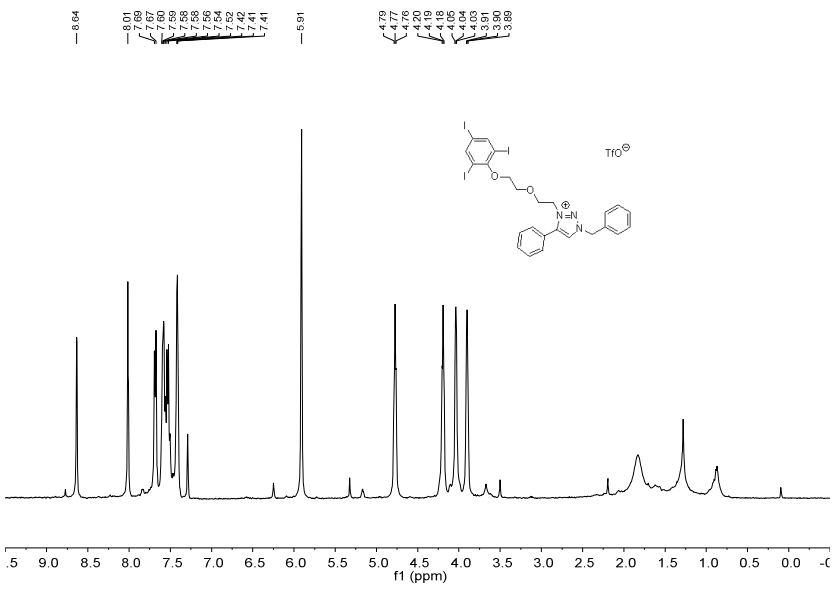

**Spectrum 28.** $^{13}$C NMR (101 MHz, $CDCl_3$) spectra of compound **10**.



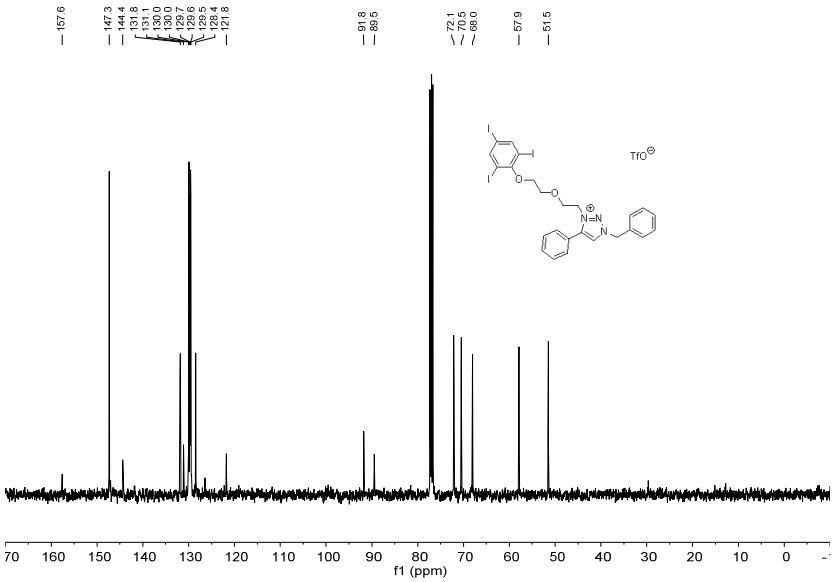

**Spectrum 29.** $^{1}$H NMR (400 MHz, $CDCl_3$) spectra of compound **50**.



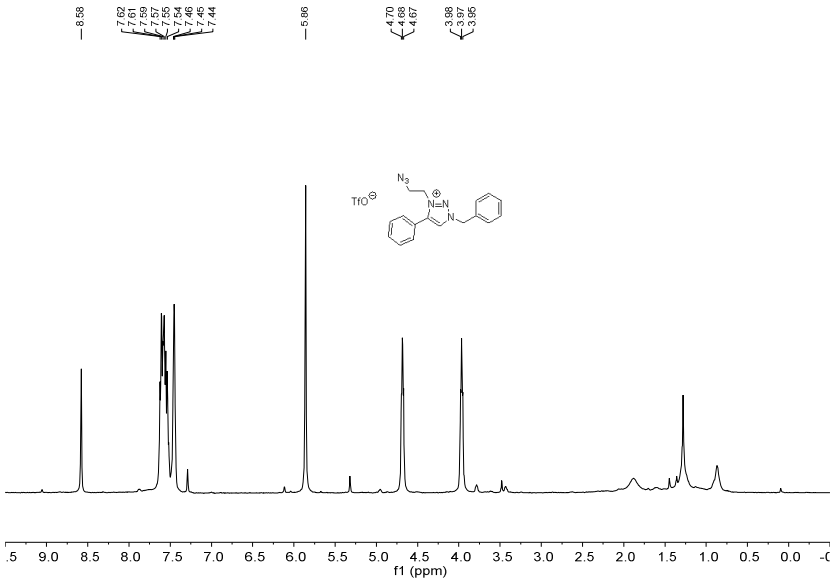

**Spectrum 30.** $^{13}$C NMR (101 MHz, $CDCl_3$) spectra of compound **50**.



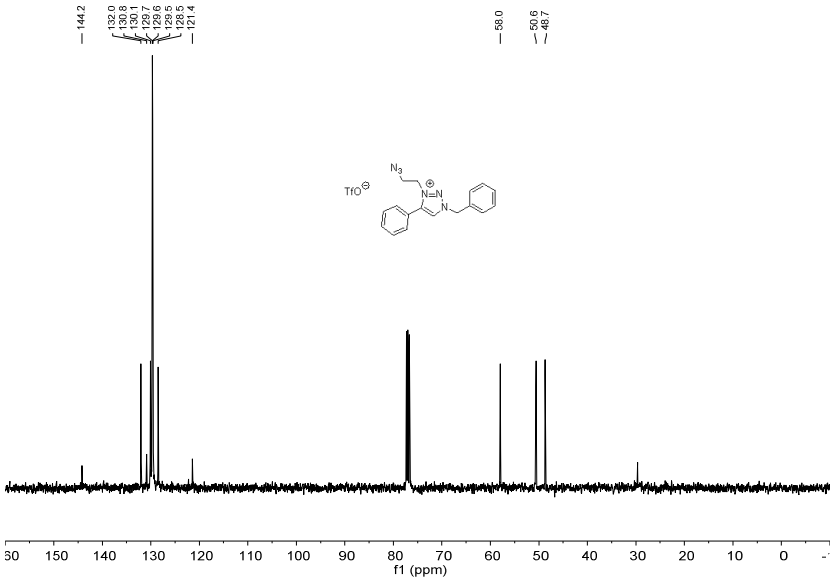

**Spectrum 31.** $^{1}$H NMR (400 MHz, $CDCl_3$) spectra of compound **41**.



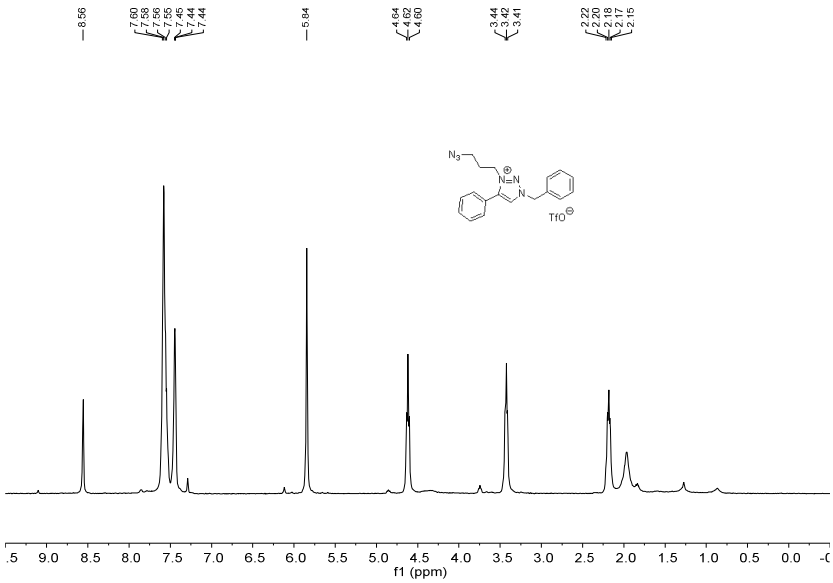

**Spectrum 32.** $^{13}$C NMR (101 MHz, $CDCl_3$) spectra of compound **41**.



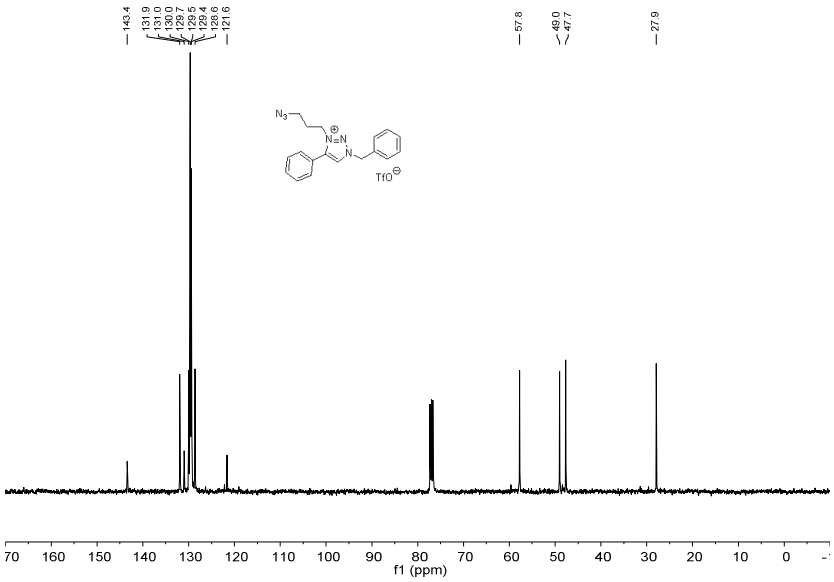

**Spectrum 33.** $^{1}H$ NMR (400 MHz, $CDCl_3$) spectra of compound **42**.



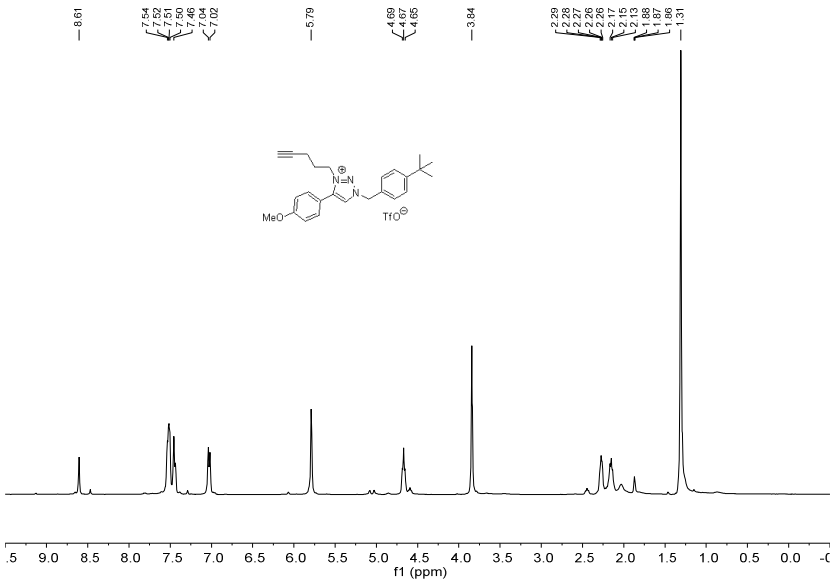

**Spectrum 34.** $^{13}C$ NMR (101 MHz, $CDCl_3$) spectra of compound **42**.



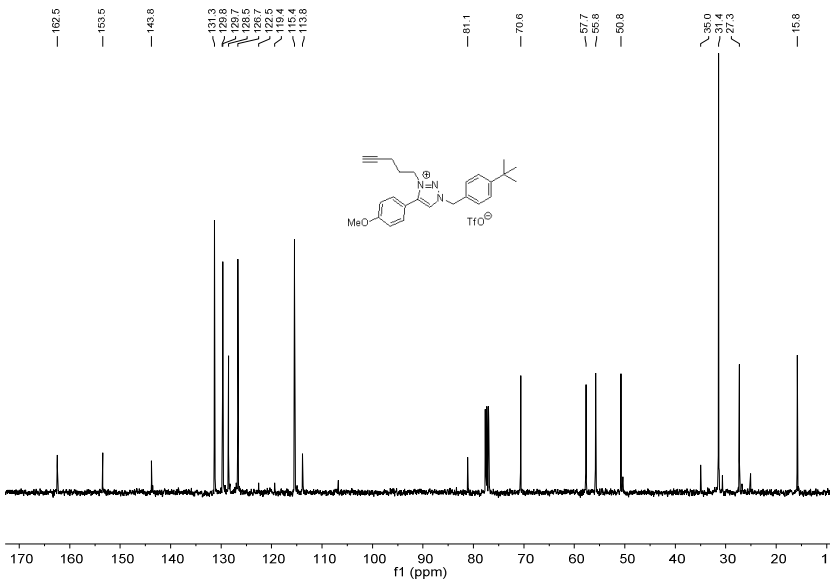

**Spectrum 35.** $^{1}$H NMR (400 MHz, $CDCl_3$) spectra of compound **43**.



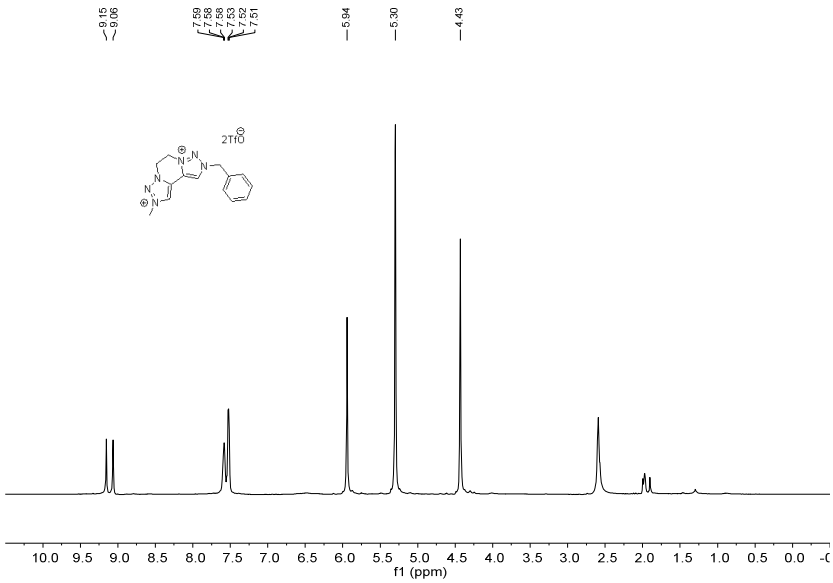

**Spectrum 36.** $^{13}$C NMR (101 MHz, $CDCl_3$) spectra of compound **43**.



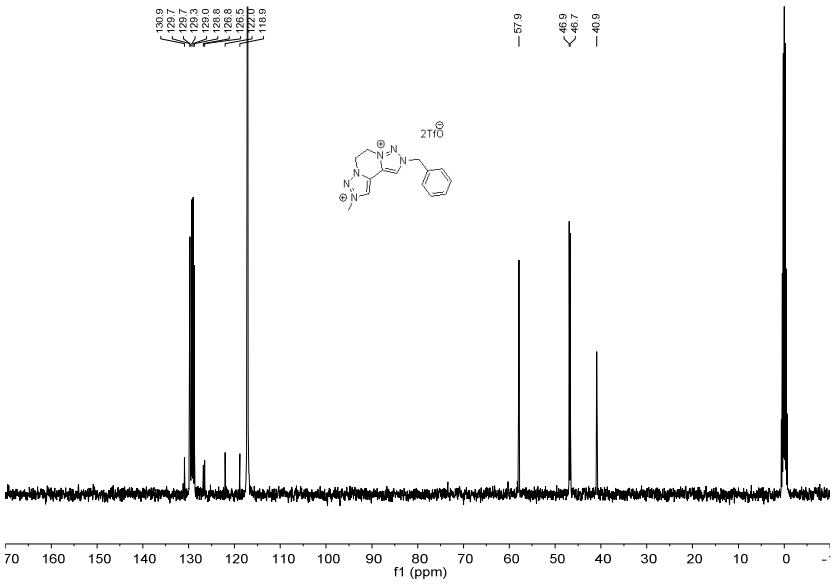

**Spectrum 37.** $^{1}$H NMR (400 MHz, $CDCl_3$) spectra of compound **69**.



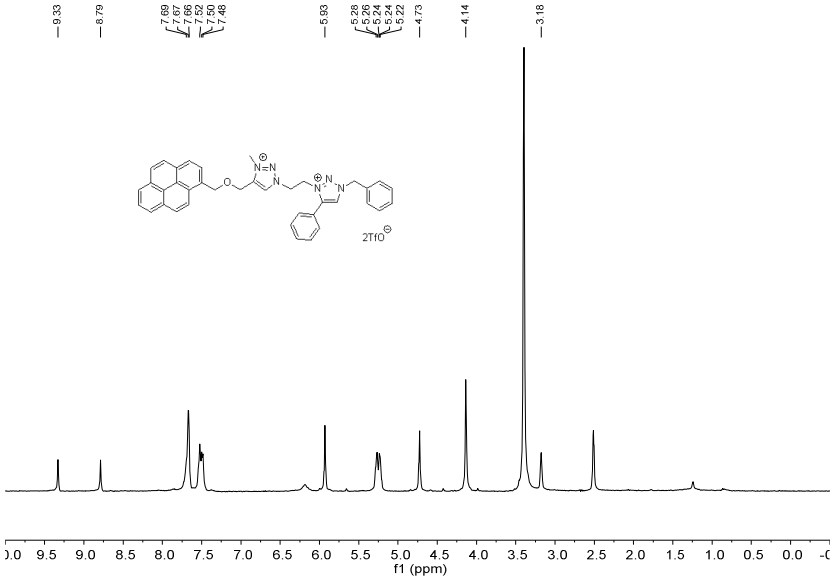

**Spectrum 38.** $^{13}$C NMR (101 MHz, $CDCl_3$) spectra of compound **69**.



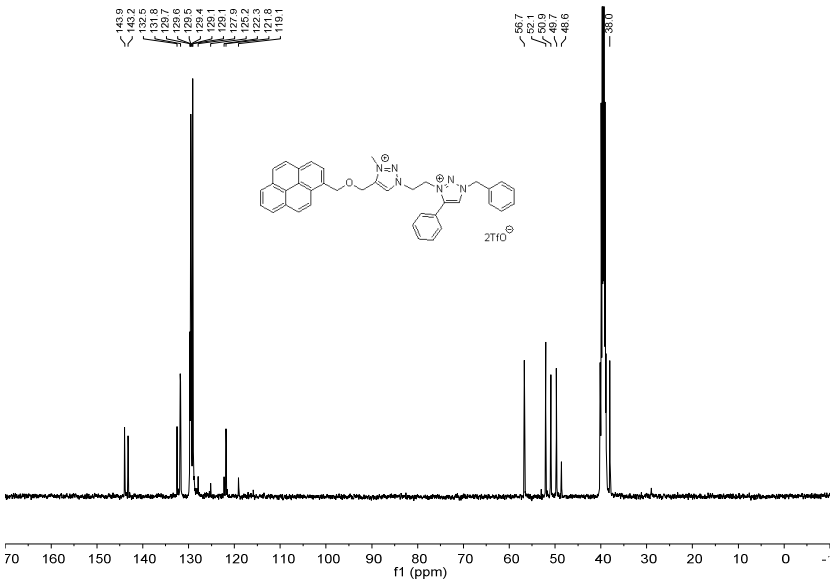

**Spectrum 39.** $^{1}$H NMR (400 MHz, MeCN-$d_3$) spectra of compound **72a**.



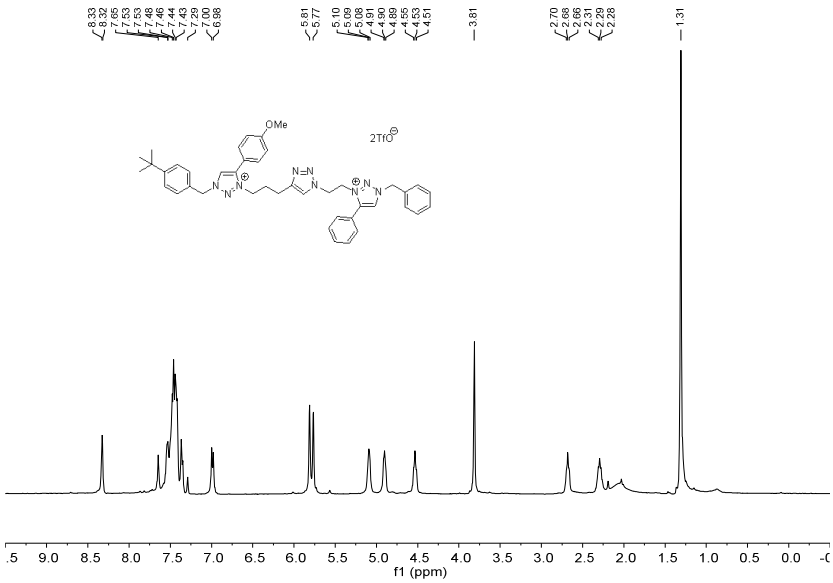

**Spectrum 40.** $^{13}$C NMR (101 MHz, MeCN-$d_3$) spectra of compound **72a**.



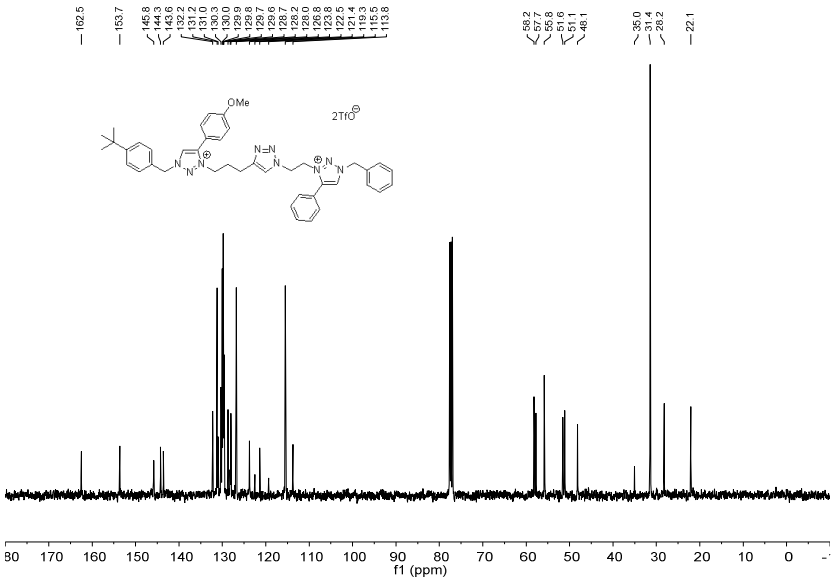

**Spectrum 41.** $^{1}$H NMR (400 MHz, DMSO-$d_6$) spectra of compound **66**.



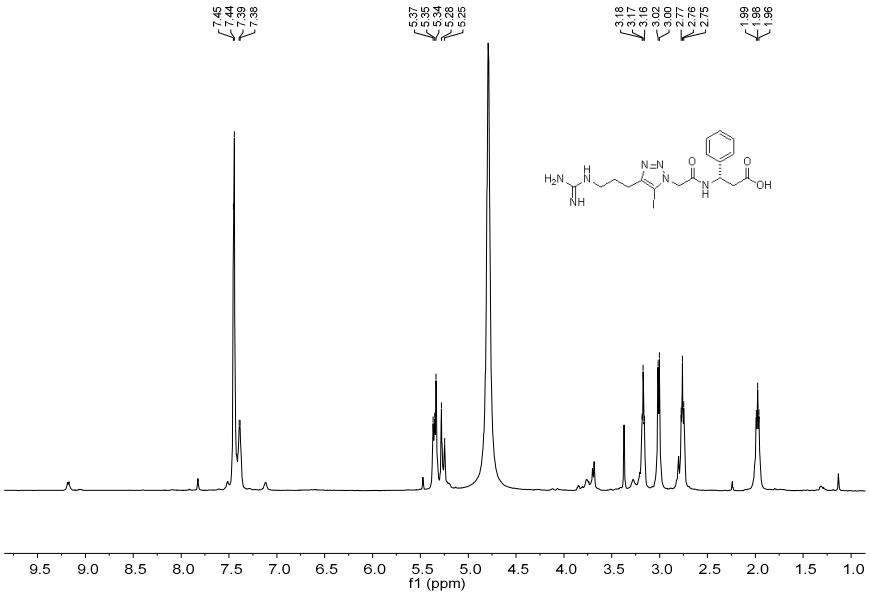

**Spectrum 42.** $^{13}$C NMR (101 MHz, DMSO-$d_6$) spectra of compound **66**.



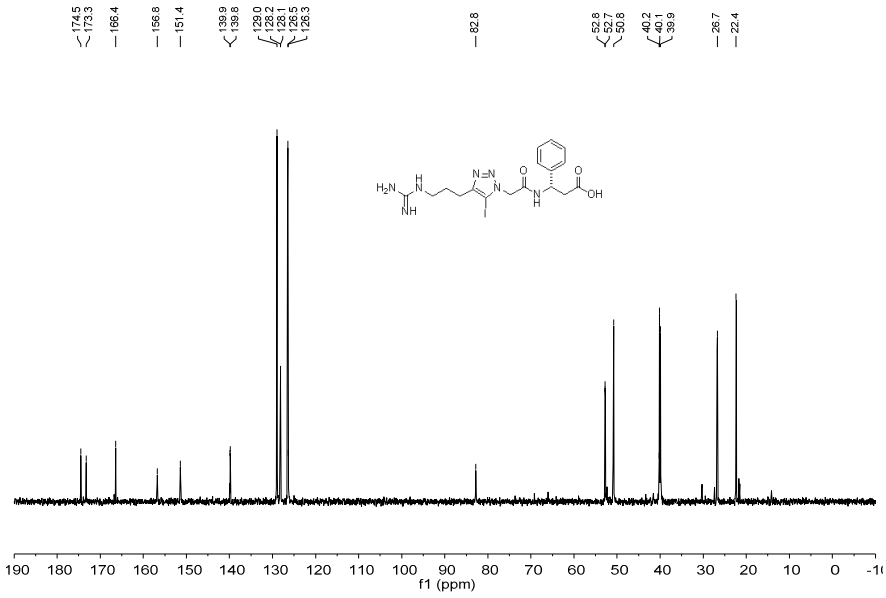

**Spectrum 43.** $^{1}$H NMR (400 MHz, $CDCl_3$) spectra of compound **67**.



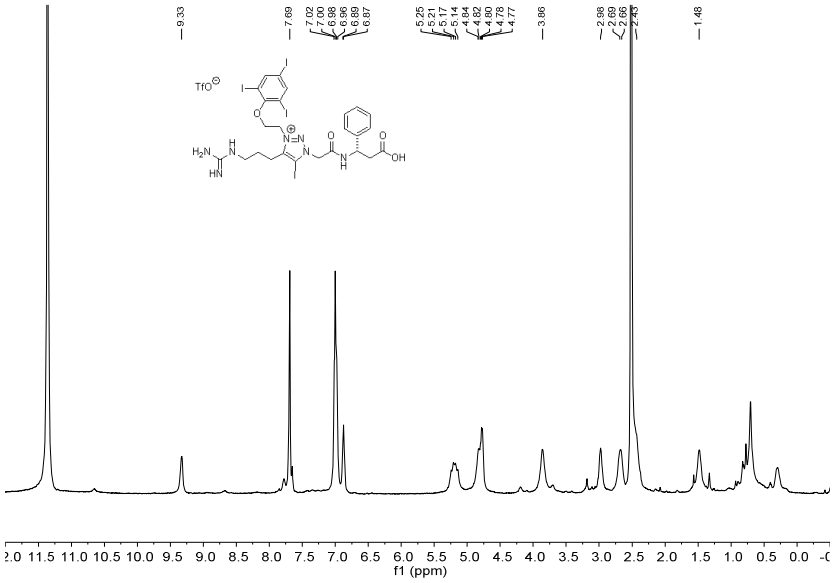

