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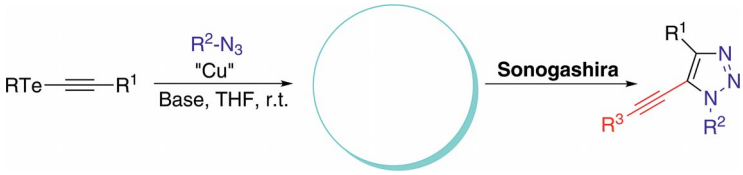
Heterocyclic Synthesis



An efficient synthesis of 5-organotellanyl-1*H*-1,2,3-triazole compounds through [3+2] cycloaddition reaction of organic azides and (organotellanyl)alkynes is presented. The 5-organotellanyl-1*H*-1,2,3-triazoles were readily functionalized at the 5-position to give highly functionalized triazoles.

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Synthesis of 5-Organotellanyl-1*H*-1,2,3-triazoles: Functionalization of the 5-Position Scaffold by the Sonogashira Cross-Coupling Reaction

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Keywords: Heterocycles / Tellurium / Alkynes / Click chemistry / Cycloaddition / Cross-coupling

An efficient synthesis of 5-organotellanyl-1*H*-1,2,3-triazole compounds was accomplished through [3+2] cycloaddition reaction of organic azides and (organotellanyl)alkynes. Additionally, 5-organotellanyl-1*H*-1,2,3-triazoles were readily functionalized at the 5-position by using a Sonogashira cross-coupling reaction, leading to highly functionalised triazoles. The regiochemistry of the products was assessed by two-dimensional NMR spectroscopic experiments and X-ray crystallography.

Introduction

The synthesis of 1,2,3-triazoles is one of the most studied topics in organic chemistry owing to the applications of these compounds in the chemical industry. Their use as bioactive molecules in medicinal chemistry has increased,[1,2] although the 1,2,3-triazole ring does not occur in nature. There are many examples of the biological activity of triazole compounds, including anti-HIV activity,[3] antimicrobial activity against Gram-positive bacteria[4] and selective β_3 adrenergic receptor agonist.[5]

The main route for the synthesis of 1,2,3-triazolic compounds is the Cu^I-catalyzed azide–alkyne 1,3-dipolar [3+2] cycloaddition reaction, which was improved in 2002, when the groups of Sharpless[6] and Medal[7] independently introduced the use of copper salts to obtain better yields and good regioselectivity, among other advantages.

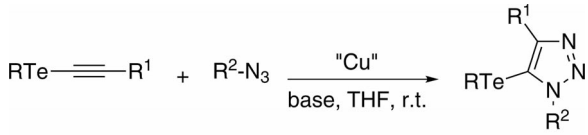
This kind of reaction can be performed under different conditions, considered non-classical ones, including microwave dielectric heating, ultrasound processing, ionic liquids as the reaction media and continuous flow processing.[8]

Some reports that describe the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles are available such as 1,5-disubstituted 4-magnesio-1,2,3-triazoles,[9] 4-gold-5-organo-1,2,3-triazoles,[10] and 1,4-disubstituted 5-alumino-1,2,3-triazoles.[11] Although there are a lot of protocols that describe the 1,5-regioselective azide–alkyne cycloaddition reaction for the synthesis of this class of triazole.[12] In this context, we envisaged the synthesis of 1,4,5-trisubstituted triazoles bearing an appropriate substituent at C-5 would allow further transformations.

The transition-metal-catalyzed cross-coupling reaction of organometallics is a methodology widely used to produce products prevalent in pharmaceuticals, ligands and materials. Extensive research has focused on a variety of ways to form C–C bonds by using transition-metal catalysts.[13]

Tellurium/metal-exchange reactions have attracted the interest of chemists owing to the special regio- and stereoselectivity properties that are unique to tellurium species. In this sense, cross-coupling reactions such as Suzuki–Miyaura,[14] Sonogashira,[15] Negishi,[16] Heck[17] and homo coupling reactions[18] have attracted attention. Moreover, unnamed reactions involving various metals and nonmetals such as magnesium,[19] zinc,[20] aluminum,[21] tin,[22] phosphorus,[23] iodine,[24] and a Te/halide[25] exchange process have been developed.