**Spectrum 44.** $^{13}$C NMR (101 MHz, $CDCl_3$) spectra of compound **67**.



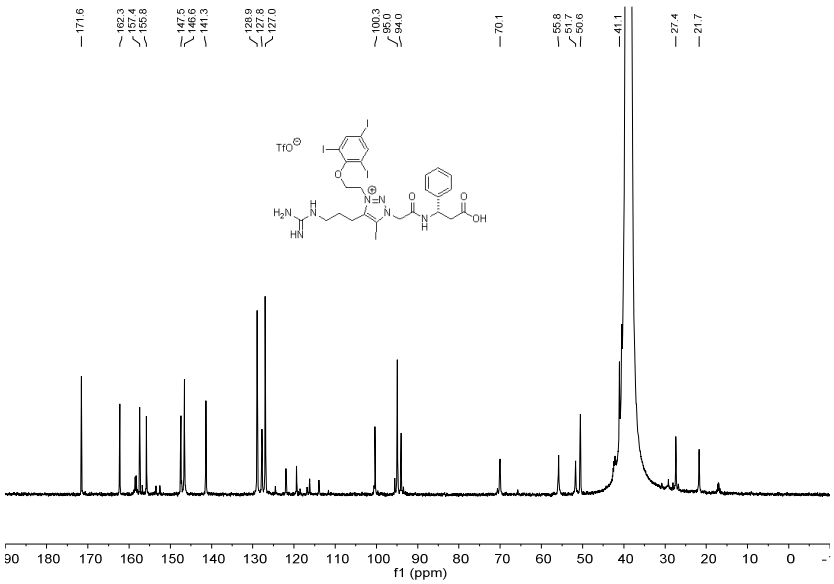

**Spectrum 45.** $^{1}$H NMR (500 MHz, $D_2O$) spectra of compound **35**.



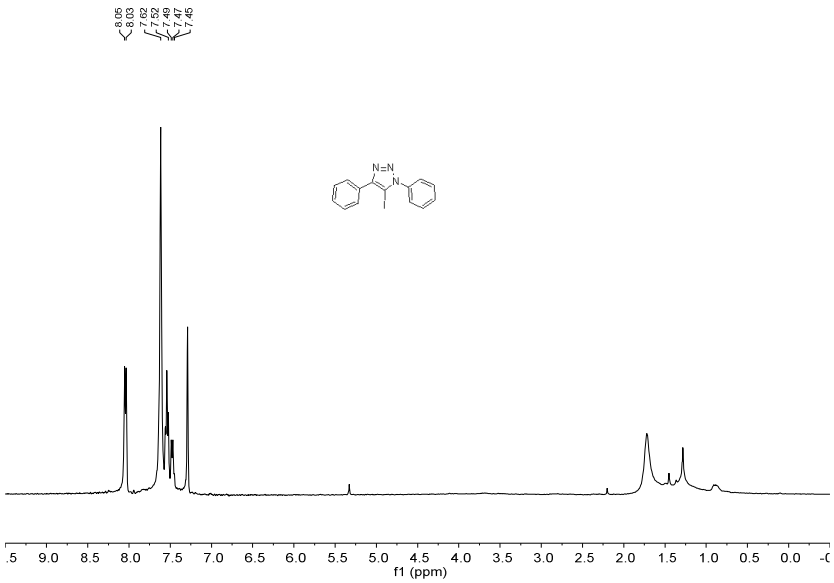

**Spectrum 46.** $^{13}$C NMR (126 MHz, MeCN-$d_3$) spectra of compound **35**.



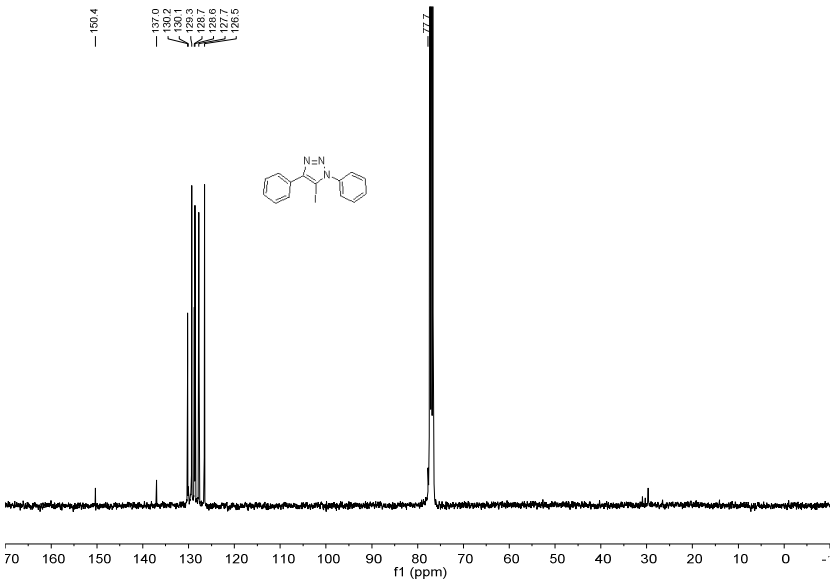

**Spectrum 47.** $^{1}$H NMR (500 MHz, DMSO-$d_6$) spectra of compound **60**.



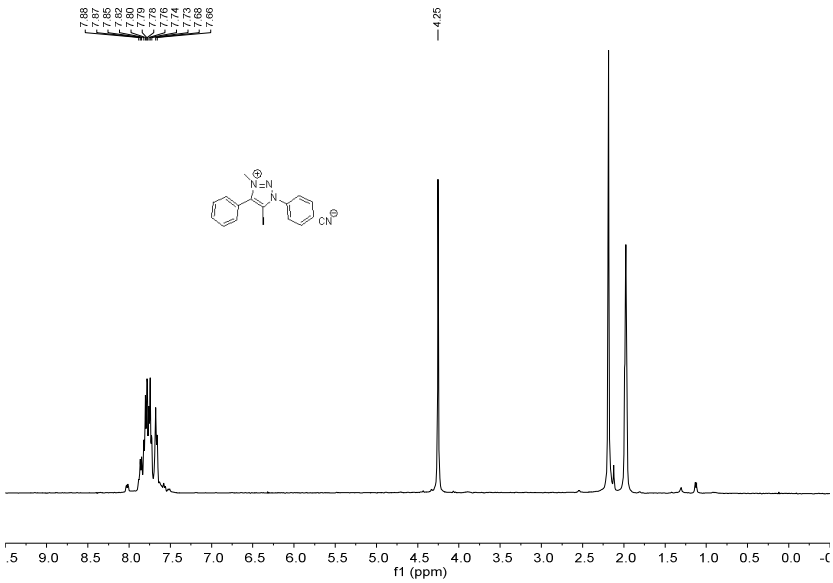

**Spectrum 48.** $^{13}$C NMR (126 MHz, DMSO-$d_6$) spectra of compound **60**.



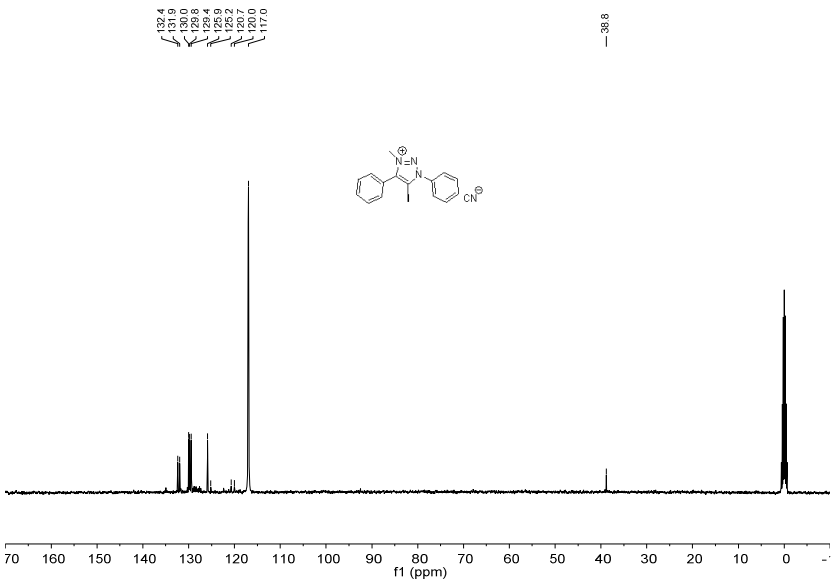

**Spectrum 49.** $^{1}$H NMR (400 MHz, $CDCl_3$) spectra of compound **86**.



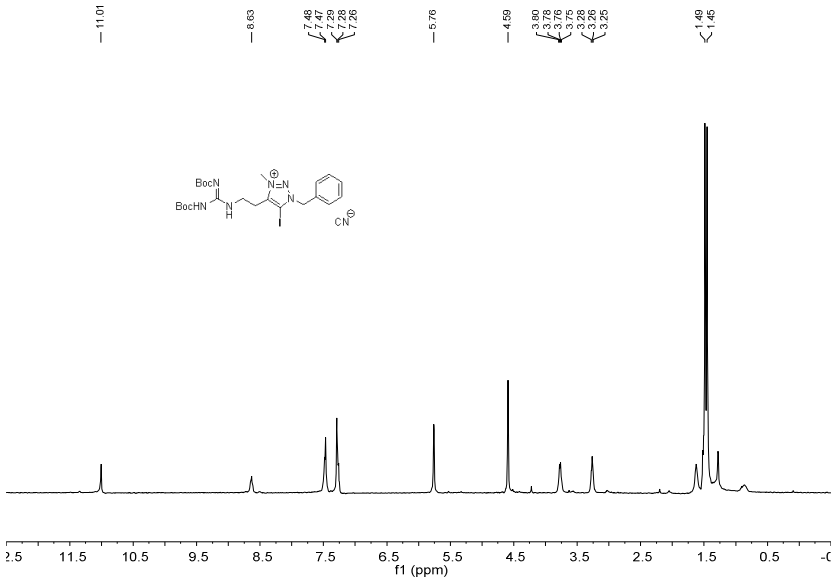

**Spectrum 50.** $^{13}$C NMR (101 MHz, $CDCl_3$) spectra of compound **86**.



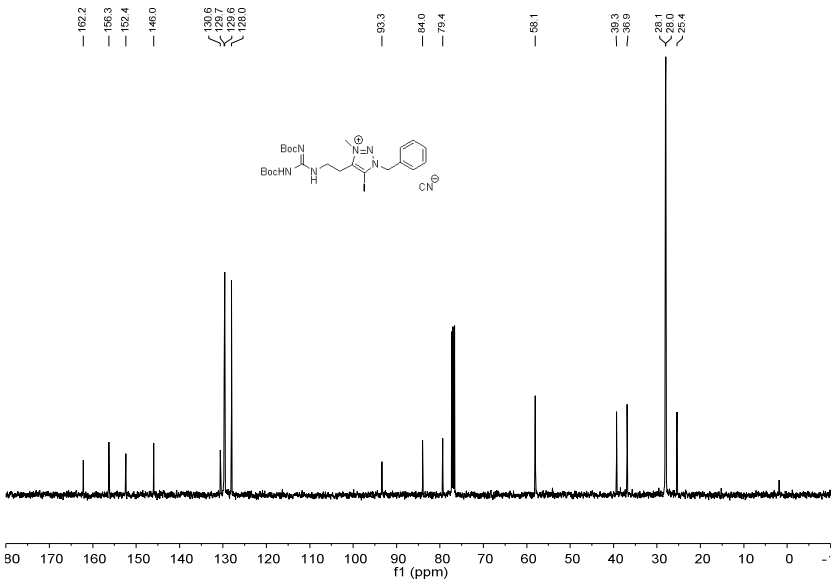

**Spectrum 51.** $^{1}$H NMR (400 MHz, MeCN-$d_3$) spectra of compound **85**.



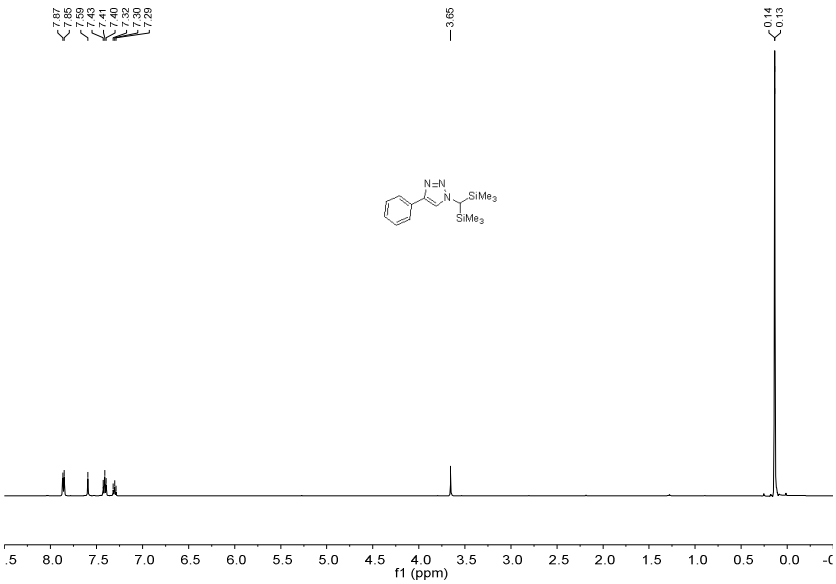

**Spectrum 52.** $^{13}$C NMR (101 MHz, MeCN-$d_3$) spectra of compound **85**.



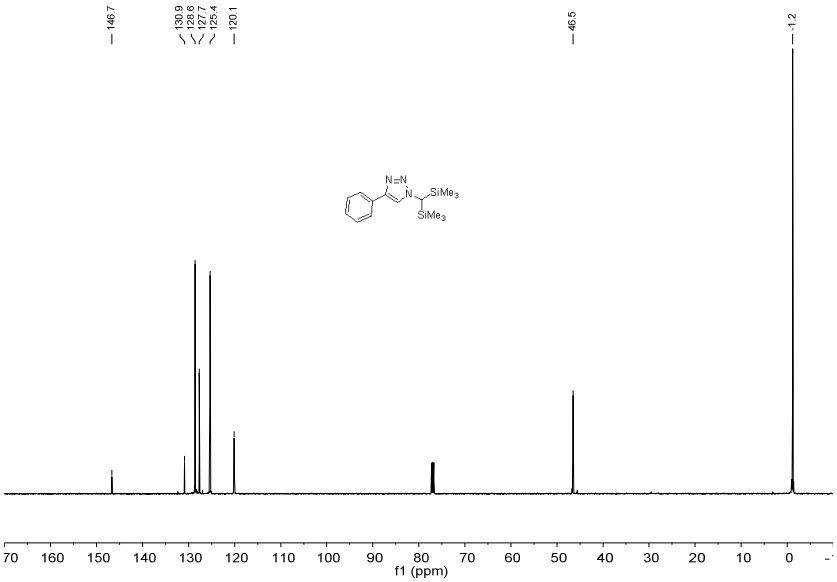

**Spectrum 53.** $^{1}$H NMR (400 MHz, $CDCl_3$) spectra of compound **78e**.



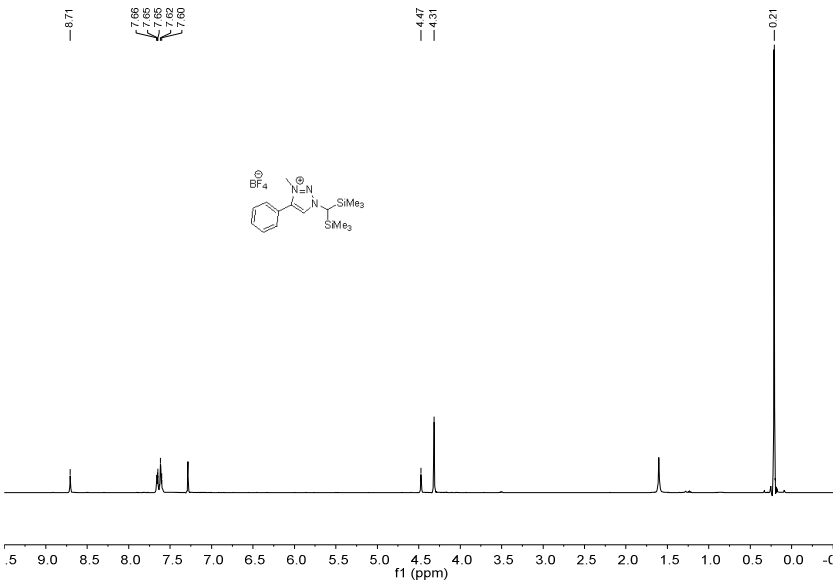

**Spectrum 54.** $^{13}$C NMR (101 MHz, $CDCl_3$) spectra of compound **78e**.



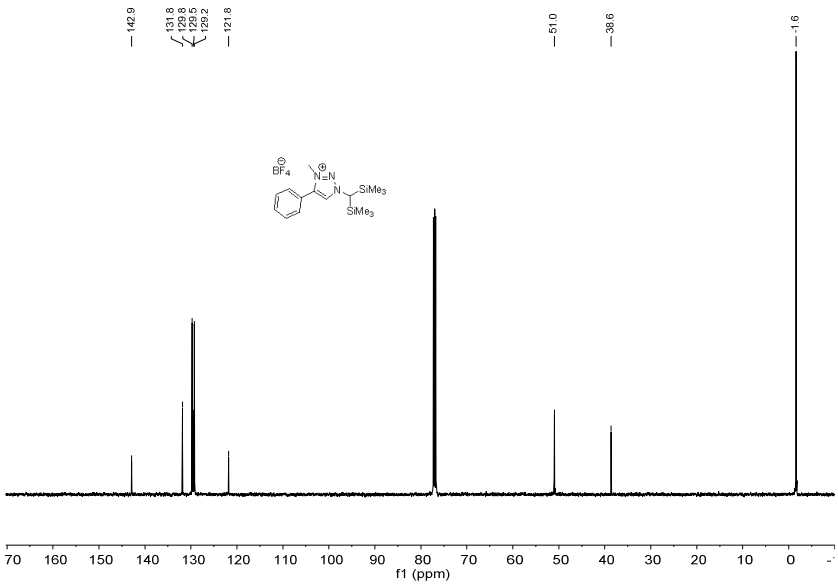

**Spectrum 55.** $^{1}$H NMR (500 MHz, $CDCl_3$) spectra of compound **106b**.



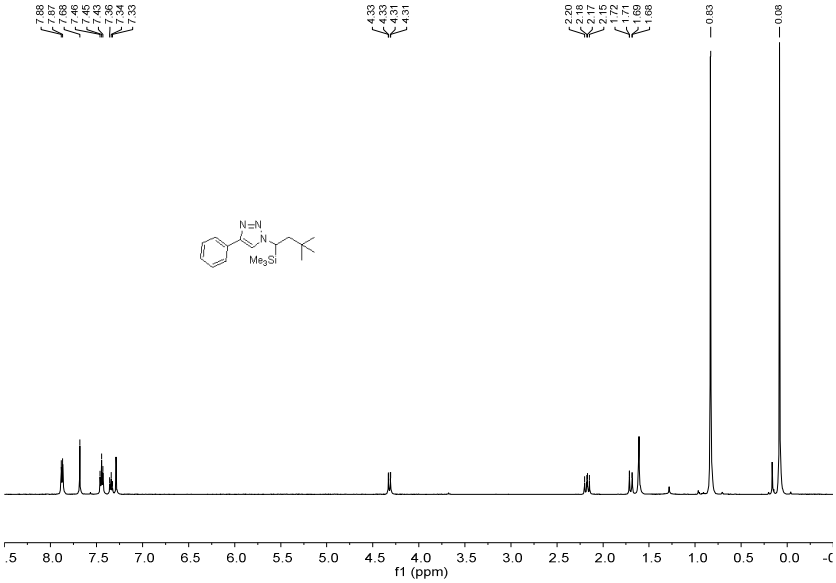

**Spectrum 56.** $^{13}$C NMR (126 MHz, $CDCl_3$) spectra of compound **106b**.



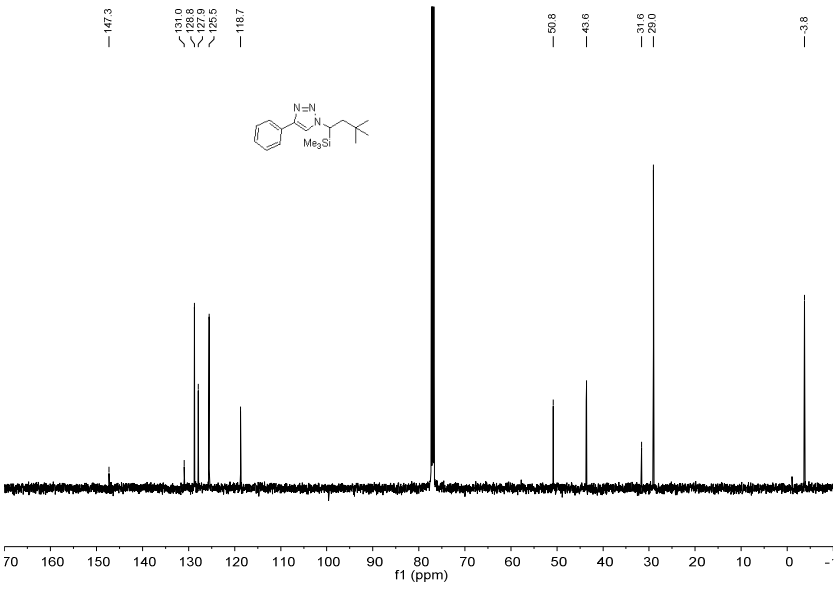

**Spectrum 57.** $^{1}$H NMR (500 MHz, $CDCl_3$) spectra of compound **107b**.



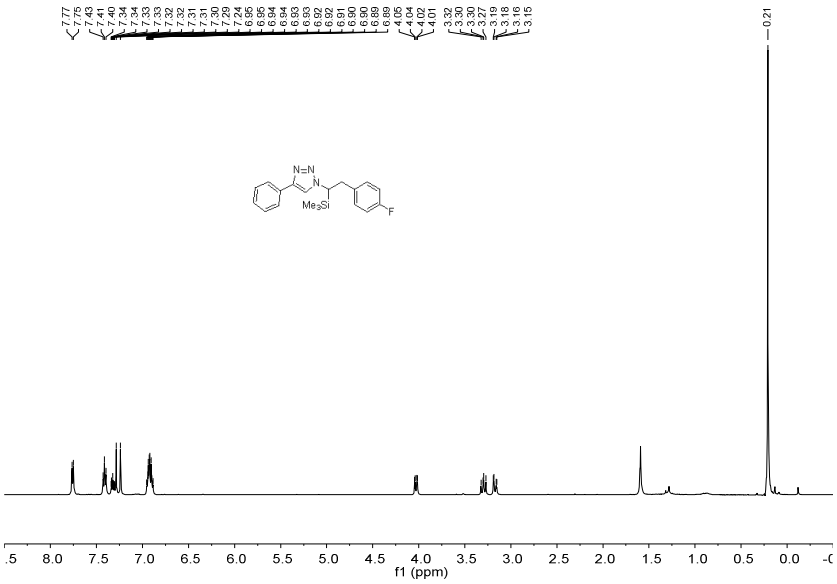

**Spectrum 58.** $^{13}$C NMR (126 MHz, $CDCl_3$) spectra of compound **107b**.



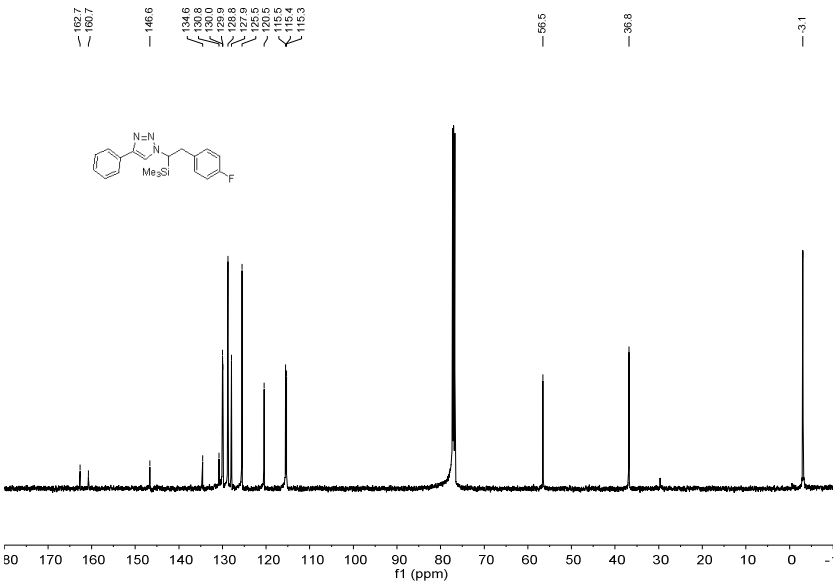

**Spectrum 59.** $^{1}$H NMR (500 MHz, $CDCl_3$) compound **112b**.



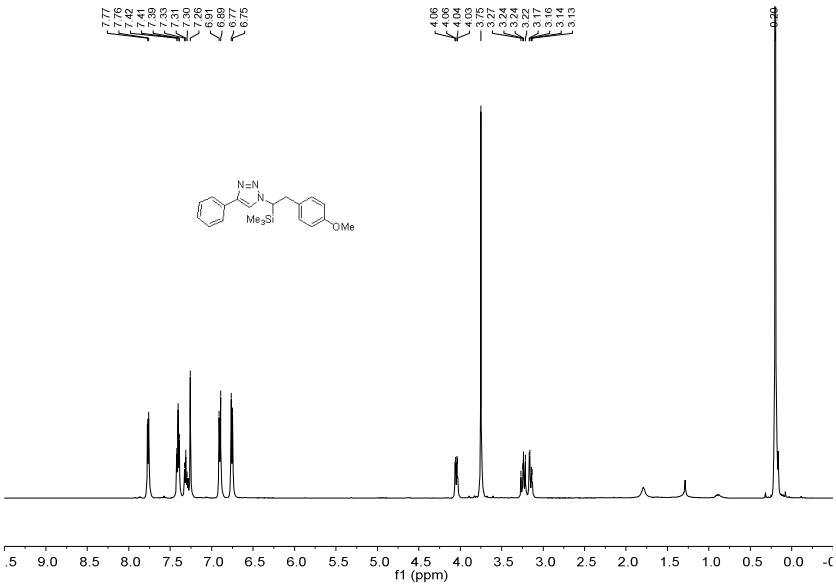

**Spectrum 60.** $^{13}$C NMR (126 MHz, $CDCl_3$) spectra of compound **112b**.



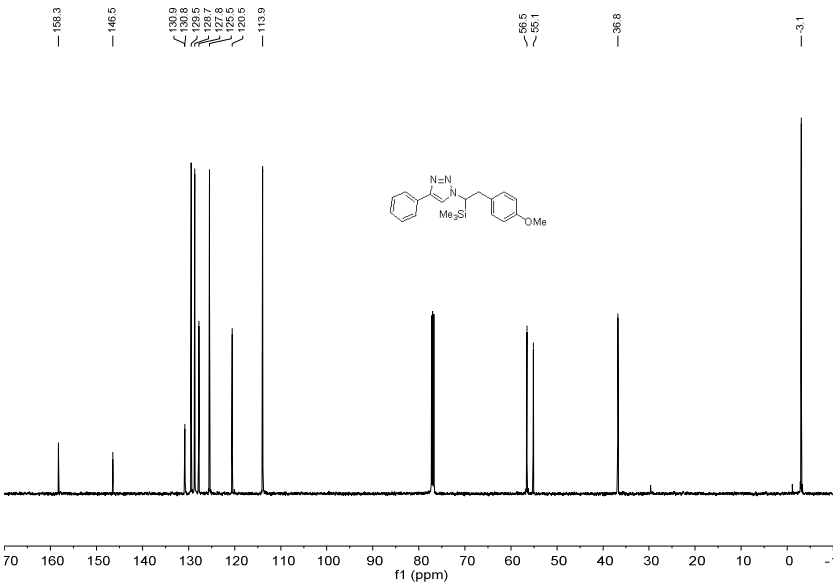

**Spectrum 61.** $^{1}$H NMR (500 MHz, $CDCl_3$) spectra of compound **112d**.



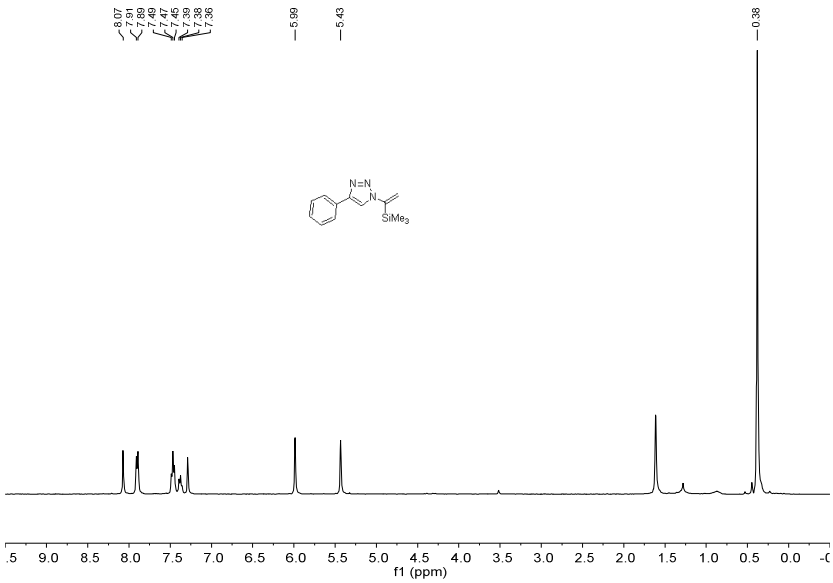

**Spectrum 62.** $^{13}$C NMR (126 MHz, $CDCl_3$) spectra of compound **112d**.



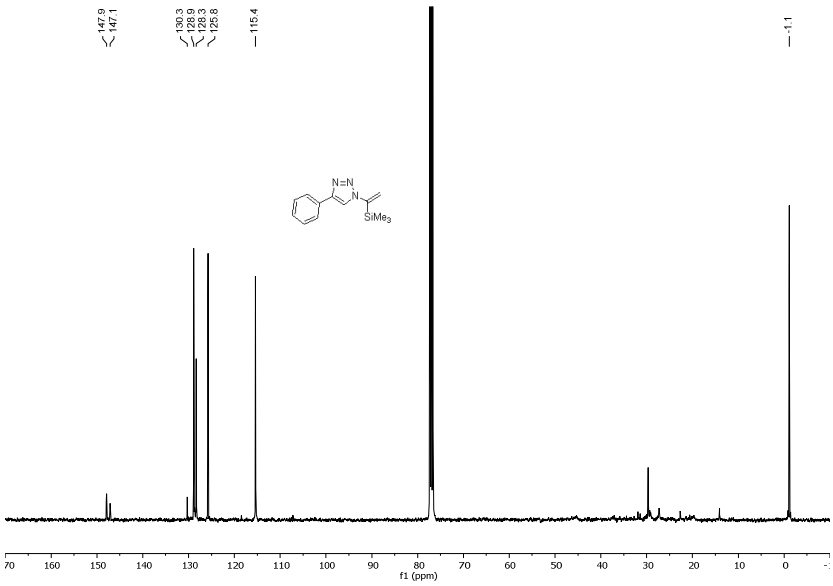

**Spectrum 63.** $^{1}$H NMR (500 MHz, $CDCl_3$) spectra of compound **112c**.



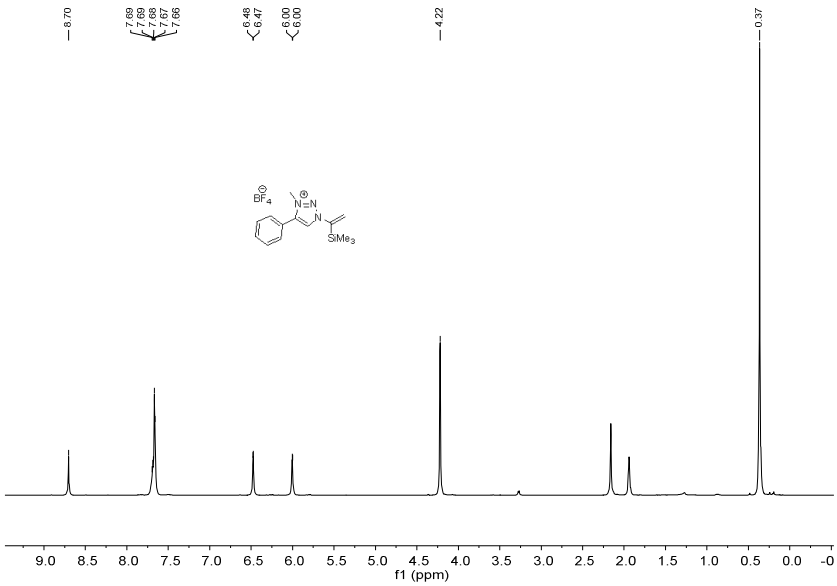

**Spectrum 64.** $^{13}$C NMR (126 MHz, $CDCl_3$) spectra of compound **112c**.



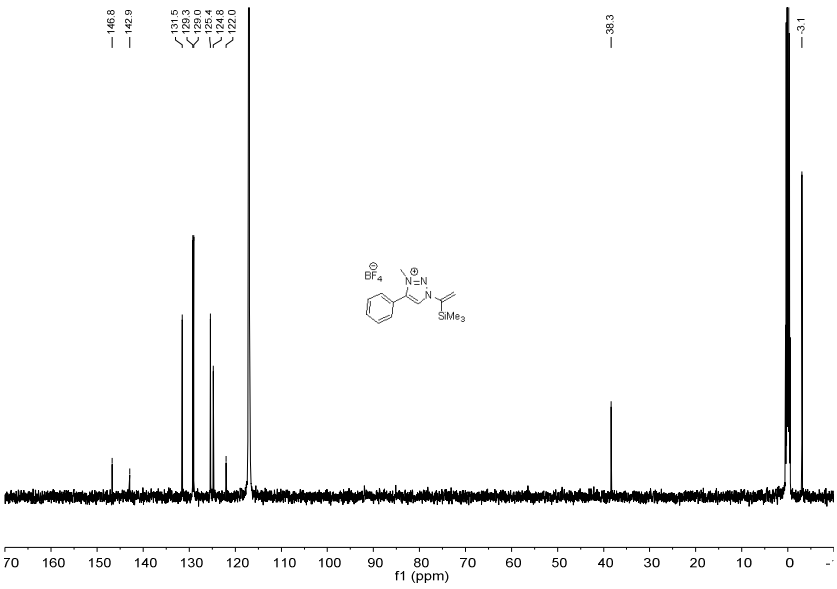

**Spectrum 65.** $^{1}$H NMR (400 MHz, $CDCl_3$) spectra of compound **111a**.



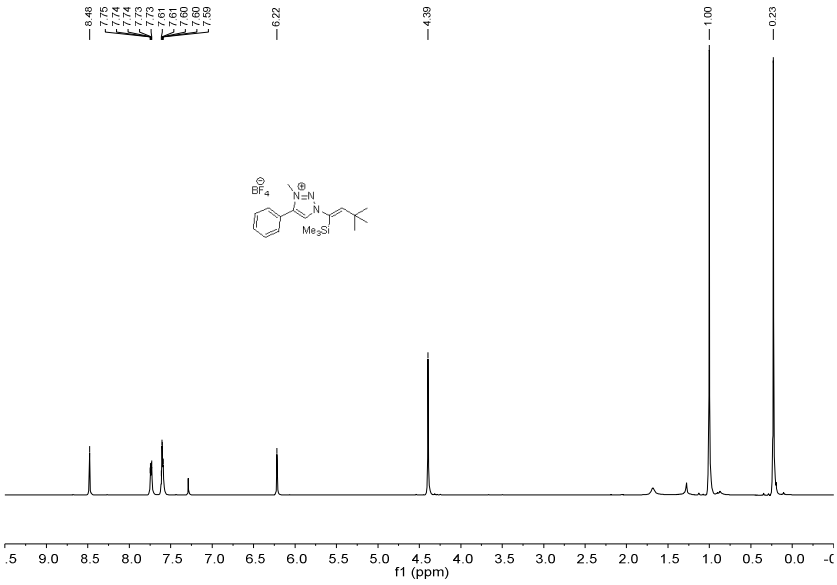

**Spectrum 66**. $^{13}$C NMR (101 MHz, $CDCl_3$) spectra of compound **111a**.



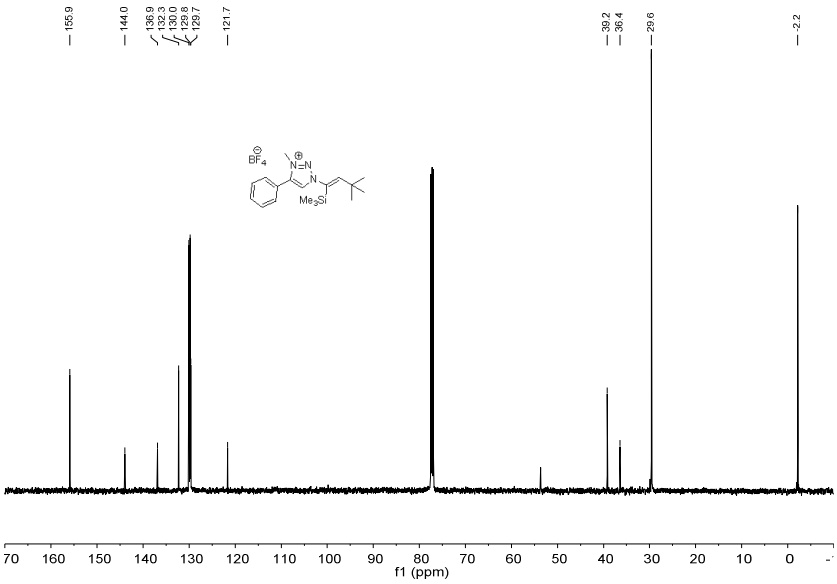

**Spectrum 67.** $^{1}$H NMR (500 MHz, MeCN-$d_3$) spectra of compound **109a**.




**Spectrum 68.** $^{13}$C NMR (126 MHz, MeCN-$d_3$) spectra of compound **109a**.



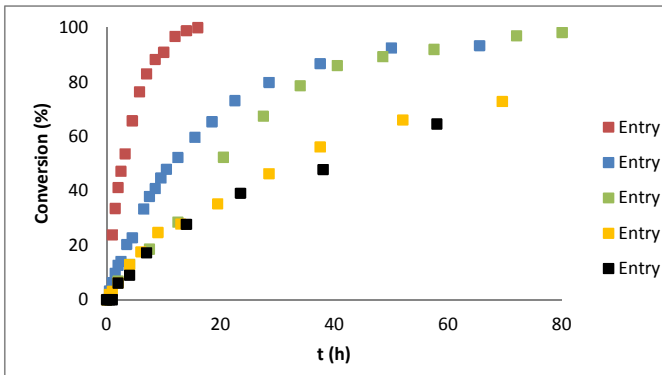

**Spectrum 69.** $^{1}$H NMR (500 MHz, $CDCl_3$) spectra of compound **109b**.




**Spectrum 70.** $^{13}$C NMR (126 MHz, $CDCl_3$) spectra of compound **109b**.

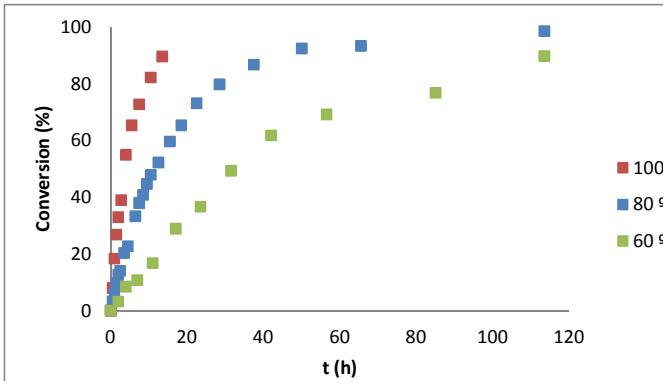
## APPENDIX 2: Plots and tables related to chapter 2.

**Experimental study of the activating effect of triazolium groups in the alkyne-azide cycloaddition reaction: Azide structure effect.**



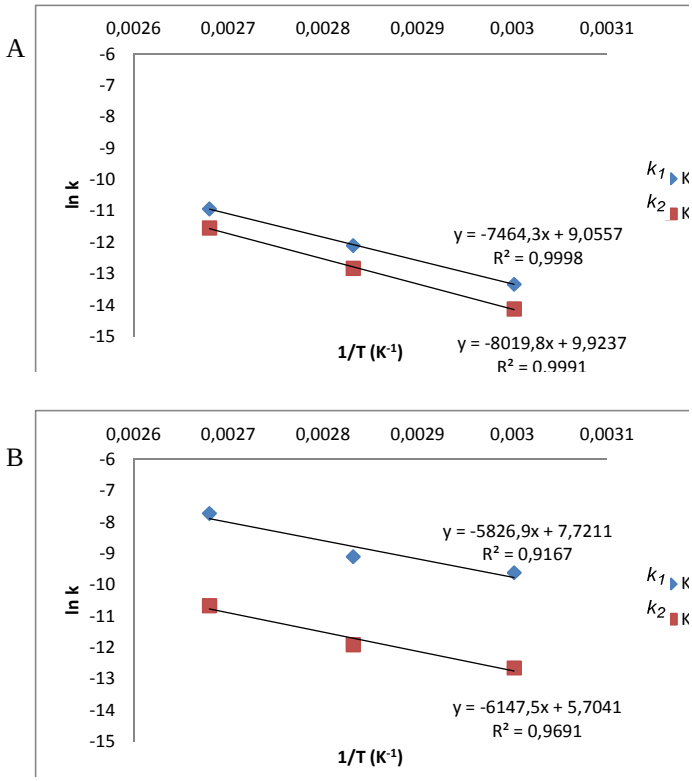

Conversion-time plot for cycloaddition reaction depicted in **Scheme 2.15** with different azides in DMSO-$d_6$.

**Experimental study of the activating effect of triazolium groups in the alkyne-azide cycloaddition reaction: Temperature effect.**



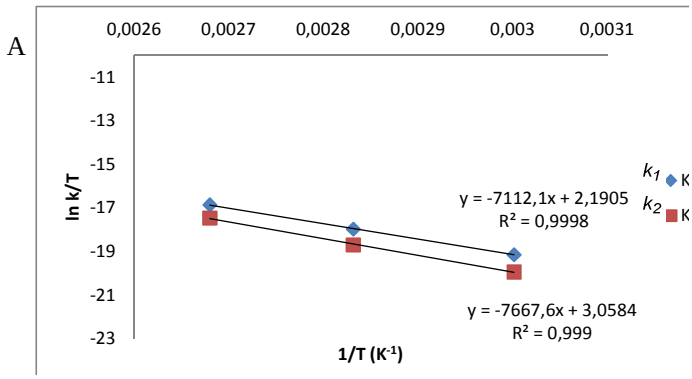

Conversion-time plot for cycloaddition reaction of 4-ethynyl-3-methyl-1,2,3-triazolium salt at 60, 80 and 100 ºC in DMSO-$d_6$ depicted in **Scheme 2.16**.