Herein, we report an efficient [3+2] cycloaddition reaction of organic azides and disubstituted (organotellanyl)alkynes for the synthesis of 5-organotellanyl-1*H*-1,2,3-triazoles to obtain a pool of highly substituted 1,2,3-triazoles (Scheme 1).



R = *n*Bu, Ph
R^1, R^2 = aryl, alkyl, heteroaryl

Scheme 1. General scheme.

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Results and Discussion

Initially, we focused our attention on the optimization of the reaction conditions, and investigated parameters such as: copper salts loading, base, additive and solvents (see Supporting Information, Table S1). The standard reaction was carried out with phenyl-*n*-butyltellanyl-acetylene (**1a**; 0.5 mmol), benzyl azide (**2a**; 0.6 mmol), CuI (1 equiv.), pentamethyldiethylenetriamine (PMDETA; 1 equiv.) and tetrahydrofuran (THF) as solvent. Under these conditions, product **3a** was obtained in 83% yield. However, under the same conditions, but in the absence of a base, the product was isolated in only 20% yield, thus showing the crucial role of the base in the reaction.

To evaluate the copper salt loading, we carried out the reaction and reduced the amount of CuI, however, the resulting yield was lower. Other copper sources were also tested, such as CuBr, CuCl, CuCN, $Cu(OAc)_2$ and $CuSO_4$, and similar results were obtained when CuBr and $Cu(OAc)_2$ were used.

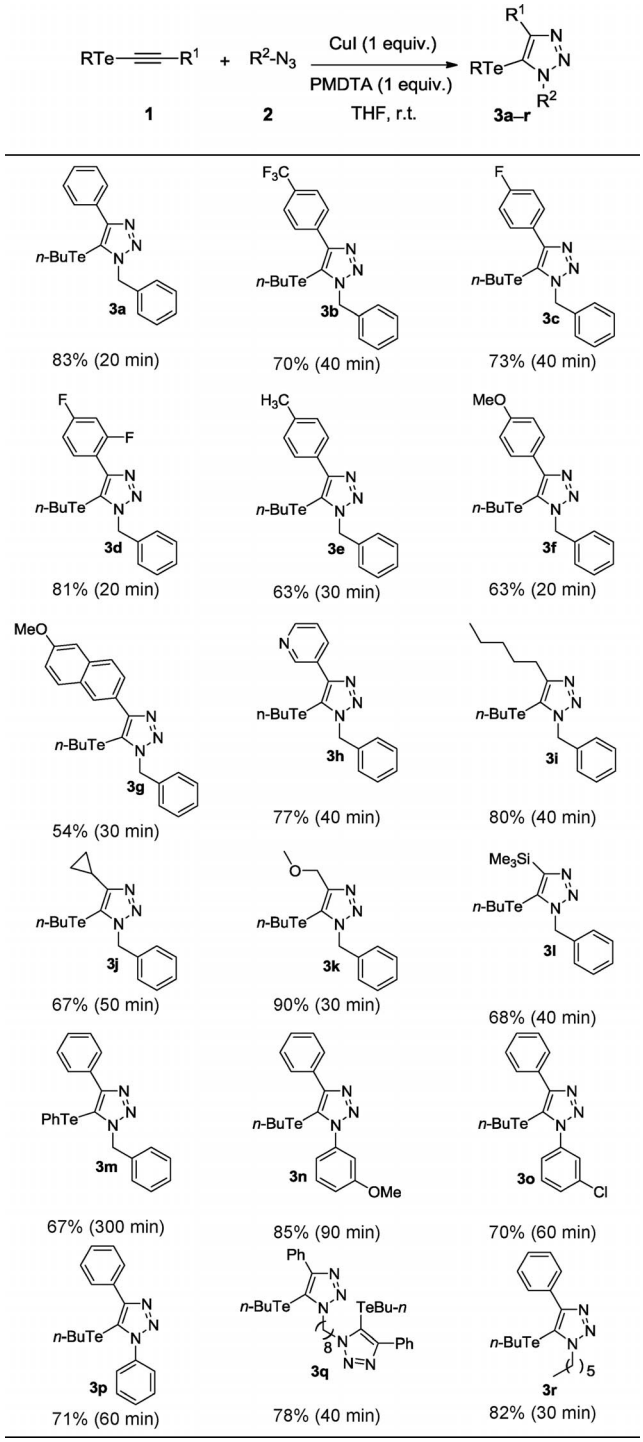
Various and different stoichiometries of base were evaluated. All of the commonly used bases such as triethylamine, tetramethylethylenediamine, and diisopropylethylamine (DIPEA) gave yields from moderate to good (51% to 72%) independently of the equivalents used (1 or 2 equiv.) or the use of sodium ascorbate as additive. However, when PMDETA was used, improved yields were observed (up to 83%) with 1 equiv. The choice of the solvent was of paramount importance for the success of the reaction. THF provided the optimal environment, and resulted in 83% yield in a very short time (20 min). The use of solvents such as *t*BuOH (78%), dimethylformamide (70%), acetonitrile (75%) and CH_2Cl_2 (74%) all gave good yields in reaction times ranging from 10 to 240 min.

After determining the optimal conditions for the [3+2] cycloaddition reaction of organic azides and (organotellanyl)alkynes, we explored the generality of the protocol, as indicated in Table 1.

Analysis of Table 1 shows that all reactions proceeded with acceptable yields. Initially, we evaluated the influence of different substituents on the aromatic ring attached to the triple bond. The reaction seemed to be sensitive to electronic effects. Tellanylacetylenes containing electron-withdrawing groups in the aromatic ring, F and CF_3, gave the desired product in better yields than their analogues containing electron-donating groups (Table 1, **3b**–**3f**).

A heteroaromatic ring, pyridine, did not negatively affect the performance of the reaction, leading to product **3h** in 77% yield. Cyclopropyl and trimethylsilyl substituents afforded corresponding triazoles in 67% (**3j**) and 68% (**3l**) yields. Resulting compound **3l** bearing a tellurium derivative and a silyl substituent would represent an attractive target, because the trimethylsilyl group can be easily converted into the corresponding bromide and iodide by using *N*-halosuccinimide[26] as the halogen source. The resulting compound, a 4-halo-5-organotellanyl-1,2,3-1*H*-triazole, could be employed as a useful intermediate in cross-coupling reactions.

Table 1. Exploring the scope of the [3+2] cycloaddition reaction between (organotellanyl)alkynes and organic azides.[a]



[a] Yields are given for isolated products.

The alkynes with alkane substituents showed a beneficial effect on the reaction, affording products in high yields (80 and 90% for **3i** and **3k**, respectively).

The reaction also allowed the use of an aryl group attached to the tellurium atom, providing desired product **3m** in moderate yield albeit with a longer reaction time. All

reactions were performed with reaction times ranging from 20 to 300 min.

Next, we turned our attention to evaluating the scope of organic azides. Aryl groups containing electron-withdrawing substituent such *m*-Cl gave a good yield (70%). However, an aryl group containing electron-donor substituent OMe gave 85% yield and a phenyl group gave 74% yield. It is noteworthy that the electron-donating group in the aromatic ring increased the nucleophilicity of the azide, furnishing the product in higher yield. Alkyl azides gave good to high yields (78 and 82% for **3q** and **3r**, respectively).

To identify the formation of copper σ-acetylide as a possible intermediate, which exhibits a vibrational absorption at 1930 cm^{-1},[27] the reaction of tellanylacetylene **1a** with CuI (1 equiv.) in MeCN was monitored by using in-situ React IR spectroscopy. The characteristic vibrational stretching was not observed, indicating that the copper acetylide is not formed during the reaction, suggesting that the C–Te bond is not broken during the process.

A mechanism was proposed based on experimental data obtained by using HRMS and in-situ React IR spectroscopy (Figure 1). The copper may be complexing with tellanylacetylene forming intermediate **2** (see Supporting Information). Addition of base allows the activation of tellanylacetylene through formation of π-complex intermediate **3**, followed by coordination of the azide through the proximal nitrogen center to produce complex **4**. Cyclization occurs through attack of carbon β-vinylidenic to electrophilic terminal nitrogen in transient species **5**, and new C–N bond formation favoring copper complex **6** to give triazole ring **7** (Scheme 2).