**Determination of thermodynamic parameters: Activation energy.**

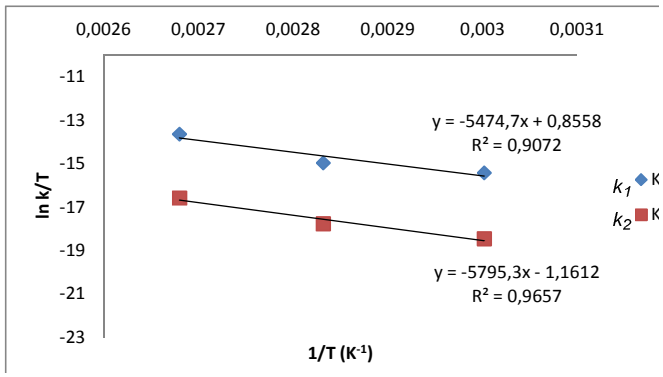



Plots of *ln k* vs. *1/T*, for the reaction of benzylazide with triazole alkyne **1c** (plot A) and triazolium alkyne **2c** (plot B) between 60 ºC and 100 ºC in DMSO-$d_6$.

**Determination of thermodynamic parameters: Enthalpy and entropy.**



B




Plots of *ln k/T* vs. *1/T*, for the reaction of benzylazide with triazole alkyne **1c** (plot A) and triazolium alkyne **2c** (plot B) between 60 ºC and 100 ºC in DMSO-$d_6$.

## APPENDIX 3: Cartesian coordinates

**1c**


E(RB3LYP) = -641.676792013 Hartree

| | | | |
|---|---|---|---|
| C | -1.97600 | -0.69604 | -0.18255 |
| H | -1.75577 | -1.71006 | -0.47386 |
| C | -3.17313 | -0.02633 | -0.01121 |
| C | -4.49749 | -0.51549 | -0.14885 |
| N | -1.60039 | 1.43512 | 0.37425 |
| N | -1.02309 | 0.23836 | 0.06270 |
| N | -2.88678 | 1.27874 | 0.33015 |
| H | -6.62457 | -1.29904 | -0.36934 |
| C | -5.62710 | -0.93151 | -0.26560 |
| C | 0.39185 | 0.10703 | 0.03520 |
| C | 3.16020 | -0.13558 | -0.03007 |
| C | 0.98007 | -1.13737 | 0.28345 |
| C | 1.17528 | 1.23381 | -0.23880 |
| C | 2.55854 | 1.11283 | -0.26551 |
| C | 2.36383 | -1.26005 | 0.24320 |
| H | 0.37068 | -2.00093 | 0.52449 |
| H | 0.70023 | 2.18758 | -0.43167 |
| H | 3.17383 | 1.97989 | -0.47879 |
| H | 2.82749 | -2.22132 | 0.43455 |
| C | 4.58707 | -0.26126 | -0.06738 |
| N | 5.74588 | -0.36313 | -0.09804 |

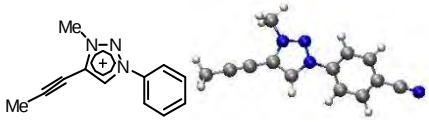
**2c**


E(RB3LYP) = -681.422669462 Hartree

| | | | |
|---|---|---|---|
| C | -1.57434 | -1.01728 | -0.22081 |
| H | -1.25999 | -2.01687 | -0.47328 |
| C | -2.83754 | -0.47040 | -0.10441 |
| C | -4.11892 | -1.03620 | -0.24622 |
| N | -1.33911 | 1.14664 | 0.27013 |
| N | -0.71160 | 0.00616 | 0.01585 |
| N | -2.61553 | 0.85456 | 0.19130 |
| C | -3.62098 | 1.89714 | 0.42178 |
| H | -3.08853 | 2.82348 | 0.62705 |