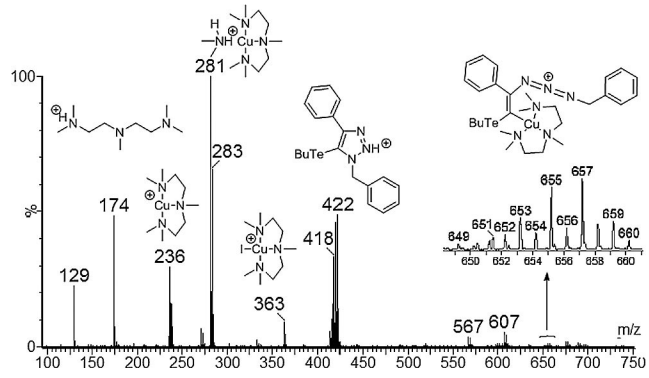
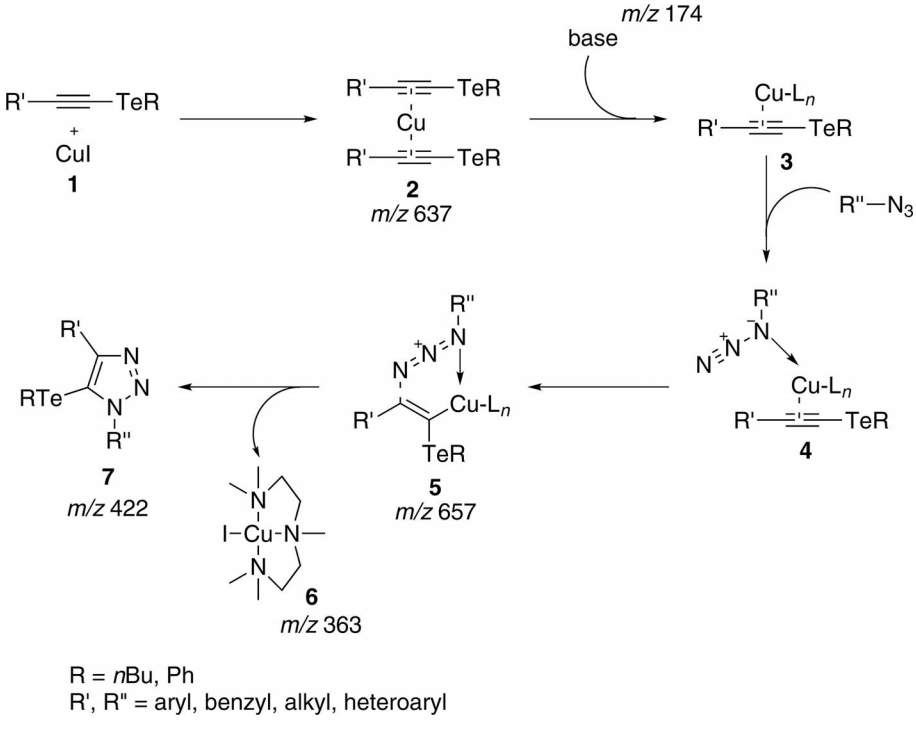


Figure 1. Mass spectrum of the reaction between telluride **1a** and benzyl azide (**2a**).

Additionally, exclusive formation of 5-organotellanyl-1*H*-1,2,3-triazole, even when the reaction is carried out protic solvent *t*BuOH, supports this pathway. In our experiments we do not observed the formation of 5-*H*-triazole as a byproduct.

The regiochemistry of **3a** was assigned by reducing the 5-tellanyltriazole to give 5-*H*-triazole (see the Supporting Information for more details). The long-range COSY (Figure 2, a) shows correlation between the triazolic hydrogen and the methylene. Analysis by using HMBC (Figure 2, b) showed a correlation between the methylene hydrogen and carbon 1, but not with carbon 2. This data suggests that the organotellanyl group is in position 5 of the triazole.

Considering that the reaction could lead to the 1,4- or the 1,5-organotellanyl compound a theoretical DFT study



Scheme 2. Proposed mechanism.

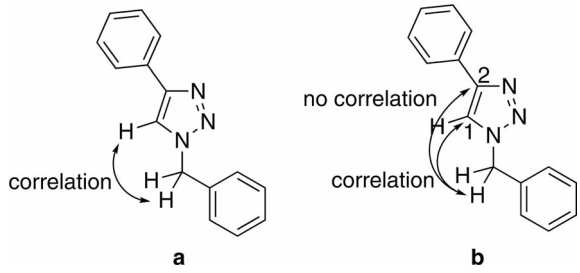


Figure 2. Analysis with long-COSY NMR spectroscopy (**a**) and HMBC NMR spectroscopy (**b**).

(B3LYP/STO-3G**) with compound **3a** as a model was carried out on both possible compounds. The results showed (see Supporting Information, Table S3) that the 1,4,5-trisubstituted 5-(butyltellanyl)-1,2,3-triazole has energy lower by about 3 kcal mol^{-1} than its 1,4,5-trisubstituted 4-(butyltellanyl)-1,2,3-triazole isomer. Moreover, calculations of geometric parameters and Natural Bond Order (NBO) analysis for the intramolecular interactions showed (see Supporting Information, Table S4 and Figure S1 of SI) that the main difference relies on a C–H···Te interaction (NBO, –8.40 kcal/mol). Also NBO steric hindrance of the *n*-butyl telluride moiety was calculated (see Supporting Information, Table S5). These results showed that the steric hindrance in the 5-substituted compound is largely compensated for by both the C–H···N and C–H···Te interactions (see Supporting Information, Table S4). Hence the 1,4,5-trisubstituted 5-(butyltellanyl)-1,2,3-triazole is the thermodynamic product of the cycloaddition reaction between benzyl azide and internal alkyne (substituted by phenyl and butyltellanyl).

Confirmation of the two-dimensional NMR spectroscopic results and the theoretical calculations were accomplished by the X-ray crystal structure of 1-benzyl-5-(butyltellanyl)-4-(6-methoxynaphthalen-2-yl)-1*H*-1,2,3-triazole (**3g**; Figure 3). Slow recrystallization from ethyl acetate provided crystals suitable for the crystal structure determination.

The presence of an organotellanyl moiety in the triazole ring makes these compounds versatile intermediates in organic synthesis and it is possible to subject them to a wide range of cross-coupling reactions catalyzed by transition metals.[11–19] The 5-organotellanyl-1*H*-1,2,3-triazoles were then subjected to Sonogashira cross-coupling reactions, and different conditions, such as the Pd catalyst, base, solvent and stoichiometry were evaluated.

We started by analyzing a series of catalysts: Pd_2dba_3, $Pd(dppf)Cl_2$, $PdCl_2$ and $Pd(OAc)_2$ (all at 10 mol-%). In all cases, low to moderate yields were obtained and a significant amount of the detellurated product (25–59%) was produced (see Supporting Information, Table S2). $Pd(PPh_3)_2Cl_2$ (10 mol-%) gave a better product yield (58%) and 22% of the detellurated product. Variations in the stoichiometry of this catalyst, such as 1 and 5%, afforded yields from 17 to 52%.

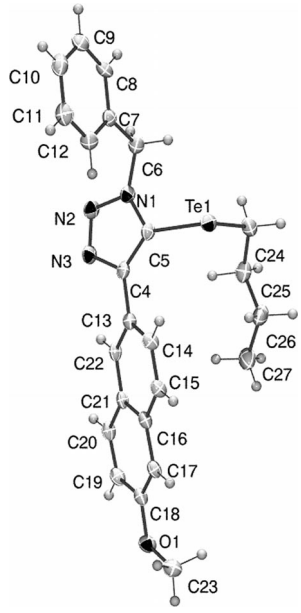


Figure 3. The molecular structure of 1-benzyl-5-(butyltellanyl)-4-(6-methoxynaphthalen-2-yl)-1*H*-1,2,3-triazole (**3g**).