| | | | |
|---|---|---|---|
| H | -4.23686 | 1.60948 | 1.27501 |
| H | -4.23601 | 1.99636 | -0.47370 |
| H | -6.19778 | -1.93830 | -0.47161 |
| C | -5.22222 | -1.51316 | -0.36507 |
| C | 0.72417 | -0.02343 | 0.00791 |
| C | 3.48472 | -0.08117 | -0.01992 |
| C | 1.37915 | -1.16237 | 0.47714 |
| C | 1.41673 | 1.08972 | -0.47106 |
| C | 2.80596 | 1.06029 | -0.47917 |
| C | 2.76915 | -1.19181 | 0.45624 |
| H | 0.82523 | -2.00544 | 0.87416 |
| H | 0.87982 | 1.95597 | -0.83857 |
| H | 3.36293 | 1.91324 | -0.84941 |
| H | 3.29671 | -2.06652 | 0.81852 |
| C | 4.91884 | -0.11198 | -0.03634 |
| N | 6.08142 | -0.13700 | -0.04992 |

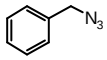
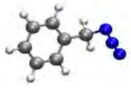
**4**




E(RB3LYP) = -720.722303394 Hartree

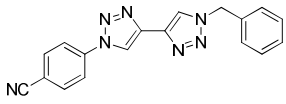
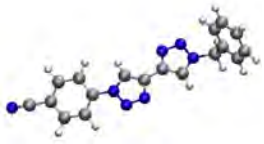
| | | | |
|---|---|---|---|
| C | -1.18445 | -0.77352 | -0.12628 |
| H | -0.95202 | -1.80503 | -0.33584 |
| C | -2.40387 | -0.12704 | -0.01790 |
| N | -0.23777 | 0.18790 | 0.04785 |
| C | -3.72357 | -0.59472 | -0.11371 |
| C | -4.86359 | -1.00020 | -0.19609 |
| N | -0.76742 | 1.38435 | 0.25703 |
| N | -2.06804 | 1.18960 | 0.21152 |
| C | -2.98174 | 2.31993 | 0.40309 |
| H | -2.37616 | 3.19814 | 0.61974 |
| H | -3.64830 | 2.09747 | 1.23779 |
| H | -3.56091 | 2.46834 | -0.51006 |
| C | 1.19148 | 0.03907 | 0.02085 |
| C | 3.93971 | -0.25398 | -0.04285 |
| C | 1.75808 | -1.12951 | 0.53149 |
| C | 1.96761 | 1.06731 | -0.51666 |
| C | 3.34931 | 0.91902 | -0.54293 |
| C | 3.14025 | -1.27676 | 0.49306 |

| | | | |
|---|---|---|---|
| H | 1.14266 | -1.90423 | 0.97603 |
| H | 1.49992 | 1.96069 | -0.91372 |
| H | 3.97083 | 1.70435 | -0.95814 |
| H | 3.60086 | -2.17476 | 0.88868 |
| C | 5.36557 | -0.40806 | -0.07800 |
| N | 6.52084 | -0.53357 | -0.10704 |
| C | -6.22794 | -1.49290 | -0.29717 |
| H | -6.91502 | -0.68100 | -0.55893 |
| H | -6.55488 | -1.92556 | 0.65526 |
| H | -6.30137 | -2.26830 | -1.06769 |

**6b**  

E(RB3LYP) = -435.150311081 Hartree

| | | | |
|---|---|---|---|
| N | 2.81600 | 1.31800 | -0.91300 |
| N | 2.47900 | 0.32200 | -0.46200 |
| N | 2.20800 | -0.81100 | -0.06100 |
| C | 1.14600 | -0.89000 | 0.99400 |
| H | 1.12400 | -1.94700 | 1.26600 |
| H | 1.46800 | -0.32000 | 1.87300 |
| C | -0.20900 | -0.42100 | 0.51400 |
| C | -2.70000 | 0.47000 | -0.42500 |
| C | -0.99300 | -1.24100 | -0.31000 |
| C | -0.68700 | 0.84900 | 0.86200 |
| C | -1.92700 | 1.29300 | 0.39600 |
| C | -2.23100 | -0.80000 | -0.77800 |
| H | -0.63000 | -2.22900 | -0.58500 |
| H | -0.09000 | 1.49000 | 1.50600 |
| H | -2.28800 | 2.27800 | 0.67600 |
| H | -2.83100 | -1.44600 | -1.41200 |
| H | -3.66600 | 0.81300 | -0.78700 |

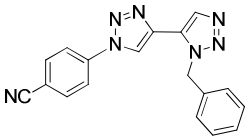
**8** $_{1,4}$  

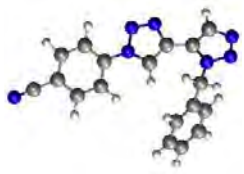
E(RB3LYP) = -1076.92634485 Hartree

| | | | |
|---|---|---|---|
| C | 1.42313 | -0.72064 | -0.06619 |

| | | | |
|---|---|---|---|
| H | 1.62481 | -1.64438 | 0.44967 |
| C | 0.25626 | -0.20128 | -0.58073 |
| N | 2.37608 | 0.20033 | -0.38609 |
| N | 1.81462 | 1.24233 | -1.06924 |
| N | 0.54692 | 0.99759 | -1.18284 |
| C | 3.76400 | 0.19681 | -0.10480 |
| C | 6.50389 | 0.19678 | 0.42834 |
| C | 4.27512 | -0.61973 | 0.91078 |
| C | 4.61651 | 1.02047 | -0.85140 |
| C | 5.97811 | 1.02204 | -0.58101 |
| C | 5.64027 | -0.62402 | 1.17118 |
| H | 3.61325 | -1.23655 | 1.50856 |
| H | 4.20075 | 1.64810 | -1.62968 |
| H | 6.64388 | 1.65719 | -1.15576 |
| H | 6.04099 | -1.25524 | 1.95718 |
| C | 7.91092 | 0.19416 | 0.69978 |
| N | 9.05324 | 0.19134 | 0.92019 |
| C | -4.63610 | -1.14973 | -0.99161 |
| H | -4.80373 | -0.93114 | -2.05071 |
| C | -5.37861 | -0.16027 | -0.11492 |
| C | -6.77354 | 1.64754 | 1.51019 |
| C | -5.31630 | -0.27012 | 1.28082 |
| C | -6.00834 | 0.63021 | 2.08808 |
| C | -6.84122 | 1.76083 | 0.12204 |
| H | -4.71824 | -1.05969 | 1.72917 |
| H | -5.95319 | 0.53771 | 3.16931 |
| H | -7.43252 | 2.55012 | -0.33404 |
| H | -4.96368 | -2.17581 | -0.80265 |
| C | -1.08457 | -0.75273 | -0.54487 |
| C | -2.25911 | -0.23671 | -1.05739 |
| H | -2.48037 | 0.67738 | -1.58505 |
| H | -7.31350 | 2.34812 | 2.14126 |
| N | -3.19333 | -1.16692 | -0.74731 |
| N | -2.63731 | -2.20188 | -0.07200 |
| N | -1.36380 | -1.95336 | 0.04908 |
| C | -6.14321 | 0.86061 | -0.68668 |
| H | -6.19671 | 0.95275 | -1.76942 |

**$8_{1,5}$**



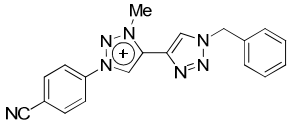



E(RB3LYP) = -1076.91991157 Hartree

| | | | |
|---|---|---|---|
| C | 0.11332 | -0.72550 | 0.09672 |
| H | 0.19784 | 0.32052 | 0.33879 |
| C | 1.05957 | -1.71364 | -0.08460 |
| N | -1.07939 | -1.34712 | -0.11988 |
| N | 4.60856 | -1.07713 | 0.44464 |
| N | -0.87600 | -2.66255 | -0.42628 |
| N | 0.39816 | -2.87901 | -0.40481 |
| C | -2.39241 | -0.81440 | -0.07590 |
| C | -4.98464 | 0.21325 | 0.02227 |
| C | -2.59561 | 0.56749 | -0.16804 |
| C | -3.47965 | -1.68727 | 0.05668 |
| C | -4.76875 | -1.17345 | 0.10078 |
| C | -3.88700 | 1.07833 | -0.11257 |
| H | -1.75792 | 1.24384 | -0.29988 |
| H | -3.30158 | -2.75350 | 0.12076 |
| H | -5.61556 | -1.84361 | 0.20407 |
| H | -4.05084 | 2.14828 | -0.18430 |
| C | -6.31508 | 0.74289 | 0.07753 |
| N | -7.39393 | 1.17552 | 0.12370 |
| C | 2.94506 | 0.40286 | 1.39522 |
| H | 2.13988 | 0.12896 | 2.08539 |
| H | 3.83708 | 0.60901 | 1.99504 |
| C | 2.55636 | 1.62375 | 0.57786 |
| C | 1.86859 | 3.93162 | -0.86284 |
| C | 3.18259 | 1.90877 | -0.64109 |
| C | 1.58735 | 2.50720 | 1.07067 |
| C | 1.24579 | 3.65769 | 0.35579 |
| C | 2.83731 | 3.05535 | -1.35721 |
| H | 3.94237 | 1.23380 | -1.02462 |
| H | 1.10490 | 2.30093 | 2.02466 |
| H | 0.49615 | 4.33737 | 0.75217 |
| H | 3.32865 | 3.26529 | -2.30322 |
| H | 1.60286 | 4.82379 | -1.42297 |

| | | | |
|---|---|---|---|
| C | 2.50864 | -1.69524 | -0.02575 |
| C | 3.42283 | -2.58399 | -0.56630 |
| N | 4.67936 | -2.17090 | -0.26279 |
| N | 3.29487 | -0.76937 | 0.60301 |
| H | 3.22904 | -3.47494 | -1.14437 |

**$9_{1,4}$**

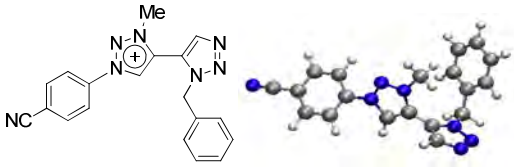



E(RB3LYP) = -1116.61459200 Hartree

| | | | |
|---|---|---|---|
| C | 1.45659 | -0.71801 | -0.15659 |
| H | 1.71978 | -1.76306 | -0.14411 |
| C | 0.21625 | -0.11471 | -0.27471 |
| N | 2.36011 | 0.29656 | -0.09956 |
| N | 1.78795 | 1.48638 | -0.17265 |
| C | 3.78972 | 0.19756 | 0.02085 |
| C | 6.54086 | -0.00819 | 0.24349 |
| C | 4.33199 | -0.85145 | 0.76559 |
| C | 4.59184 | 1.14962 | -0.61113 |
| C | 5.97279 | 1.04520 | -0.49353 |
| C | 5.71461 | -0.95506 | 0.87140 |
| H | 3.69447 | -1.56371 | 1.27906 |
| H | 4.14476 | 1.95039 | -1.18874 |
| H | 6.61569 | 1.77133 | -0.97861 |
| H | 6.15686 | -1.75961 | 1.44835 |
| C | 7.96613 | -0.11570 | 0.35648 |
| N | 9.12156 | -0.20286 | 0.44778 |
| C | -4.56627 | -1.60674 | -0.73389 |
| H | -4.75292 | -1.66686 | -1.81053 |
| C | -5.36054 | -0.48830 | -0.10312 |
| C | -6.83576 | 1.58834 | 1.06254 |
| C | -5.55466 | -0.45105 | 1.28526 |
| C | -6.28806 | 0.58286 | 1.86461 |
| C | -6.64984 | 1.55623 | -0.31993 |
| H | -5.14128 | -1.23918 | 1.91048 |
| H | -6.44354 | 0.59828 | 2.93939 |
| H | -7.08586 | 2.32767 | -0.94790 |

| | | | |
|---|---|---|---|
| H | -4.79639 | -2.58090 | -0.29671 |
| C | -1.06861 | -0.76389 | -0.37418 |
| C | -2.37098 | -0.31248 | -0.53414 |
| H | -2.82560 | 0.66057 | -0.62755 |
| H | -7.41548 | 2.38786 | 1.51456 |
| N | -3.10655 | -1.44223 | -0.54160 |
| N | -2.32005 | -2.53634 | -0.39719 |
| N | -1.09363 | -2.13331 | -0.29439 |
| N | 0.49127 | 1.22648 | -0.28411 |
| C | -0.43934 | 2.35221 | -0.38510 |
| H | -0.95702 | 2.31108 | -1.34638 |
| H | 0.14649 | 3.26769 | -0.31545 |
| H | -1.15621 | 2.30318 | 0.43769 |
| C | -5.91362 | 0.52109 | -0.90068 |
| H | -5.78704 | 0.48733 | -1.98074 |

**$9_{1,5}$**

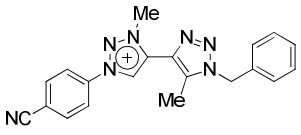



E(RB3LYP) = -1116.59802509 Hartree

| | | | |
|---|---|---|---|
| C | -0.60692 | -1.30129 | -0.21073 |
| H | -0.94307 | -1.96162 | -0.99444 |
| C | 0.64268 | -1.13322 | 0.34862 |
| N | -1.42572 | -0.41087 | 0.41533 |
| N | 3.85788 | -2.38096 | -0.76957 |
| N | -0.77674 | 0.29951 | 1.32673 |
| N | 0.46348 | -0.13589 | 1.28007 |
| C | 1.46788 | 0.47731 | 2.16267 |
| H | 2.21972 | -0.27627 | 2.39423 |
| H | 0.95778 | 0.80449 | 3.06800 |
| H | 1.92637 | 1.32376 | 1.64704 |
| C | -2.83048 | -0.18898 | 0.19908 |
| C | -5.53099 | 0.23635 | -0.23211 |
| C | -3.63973 | -1.27332 | -0.14602 |
| C | -3.34188 | 1.10261 | 0.34034 |
| C | -4.69938 | 1.31121 | 0.12694 |
| C | -4.99515 | -1.05544 | -0.36710 |
| H | -3.23583 | -2.27829 | -0.21401 |

| | | | |
|---|---|---|---|
| H | -2.69064 | 1.92739 | 0.60600 |
| H | -5.11853 | 2.30616 | 0.22841 |
| H | -5.64314 | -1.88389 | -0.63086 |
| C | -6.92911 | 0.45781 | -0.45899 |
| N | -8.06226 | 0.63782 | -0.64441 |
| C | 2.90568 | -0.36115 | -1.73674 |
| H | 3.71245 | -0.61875 | -2.42769 |
| H | 1.97406 | -0.32167 | -2.30918 |
| C | 3.16945 | 0.95231 | -1.02790 |
| C | 3.67756 | 3.38888 | 0.26164 |
| C | 2.28480 | 2.02691 | -1.17301 |
| C | 4.31722 | 1.10749 | -0.23669 |
| C | 4.56762 | 2.31925 | 0.40621 |
| C | 2.53836 | 3.24343 | -0.53222 |
| H | 1.40595 | 1.92332 | -1.80643 |
| H | 5.01638 | 0.28138 | -0.13245 |
| H | 5.46312 | 2.43430 | 1.00984 |
| H | 1.85390 | 4.07683 | -0.66246 |
| H | 3.88005 | 4.33518 | 0.75468 |
| C | 1.89438 | -1.84432 | 0.11962 |
| C | 2.40359 | -2.98426 | 0.71799 |
| N | 3.60003 | -3.27132 | 0.14806 |
| N | 2.83900 | -1.50452 | -0.81334 |
| H | 1.97836 | -3.59826 | 1.49952 |

**$10_{1,4}$**

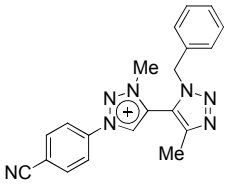


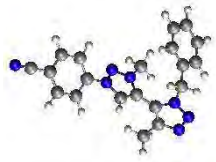

E(RB3LYP) = -1155.93945760 Hartree

| | | | |
|---|---|---|---|
| C | -1.30182 | 0.14456 | -0.42686 |
| H | -1.24652 | -0.84597 | -0.84571 |
| C | -0.32863 | 1.10962 | -0.22747 |
| N | -2.46372 | 0.67373 | 0.04769 |
| N | -2.29664 | 1.89397 | 0.52219 |
| C | -3.76660 | 0.06685 | 0.07711 |
| C | -6.26908 | -1.11552 | 0.13944 |
| C | -4.14230 | -0.77946 | -0.96769 |

| | | | |
|---|---|---|---|
| C | -4.61760 | 0.34140 | 1.14930 |
| C | -5.87493 | -0.25079 | 1.17490 |
| C | -5.39774 | -1.37629 | -0.93121 |
| H | -3.48524 | -0.95105 | -1.81407 |
| H | -4.29919 | 1.00023 | 1.94891 |
| H | -6.55138 | -0.05383 | 1.99924 |
| H | -5.71202 | -2.03277 | -1.73500 |
| C | -7.56308 | -1.73212 | 0.17377 |
| N | -8.61078 | -2.23457 | 0.20140 |
| C | 4.43531 | 0.13739 | -1.43957 |
| H | 4.29727 | -0.50345 | -2.31485 |
| C | 5.09893 | -0.61945 | -0.30643 |
| C | 6.38668 | -2.00522 | 1.75895 |
| C | 5.35379 | 0.01479 | 0.91724 |
| C | 5.49690 | -1.94864 | -0.48776 |
| C | 6.14149 | -2.63943 | 0.54133 |
| C | 5.99210 | -0.67705 | 1.94483 |
| H | 5.31968 | -2.44262 | -1.44096 |
| H | 6.45231 | -3.66873 | 0.38825 |
| H | 6.19120 | -0.17752 | 2.88855 |
| H | 5.02378 | 1.00524 | -1.74832 |
| C | 1.08445 | 1.12275 | -0.52980 |
| C | 1.93744 | 0.07421 | -0.87680 |
| H | 6.88908 | -2.54006 | 2.55960 |
| N | 3.12154 | 0.70066 | -1.07588 |
| N | 3.02013 | 2.03795 | -0.85888 |
| N | 1.79516 | 2.29342 | -0.52968 |
| N | -1.00964 | 2.15116 | 0.36241 |
| C | -0.51215 | 3.46345 | 0.80838 |
| H | 0.31322 | 3.31256 | 1.50432 |
| H | -1.34876 | 3.96685 | 1.29089 |
| H | -0.15076 | 4.02381 | -0.05304 |
| C | 1.73295 | -1.39769 | -1.02459 |
| H | 1.49087 | -1.66849 | -2.06027 |
| H | 0.91691 | -1.74230 | -0.38267 |
| H | 2.63143 | -1.94785 | -0.73321 |
| H | 5.05931 | 1.05162 | 1.06104 |