A survey of the copper salts showed CuI to be the best, leading to 58% yield. Other copper co-catalysts were tested, but yields were slightly lower: $Cu(OTf)_2$, 52%, CuCN, 43% and $Cu(OAc)_2$, 50%. Also the amount of CuI (0.2 to 2.0 equiv.) was surveyed, unfortunately with low yields. K_2CO_3 proved to be the best base with 58% yield and 22% yield of the detellurated triazole. Other organic bases such as Cs_2CO_3, Et_3N, diisopropylamine and DIPEA all led to very poor yields (24 to 31%) and high amounts of detellurated triazole (56 to 73%).

Finally, different solvents were investigated, with dimethyl sulfoxide (DMSO) providing the best result (58%). Solvents such as toluene and methanol did not give any product. Dimethylphormamide and 1,4-dioxane gave very poor yields (19 and 36%, respectively).

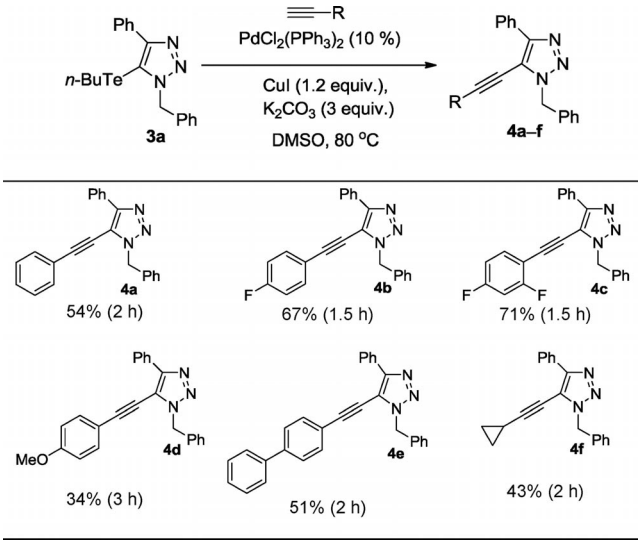
Next, we explored the scope of our methodology with terminal alkynes by performing the reaction with DMSO as the solvent, $Pd(PPh_3)_2Cl_2$ (10 mol-%) as the catalyst, CuI (1.2 equiv.) as the co-catalyst and K_2CO_3 as the base (Table 2).

The results summarized in Table 2, show that the reaction worked well for a variety of acetylenes. The reaction seems to be sensitive to electronic effects of the substituents on the aromatic ring attached to triple bond. An aromatic ring with an electron-withdrawing substituent gave better yields of alkynylated products.

Conclusions

In summary, we have developed a simple and versatile [3+2] cycloaddition reaction protocol for the synthesis of 5-organotellanyl-1*H*-1,2,3-triazole compounds involving organic azides and organotellanyl-substituted alkynes. The [3+2] cycloaddition reaction could be successfully per-

Table 2. Sonogashira reaction of 1,4,5-trisubstituted 5-(butyltellanyl)-1,2,3-triazole and acetylenes.



formed with a variety of organic azides and (organotellanyl)-alkynes under mild conditions. On the basis of X-ray crystallographic data, it was possible to determine the regiochemistry of the reaction, and a mechanism for the formation of the 5-organotellanyl-1*H*-1,2,3-triazole compounds was proposed based on the results of HRMS. 5-Organotellanyl-1*H*-1,2,3-triazole compounds are valuable intermediates that can be used in cross-coupling reactions, such as Sonogashira, leading to interesting functionalized compounds.