**10** $_{1,5}$



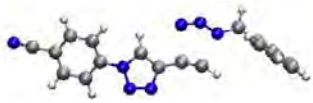



E(RB3LYP) = -1155.92162187 Hartree

| | | | |
|---|---|---|---|
| C | 0.66750 | 1.12967 | -0.39770 |
| H | 1.00008 | 1.73248 | -1.22779 |
| C | -0.58902 | 0.97365 | 0.15142 |
| N | 1.49753 | 0.31432 | 0.31035 |
| N | -3.81786 | 2.00184 | -1.11958 |
| N | 0.85000 | -0.33948 | 1.26440 |
| N | -0.39966 | 0.05745 | 1.16281 |
| C | -1.40149 | -0.50938 | 2.07816 |
| H | -2.21880 | 0.20508 | 2.16592 |
| H | -0.92068 | -0.66805 | 3.04303 |
| H | -1.76801 | -1.45172 | 1.66569 |
| C | 2.91071 | 0.11188 | 0.13578 |
| C | 5.62907 | -0.27810 | -0.21304 |
| C | 3.69680 | 1.17821 | -0.30559 |
| C | 3.45456 | -1.14396 | 0.41335 |
| C | 4.82048 | -1.33436 | 0.24103 |
| C | 5.06101 | 0.97771 | -0.48521 |
| H | 3.26785 | 2.15957 | -0.48043 |
| H | 2.82145 | -1.95600 | 0.75179 |
| H | 5.26429 | -2.30185 | 0.44818 |
| H | 5.69070 | 1.79343 | -0.82265 |
| C | 7.03620 | -0.48154 | -0.39703 |
| N | 8.17675 | -0.64702 | -0.54745 |
| C | -2.81120 | -0.09049 | -1.83610 |
| H | -3.60773 | 0.07026 | -2.56735 |
| H | -1.86751 | -0.17722 | -2.38357 |
| C | -3.06742 | -1.32285 | -0.99120 |
| C | -3.56474 | -3.61358 | 0.54724 |
| C | -2.17195 | -2.39791 | -1.01393 |
| C | -4.22054 | -1.40490 | -0.19697 |
| C | -4.46547 | -2.54350 | 0.56968 |
| C | -2.42004 | -3.54197 | -0.24907 |

| | | | |
|---|---|---|---|
| H | -1.28813 | -2.35332 | -1.64742 |
| H | -4.92778 | -0.57912 | -0.18635 |
| H | -5.36508 | -2.60232 | 1.17538 |
| H | -1.72660 | -4.37742 | -0.28442 |
| H | -3.76259 | -4.50373 | 1.13721 |
| C | -1.83662 | 3.82638 | 1.26699 |
| H | -2.51511 | 3.94900 | 2.11763 |
| H | -1.73843 | 4.80658 | 0.78935 |
| H | -0.85522 | 3.52857 | 1.64789 |
| C | -1.85291 | 1.62742 | -0.15906 |
| C | -2.38294 | 2.82780 | 0.29793 |
| N | -3.58515 | 3.00286 | -0.31821 |
| N | -2.78371 | 1.15068 | -1.04979 |

**TS-$8_{1,4}$**



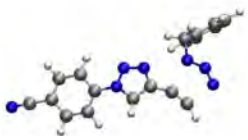
E(RB3LYP) = -1076.79675803 Hartree

freq. -428.0066

| | | | |
|---|---|---|---|
| C | 1.49293 | -0.08815 | 0.03115 |
| H | 1.54585 | -1.15677 | -0.08756 |
| C | 0.41304 | 0.77048 | 0.10619 |
| N | 2.58344 | 0.71617 | 0.10070 |
| C | -0.98741 | 0.49703 | 0.07197 |
| C | -2.19715 | 0.76565 | 0.08305 |
| H | -3.10948 | 1.31984 | 0.14020 |
| N | 2.20101 | 2.02341 | 0.21707 |
| N | 0.90558 | 2.05628 | 0.22039 |
| N | -3.20770 | -1.13779 | -0.04433 |
| N | -1.01187 | -1.75434 | -0.16857 |
| N | -2.17528 | -1.83031 | -0.21731 |
| C | 3.96027 | 0.37033 | 0.06847 |
| C | 6.66095 | -0.29427 | -0.00883 |
| C | 4.36800 | -0.90923 | 0.46095 |
| C | 4.89351 | 1.32287 | -0.35758 |
| C | 6.24182 | 0.99213 | -0.39059 |
| C | 5.71612 | -1.24331 | 0.41549 |
| H | 3.64695 | -1.63695 | 0.81514 |
| H | 4.55922 | 2.30676 | -0.66176 |

| | | | |
|---|---|---|---|
| H | 6.97027 | 1.72431 | -0.72119 |
| H | 6.03811 | -2.23339 | 0.71862 |
| C | 8.05132 | -0.63731 | -0.05081 |
| N | 9.18076 | -0.91579 | -0.08523 |
| C | -4.41368 | -1.41860 | -0.85324 |
| H | -4.64895 | -2.48602 | -0.76505 |
| C | -5.57092 | -0.58090 | -0.35434 |
| C | -7.76178 | 0.92598 | 0.54808 |
| C | -6.26923 | 0.25359 | -1.23368 |
| C | -5.97820 | -0.65121 | 0.98565 |
| C | -7.06480 | 0.09891 | 1.43471 |
| C | -7.36254 | 1.00116 | -0.78702 |
| H | -5.95851 | 0.31833 | -2.27364 |
| H | -5.43804 | -1.29294 | 1.67684 |
| H | -7.37040 | 0.03644 | 2.47560 |
| H | -7.89614 | 1.64396 | -1.48174 |
| H | -8.60946 | 1.50862 | 0.89816 |
| H | -4.21467 | -1.20657 | -1.91047 |

**TS-$8_{1,5}$**



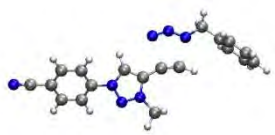
E(RB3LYP) = -1076.79723968 Hartree

freq. -423.3934

| | | | |
|---|---|---|---|
| C | 1.28544 | 1.47945 | -0.32194 |
| H | 1.80584 | 2.40866 | -0.48718 |
| C | -0.06416 | 1.18470 | -0.24269 |
| N | 1.91259 | 0.29739 | -0.09562 |
| C | -1.15361 | 2.08662 | -0.43056 |
| C | -1.76553 | 3.09653 | -0.80608 |
| H | -1.92070 | 4.00053 | -1.35638 |
| N | -3.68617 | 3.06591 | 0.03684 |
| N | -3.60977 | 2.05821 | 0.63804 |
| N | -2.76126 | 1.18309 | 0.92096 |
| N | 0.99600 | -0.69152 | 0.11065 |
| N | -0.18388 | -0.15987 | 0.02414 |
| C | 3.30360 | 0.00903 | -0.05350 |
| C | 6.02277 | -0.56400 | 0.04501 |

| | | | |
|---|---|---|---|
| C | 4.20350 | 0.81321 | -0.76050 |
| C | 3.75053 | -1.08370 | 0.69812 |
| C | 5.10823 | -1.37257 | 0.74205 |
| C | 5.56320 | 0.53112 | -0.70513 |
| H | 3.85153 | 1.64223 | -1.36360 |
| H | 3.03892 | -1.69213 | 1.24199 |
| H | 5.46311 | -2.21630 | 1.32342 |
| H | 6.26643 | 1.15036 | -1.25065 |
| C | 7.42421 | -0.85769 | 0.09824 |
| N | 8.56234 | -1.09632 | 0.14192 |
| C | -3.17954 | -0.11881 | 1.48101 |
| H | -2.23913 | -0.64731 | 1.64368 |
| H | -3.64968 | 0.04512 | 2.45744 |
| C | -4.09396 | -0.91542 | 0.57195 |
| C | -5.79219 | -2.36050 | -1.13411 |
| C | -3.58126 | -1.55181 | -0.56767 |
| C | -5.46323 | -1.01049 | 0.84661 |
| C | -6.30982 | -1.73029 | -0.00092 |
| C | -4.42525 | -2.26953 | -1.41549 |
| H | -2.51812 | -1.47867 | -0.78161 |
| H | -5.86891 | -0.52289 | 1.73028 |
| H | -7.37039 | -1.79915 | 0.22582 |
| H | -4.01709 | -2.76192 | -2.29428 |
| H | -6.44843 | -2.92190 | -1.79372 |

**TS-$9_{1,4}$**



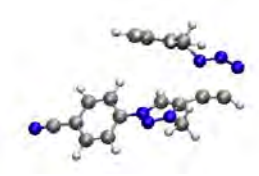
E(RB3LYP) = -1116.54729997 Hartree

freq. -421.2890

| | | | |
|---|---|---|---|
| C | 1.47004 | -0.29202 | 0.02047 |
| H | 1.56227 | -1.35852 | -0.09794 |
| C | 0.34567 | 0.50898 | 0.08933 |
| N | 2.53267 | 0.55136 | 0.09280 |
| C | -1.03566 | 0.21269 | 0.05872 |
| C | -2.25060 | 0.45882 | 0.08600 |
| H | -3.16080 | 1.01837 | 0.15611 |

| | | | |
|---|---|---|---|
| N | 2.16252 | 1.82164 | 0.20131 |
| N | 0.85087 | 1.78895 | 0.19481 |
| C | 0.09143 | 3.03629 | 0.30128 |
| H | 0.80819 | 3.84990 | 0.39220 |
| H | -0.54770 | 2.98507 | 1.18371 |
| H | -0.51689 | 3.15697 | -0.59637 |
| N | -3.21090 | -1.41754 | -0.05161 |
| N | -1.02114 | -2.06236 | -0.21939 |
| N | -2.18298 | -2.10430 | -0.24788 |
| C | 3.92973 | 0.22489 | 0.05903 |
| C | 6.61808 | -0.40630 | -0.01363 |
| C | 4.36069 | -0.96180 | 0.65305 |
| C | 4.81302 | 1.10584 | -0.56723 |
| C | 6.16557 | 0.78871 | -0.59816 |
| C | 5.71335 | -1.28089 | 0.60996 |
| H | 3.66384 | -1.61891 | 1.16081 |
| H | 4.44802 | 2.01564 | -1.02838 |
| H | 6.86764 | 1.45806 | -1.08183 |
| H | 6.06770 | -2.19716 | 1.06779 |
| C | 8.01385 | -0.73440 | -0.05310 |
| N | 9.14562 | -1.00009 | -0.08559 |
| C | -4.43851 | -1.66964 | -0.84788 |
| H | -4.72381 | -2.71743 | -0.70513 |
| C | -5.53822 | -0.74643 | -0.37371 |
| C | -7.58674 | 0.95890 | 0.50227 |
| C | -6.00480 | 0.28291 | -1.19888 |
| C | -6.10587 | -0.91371 | 0.89745 |
| C | -7.12310 | -0.06559 | 1.33383 |
| C | -7.02710 | 1.13142 | -0.76452 |
| H | -5.57042 | 0.41944 | -2.18621 |
| H | -5.74837 | -1.71076 | 1.54456 |
| H | -7.55745 | -0.20572 | 2.31977 |
| H | -7.38302 | 1.92474 | -1.41583 |
| H | -8.38151 | 1.61745 | 0.84148 |
| H | -4.22927 | -1.51283 | -1.91159 |

**TS-$9_{1,5}$**



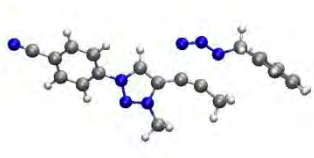
E(RB3LYP) = -1116.54395530 Hartree

freq. -448.5484

| | | | |
|---|---|---|---|
| C | 0.62902 | -0.76918 | 0.97823 |
| H | 0.65984 | -0.04461 | 1.77545 |
| C | -0.35317 | -1.67148 | 0.61242 |
| N | 1.66537 | -0.99116 | 0.12529 |
| C | -1.63361 | -1.92864 | 1.15126 |
| C | -2.52405 | -2.32233 | 1.91908 |
| H | -2.87849 | -2.79930 | 2.81118 |
| N | -4.33620 | -1.92686 | 1.09136 |
| N | -3.99950 | -1.39587 | 0.09890 |
| N | -2.96608 | -1.15411 | -0.56036 |
| N | 1.40918 | -1.95917 | -0.74169 |
| N | 0.19456 | -2.36539 | -0.44126 |
| C | -0.41801 | -3.45983 | -1.19953 |
| H | -0.50199 | -4.33544 | -0.55340 |
| H | 0.22777 | -3.67155 | -2.04931 |
| H | -1.40620 | -3.13790 | -1.52960 |
| C | 2.93507 | -0.32324 | 0.08408 |
| C | 5.38128 | 0.95754 | 0.01869 |
| C | 2.98903 | 1.04238 | 0.36436 |
| C | 4.07549 | -1.06307 | -0.23281 |
| C | 5.30451 | -0.41556 | -0.26998 |
| C | 4.22226 | 1.68411 | 0.33661 |
| H | 2.08864 | 1.60686 | 0.57878 |
| H | 4.00346 | -2.12473 | -0.43617 |
| H | 6.20258 | -0.97274 | -0.51066 |
| H | 4.28435 | 2.74523 | 0.54861 |
| C | 6.65209 | 1.62227 | -0.01268 |
| N | 7.68249 | 2.16091 | -0.03780 |
| C | -2.91376 | 0.01812 | -1.46976 |
| H | -1.88037 | 0.03887 | -1.82278 |
| H | -3.54911 | -0.19783 | -2.33591 |

| | | | |
|---|---|---|---|
| C | -3.29759 | 1.32938 | -0.81946 |
| C | -4.02953 | 3.73387 | 0.42987 |
| C | -4.62811 | 1.76800 | -0.84739 |
| C | -2.33705 | 2.11005 | -0.16344 |
| C | -2.69974 | 3.30587 | 0.45837 |
| C | -4.99316 | 2.96350 | -0.22539 |
| H | -5.38051 | 1.17500 | -1.36215 |
| H | -1.30000 | 1.78401 | -0.14504 |
| H | -1.94475 | 3.90460 | 0.96032 |
| H | -6.02739 | 3.29472 | -0.25714 |
| H | -4.31238 | 4.66575 | 0.91153 |

**TS-10$_{1,4}$**



E(RB3LYP) = -1155.85525440 Hartree

freq. -392.6860

| | | | |
|---|---|---|---|
| C | -1.72656 | -0.82225 | 0.21486 |
| H | -2.03270 | -1.85472 | 0.24576 |
| C | -0.46759 | -0.25017 | 0.28712 |
| N | -2.60083 | 0.21678 | 0.13024 |
| C | 0.81819 | -0.82427 | 0.38009 |
| C | 1.71757 | -1.50088 | 0.91287 |
| N | -1.99311 | 1.39316 | 0.14561 |
| N | -0.71085 | 1.10363 | 0.23662 |
| C | 0.27384 | 2.18555 | 0.30145 |
| H | -0.24724 | 3.11704 | 0.08910 |
| H | 1.04601 | 1.99372 | -0.44368 |
| H | 0.71161 | 2.21156 | 1.30109 |
| N | 3.21234 | -1.56648 | -0.58379 |
| N | 1.67480 | -0.26074 | -1.64499 |
| N | 2.67818 | -0.81774 | -1.43327 |
| C | -4.03134 | 0.16305 | 0.04101 |
| C | -6.78819 | 0.05468 | -0.12135 |
| C | -4.62646 | -0.88890 | -0.65628 |
| C | -4.78443 | 1.16447 | 0.65673 |
| C | -6.17017 | 1.11104 | 0.56924 |
| C | -6.01372 | -0.94510 | -0.73202 |

| | | | |
|---|---|---|---|
| H | -4.02569 | -1.64252 | -1.15236 |
| H | -4.29530 | 1.96372 | 1.20032 |
| H | -6.77237 | 1.87794 | 1.04267 |
| H | -6.49341 | -1.75334 | -1.27190 |
| C | -8.21902 | -0.00237 | -0.20364 |
| N | -9.37923 | -0.04877 | -0.27026 |
| C | 4.68385 | -1.72762 | -0.52034 |
| H | 5.01304 | -2.20974 | -1.44699 |
| C | 5.44112 | -0.44016 | -0.27031 |
| C | 6.80713 | 1.97006 | 0.18465 |
| C | 5.78313 | -0.05179 | 1.03119 |
| C | 5.79716 | 0.38862 | -1.34323 |
| C | 6.47472 | 1.58791 | -1.11771 |
| C | 6.46207 | 1.14679 | 1.25901 |
| H | 5.52665 | -0.69361 | 1.87068 |
| H | 5.54962 | 0.09185 | -2.35985 |
| H | 6.74850 | 2.21955 | -1.95823 |
| H | 6.72473 | 1.43416 | 2.27333 |
| H | 7.33777 | 2.90170 | 0.36034 |
| H | 4.84365 | -2.44148 | 0.29039 |
| C | 2.34742 | -2.29426 | 1.97881 |
| H | 3.23091 | -1.78545 | 2.37740 |
| H | 2.65766 | -3.27694 | 1.61006 |
| H | 1.63510 | -2.43867 | 2.79791 |

**TS-10$_{1,5}$**

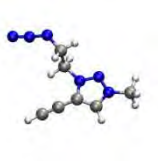
E(RB3LYP) = -1155.83646752 Hartree

freq. -413.0756

| | | | |
|---|---|---|---|
| C | 0.70652 | -0.73747 | 0.75994 |
| H | 0.73044 | -0.09749 | 1.62658 |
| C | -0.29517 | -1.55496 | 0.26627 |
| N | 1.77124 | -0.91797 | -0.06779 |
| C | -1.61004 | -1.80668 | 0.71717 |
| C | -2.50150 | -2.28295 | 1.44498 |
| N | -4.28353 | -1.72219 | 0.55888 |

| | | | |
|---|---|---|---|
| N | -3.89080 | -1.08987 | -0.34869 |
| N | -2.81027 | -0.81881 | -0.92217 |
| N | 1.51632 | -1.78081 | -1.03975 |
| N | 0.27336 | -2.16041 | -0.83160 |
| C | -0.34591 | -3.14660 | -1.72044 |
| H | -0.50001 | -4.07530 | -1.16785 |
| H | 0.33206 | -3.30654 | -2.55643 |
| H | -1.30178 | -2.74888 | -2.06266 |
| C | 3.06571 | -0.30381 | 0.00848 |
| C | 5.55946 | 0.87542 | 0.16054 |
| C | 3.16215 | 1.01789 | 0.44519 |
| C | 4.18823 | -1.04919 | -0.35626 |
| C | 5.44101 | -0.45240 | -0.28391 |
| C | 4.41851 | 1.60806 | 0.52630 |
| H | 2.27612 | 1.58988 | 0.69672 |
| H | 4.08351 | -2.07739 | -0.68106 |
| H | 6.32528 | -1.01505 | -0.56038 |
| H | 4.51319 | 2.63503 | 0.85972 |
| C | 6.85442 | 1.48721 | 0.23944 |
| N | 7.90446 | 1.98319 | 0.30289 |
| C | -2.65273 | 0.46786 | -1.64322 |
| H | -1.58980 | 0.50670 | -1.89394 |
| H | -3.20505 | 0.39752 | -2.58703 |
| C | -3.07484 | 1.68741 | -0.85272 |
| C | -3.88759 | 3.91717 | 0.64652 |
| C | -2.17444 | 2.33387 | 0.00391 |
| C | -4.38566 | 2.17233 | -0.95369 |
| C | -4.79118 | 3.28070 | -0.20772 |
| C | -2.57738 | 3.44262 | 0.74992 |
| H | -1.15229 | 1.97195 | 0.08297 |
| H | -5.09026 | 1.68381 | -1.62274 |
| H | -5.80931 | 3.64905 | -0.29782 |
| H | -1.86841 | 3.93780 | 1.40768 |
| H | -4.20107 | 4.78169 | 1.22511 |
| C | -3.01008 | -3.04817 | 2.59675 |
| H | -3.63382 | -3.88164 | 2.25895 |
| H | -3.63093 | -2.41008 | 3.23386 |
| H | -2.18019 | -3.44283 | 3.19112 |

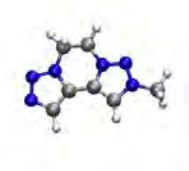
**73**



E(RB3LYP) = -600.262180717 Hartree

| | | | |
|---|---|---|---|
| C | -3.90749 | -1.36319 | 0.24626 |
| H | -4.27126 | -1.25186 | 1.26933 |
| H | -3.64302 | -2.40098 | 0.04844 |
| H | -4.66020 | -1.02090 | -0.46662 |
| N | -2.68677 | -0.55842 | 0.08108 |
| C | -2.52946 | 0.77505 | 0.27198 |
| H | -3.32765 | 1.42796 | 0.59092 |
| C | -1.20498 | 1.04419 | -0.02869 |
| N | -1.57410 | -1.14653 | -0.31483 |
| N | -0.68129 | -0.17988 | -0.38656 |
| C | 0.71000 | -0.50126 | -0.75414 |
| H | 1.11938 | 0.38480 | -1.24279 |
| H | 0.66961 | -1.32271 | -1.47059 |
| C | 1.54577 | -0.90595 | 0.48018 |
| H | 1.60776 | -0.07515 | 1.19360 |
| H | 1.06637 | -1.75479 | 0.97656 |
| N | 2.86061 | -1.35925 | 0.02231 |
| N | 3.78331 | -0.53085 | 0.12508 |
| N | 4.71816 | 0.11618 | 0.17144 |
| C | -0.47014 | 2.24446 | -0.01496 |
| H | 0.70363 | 4.19746 | 0.01094 |
| C | 0.15563 | 3.27794 | -0.00054 |

**74**

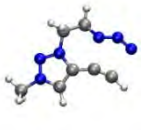


E(RB3LYP) = -600.363476011 Hartree

| | | | |
|---|---|---|---|
| C | 3.99103 | -0.64292 | 0.10604 |
| H | 4.21402 | -1.09338 | 1.07520 |
| H | 4.51890 | 0.30340 | -0.00261 |
| H | 4.26116 | -1.32396 | -0.70314 |

| | | | |
|---|---|---|---|
| N | 2.54999 | -0.35586 | 0.02852 |
| C | 1.51818 | -1.24248 | 0.09194 |
| H | 1.66569 | -2.30472 | 0.21254 |
| C | 0.37032 | -0.47933 | -0.01348 |
| N | 2.14808 | 0.89210 | -0.10269 |
| N | 0.83158 | 0.80901 | -0.12492 |
| C | -0.03852 | 1.98151 | -0.35155 |
| H | -0.19039 | 2.07297 | -1.43158 |
| H | 0.48552 | 2.86442 | 0.01666 |
| C | -1.36770 | 1.76380 | 0.38451 |
| H | -1.24592 | 1.88959 | 1.46599 |
| H | -2.11586 | 2.47571 | 0.03130 |
| N | -3.14444 | 0.07090 | 0.07164 |
| C | -1.05063 | -0.69307 | -0.01312 |
| C | -1.94784 | -1.73960 | -0.14108 |
| H | -1.77173 | -2.79591 | -0.28392 |
| N | -3.20416 | -1.22693 | -0.08549 |
| N | -1.84825 | 0.41426 | 0.10436 |

**TS 74**



E(RB3LYP) = -600.233608460 Hartree

freq. -447.0941

| | | | |
|---|---|---|---|
| C | 4.07204 | -0.44141 | 0.11137 |
| H | 4.42056 | -1.01075 | -0.75231 |
| H | 4.32295 | -0.96164 | 1.03774 |
| H | 4.50733 | 0.55690 | 0.10750 |
| N | 2.61219 | -0.28638 | 0.02600 |
| C | 1.66696 | -1.25473 | -0.01620 |
| H | 1.89553 | -2.30913 | 0.00905 |
| C | 0.44577 | -0.60083 | -0.08941 |
| N | 2.09412 | 0.92421 | -0.00951 |
| N | 0.78783 | 0.73841 | -0.07598 |
| C | -0.05902 | 1.95046 | -0.20403 |
| H | -0.14178 | 2.17387 | -1.27148 |
| H | 0.48539 | 2.75402 | 0.29331 |
| C | -1.44651 | 1.75531 | 0.39703 |

| | | | |
|---|---|---|---|
| H | -1.39920 | 1.56230 | 1.47667 |
| H | -2.01539 | 2.67712 | 0.23071 |
| N | -3.10686 | 0.10937 | -0.00212 |
| C | -0.86506 | -1.14385 | -0.10175 |
| C | -1.69834 | -2.05461 | 0.01463 |
| H | -2.13681 | -3.02652 | 0.11088 |
| N | -3.60879 | -0.92908 | 0.13275 |
| N | -2.01185 | 0.63230 | -0.34428 |

## APPENDIX 4: Publications

1. Aizpurua, J. M.; Fratila, R. M.; Monasterio, Z.; Pérez-Esnaola, N.; Andreieff, E.; Irastorza, A.; Sagartzazu-Aizpurua, M. *New J. Chem.* **2014**, *38*, 474-480. "Triazolium cations: from "click" pool to multipurpose applications".

2. Aizpurua, J. M.; Sagartzazu-Aizpurua, M.; Monasterio, Z. "Mesoionic 1,2,3-triazoles and 1,2,3-triazole carbenes" in Chemistry of 1,2,3-triazoles, *Topics in Heterocyclic Chemistry*, **2014**, *40*, 211-268. Eds. Dehaen, W.; Bakulev, V.A.; Springer-Verlag; Heidelberg.

3. Aizpurua, J. M.; Sagartzazu-Aizpurua, M.; Monasterio, Z.; Azcune, I.; Mendicute, C.; Miranda, J. I.; García-Lecina, E.; Altube, A.; Fratila, R. M. *Org. Lett.* **2012**, *14*, 1866-1868. "Introducing axial chirality into mesoionic 4,4´-bis(1,2,3-triazole) dicarbenes".

4. Aizpurua, J. M.; Sagartzazu-Aizpurua, M.; Azcune, I.; Miranda, J. I.; Monasterio, Z.; García-Lecina, E.; Fratila, R. M. *Synthesis: special topic (invited article)* **2011**, 2727-2742. "Click" Synthesis of nonsymmetrical 4,4´-bis(1,2,3-triazolium) salts.".

**Presentations at meetings and conferences**

1. **XI Simposio de Investigadores Jóvenes**, *2014*, Bilbao, Spain.
   Monasterio, Z.; Aizpurua, J. M. "Synthesis of new triazolium cations following a "Double-Click" strategy".
   Communication: Oral.

   Irastorza, A.; Fernandez, F. J.; Monasterio, Z.; Pérez-Esnaola, N.; Sagartzazu-Aizpurua, M.; Aizpurua, J. M. "One-pot synthesis of halo-heterocycles by neutral and selective reagents".
   Communication: Poster.

   Fernandez, F. J.; Monasterio, Z.; Aizpurua, J. M. "C-halogenation of terminal alkynes by halocyanogens"
   Communication: Poster.

2. **4th Brazil-Spain Workshop on Organic Chemistry**, *2014*, Donostia-San Sebastián, Spain.
   Sagartzazu-Aizpurua, M.; Monasterio, Z.; Aizpurua, J. M.; Herrero De La Parte, B.; Etxebarria-Loizate, N.; García-Alonso, I.; Echevarria-Uraga, J. J. "Synthesis and radiographic study of iodotriazole RGD mimetics for CT scanning".
   Communication: Poster.

Fernandez, F. J.; Irastorza, A.; Monasterio, Z.; Perez-Esnaola, N.; Sagartzazu-Aizpurua, M.; Aizpurua, J. M. "Halocyanogens as neutral and selective reagents for the C-halogenation of alkynes, imidazolium salts and triazolium salts".
Communication: Poster.

3. **32 Congreso de la Sociedad Española de Radiología Médica (SERAM)**, *2014*, Oviedo, Spain. Echevarria-Uraga, J. J.; García-Alonso, I.; Herrero De La Parte, B.; Aizpurua, J. M.; Saiz-López, A.; Monasterio, Z. "Evaluación del efecto antitumoral de un contraste yodado experimental de diseño selectivo molecular: resultados preliminares".
Communication: Electronic.

4. **XX Simposio de Investigadores Jóvenes**, *2013*, Madrid, Spain.
Monasterio, Z.; Sagartzazu-Aizpurua, M.; Aizpurua, J. M.; Herrero De La Parte, B.; Etxebarria-Loizate, N.; García-Alonso, I.; Echevarria-Uraga, J. J. "Synthesis and radiographic study of iodotriazole RGD mimetics for CT scanning".
Communication: Poster.

5. **XIX Simposio de Investigadores Jóvenes**, *2012*, Zaragoza, Spain.
Monasterio, Z.; Sagartzazu-Aizpurua, M.; Miranda, J. I.; Ferron, P.; Quintana, L.; Aizpurua O.; Reyes, Y.; Aizpurua, J. M. "Activación de la Reacción de Huisgen Mediante Efecto Inductivo".
Communication: Poster.

Aizpurua, J.M.; Sagartzazu-Aizpurua, M.; Monasterio, Z.; Azcune, I.; Miranda, J. I.; Fratila, R. M.; Mendicute, C.; García-Lecina, E.; Altube, A. "Dicarbenos mesoiónicos de 4,4'-bis(1,2,3-triazoles) con quiralidad axial".
Communication: Oral by Sagartzazu-Aizpurua, M.

6. **24 Reunión Bienal de Química Orgánica**, *2012*, Donostia-San Sebastián, Spain.
Aizpurua, J.M.; Sagartzazu-Aizpurua, M.; Monasterio, Z.; Azcune, I.; Miranda, J. I.; Fratila, R. M.; Mendicute, C.; García-Lecina, E.; Altube, A. "Introducing axial chirality into mesoionic 4,4'-bis(1,2,3-triazole) dicarbenes".
Communication: Oral flash by Sagartzazu-Aizpurua, M.

7. **XVI Jornadas Hispano-Francesas de Química Orgánica**, *2011*, Burgos, Spain.
Aizpurua, J.M.; Sagartzazu-Aizpurua, M.; Monasterio, Z.; Azcune, I.; Miranda, J. I.; Fratila, R. M.; Mendicute, C.; García-Lecina, E.; Altube, A. "Chemical and electrochemical generation of unsymmetrically substituted mesoionic bis-1,2,3-triazole carbenes".
Communication: Poster.

# Synthesis, applications and reactivity of 1,2,3-triazolium salts

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