Experimental Section

Materials and Methods: ^{1}H NMR spectra were obtained at 300 MHz. Spectra were recorded in $CDCl_3$ solution or in [D_6]-DMSO. Chemical shifts are referenced to the solvent peak of $CDCl_3$ or tetramethylsilane. ^{13}C NMR spectra were obtained at 75 MHz. Spectra were recorded in $CDCl_3$ solution or in [D_6]-DMSO. Chemical shifts are referenced to the solvent peak of $CDCl_3$ or DMSO. Column chromatography was performed with silica gel (230–400 mesh). TLC was performed with silica gel UV_{254}, 0.20 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine or acidic vanillin solution. THF was dried and purified by distillation from sodium with benzophenone as the indicator. All other solvents were ACS or HPLC grade unless otherwise noted. Air and moisture-sensitive reactions were conducted in flame-dried or oven-dried glassware equipped with tightly fitted rubber septa and under a positive atmosphere of dry nitrogen. Reagents and solvents were handled by using standard syringe techniques. Temperatures above room temperature were maintained by the use of a mineral oil bath with an electrically heated coil connected to a controller.

General Procedure for [3+2] Cycloaddition Reaction: To a two-necked round-bottomed flask (25 mL) under a nitrogen atmosphere containing CuI (0.190 g, 1 mmol), THF (4 mL), organic azide (1.1 mmol), acetylene (1 mmol) was added PMDETA (0.21 mL, 1 mmol) and the reaction mixture was stirred at room temperature. The reaction time was determined by monitoring with TLC. Then the reaction mixture was diluted with ethyl acetate and washed with aqueous NH_4Cl, the organic phase was collected, dried with $MgSO_4$, filtered and the solvent removed under vacuum. Purification was performed by using silica gel chromatography (ethyl acetate/hexane, 1:9).

1-Benzyl-5-(butyltellanyl)-4-phenyl-1*H*-1,2,3-triazole (3a): Yield 83%, yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.01 (d, J = 6.8 Hz, 2 H); 7.45–7.25 (m, 8 H); 5.82 (s, 2 H); 2.33 (t, J = 7.5 Hz, 2 H); 1.32 (quin., J = 7.5 Hz, 2 H); 1.06 (sex, J = 7.5 Hz, 2 H); 0.67 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 154.3; 135.9; 131.6; 128.8 (2 C); 128.3 (2 C); 128.2; 128.1; 128.1 (2 C); 127.6 (2 C); 98.9; 54.7; 32.9; 24.5; 13.1; 11.3 ppm. ^{125}Te NMR ($CDCl_3$, 94.69 MHz): δ = 209.2 ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{22}N_3Te + H^+$ 422.0876; found 422.0878. IR: $\tilde{\nu}$ = 2348, 1531, 1219, 767 cm^{-1}.

General Procedure for Sonogashira Cross-Coupling Reaction: To a two-necked round-bottomed flask (25 mL) under a nitrogen atmosphere containing $Pd(PPh_3)_2Cl_2$ (0.035 g, 10 mol-%), CuI (0.114 g, 0.6 mmol) and dry DMSO (4 mL) was added **3a** (0.210 g, 0.5 mmol), acetylene (1.5 mmol) and K_2CO_3 (0.207 g, 1.5 mmol). The reaction mixture was stirred and heated at 80 °C. The reaction time was determined by monitoring with TLC. Then the reaction mixture was diluted with ethyl acetate and washed with a saturated solution of ethylenediaminetetraacetic acid, the organic phase was collected, dried with $MgSO_4$, filtered and the solvent was removed under vacuum. Purification was performed by using silica gel chromatography (ethyl acetate/hexane, 2:8).

1-Benzyl-4-phenyl-5-(phenylethynyl)-1*H*-1,2,3-triazole (4a): Yield 58%, white solid, m.p. 94–96 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.18 (d, J = 7.1 Hz, 2 H); 7.38 (m, 13 H); 5.64 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 148.1; 134.7; 131.5 (2 C); 130.3; 129.7; 128.9 (2 C); 128.7 (4 C); 128.6; 128.5; 128.1 (2 C); 126.2 (2 C); 121.4; 117.2; 102.4; 75.6; 53.0 ppm. HRMS (ESI-TOF): calcd. for $C_{23}H_{18}N_3 + H^+$ 336.1495; found 336.1498. IR: $\tilde{\nu}$ = 3002, 2756, 2347, 1517, 1219, 767 cm^{-1}.

Supporting Information (see footnote on the first page of this article): Experimental details and analytical data for all new compounds, including ^{1}H and ^{13}C NMR spectra.

CCDC-917547 (for **3g**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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