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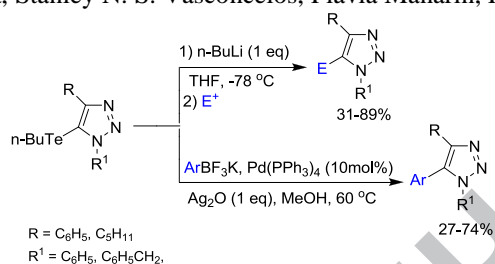
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### Functionalization of 5-telluro-1,2,3-triazoles: Te/Li exchange and Suzuki-Miyaura cross-coupling reaction

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## Functionalization of 5-telluro-1,2,3-triazoles: Te/Li exchange and Suzuki-Miyaura cross-coupling reaction

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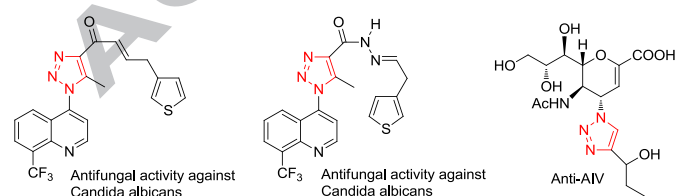
### ABSTRACT

This paper describes the functionalization of 5-telluro-1,2,3-triazoles via the Te/Li exchange or Suzuki-Miyaura cross-coupling reaction to obtain moderate to good yields of the corresponding products.

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### 1. Introduction

The 1,3-dipolar cycloaddition reaction to form 1,2,3-triazole rings is currently one of the most performed. The search for new methods and improvement of existing ones to generate 1,2,3-triazoles are largely due to their applications in many areas such as modern chemistry, drug discovery, macromolecules, radiopharmaceuticals, material sciences, synthesis of bis-bidentate Pd(II) complexes and biology (Figure 1).<sup>1,2</sup>



**Figure 1.** Structures of biologically active 1,2,3-triazoles.

The copper(I)-mediated 1,3-dipolar cycloaddition of azides and terminal alkynes<sup>2</sup> (CuAAC) increases the reaction rates and governs regioselectivity, favoring 1,4-disubstituted-1,2,3-triazole formation. This discovery by Sharpless and Meldal is considered to be the most popular reaction of the 'click' chemistry concept<sup>3</sup> and represents the most straightforward synthesis of 1,2,3-triazoles.

Cross-coupling reactions involving tellurium compounds such as Suzuki-Miyaura,<sup>4</sup> Sonogashira,<sup>5</sup> Negishi,<sup>6</sup> Heck<sup>7</sup> and homocoupling reactions<sup>8</sup> have recently attracted attention in the field of triazole formation. Moreover, unnamed reactions involving various metals and non-metals such as magnesium,<sup>9</sup> zinc,<sup>10</sup> aluminum,<sup>11</sup> tin,<sup>12</sup> phosphorus,<sup>13</sup> iodine<sup>14</sup> and the Te/halide<sup>15</sup> exchange process have also been developed.

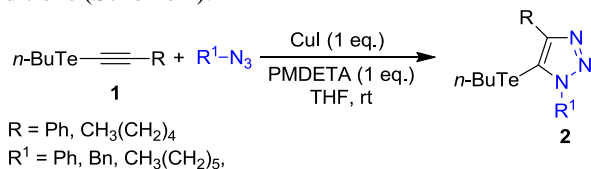
Tellurium/metal exchange reactions are currently attracting a lot of interest due to the special regio- and stereoselectivity properties that are unique to tellurium. In this sense, the formation of organolithium compounds via a tellurium/lithium exchange reaction is an important tool with many advantages over the other methods available.<sup>16,17</sup>

We describe here a tellurium/lithium exchange or Suzuki-Miyaura cross-coupling reaction of 5-telluro-1,2,3-triazoles that allows access to functionalized 1,2,3-triazoles, using different electrophiles. To the best of our knowledge, this study is the first to report functionalization of 5-telluro-1,2,3-triazoles.

### Results and Discussion

The triazoles used in the Te/Li exchange and Suzuki-Miyaura cross-coupling reactions were synthesized by a simple and versatile [3+2]-cycloaddition protocol for the synthesis of 5-organotelluro-1H-1,2,3-triazole compounds,<sup>18</sup> using

organoazides and organotelluro alkynes under mild conditions (Scheme 1).



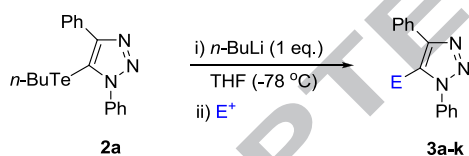
**Scheme 1.** Synthesis of 5-tellurotriazole

The regiochemistry of **2b** was assigned by detelluration of 5-tellurotriazole to give 5-*H*-triazole. The long-range COSY experiment showed a correlation between the triazolic hydrogen and methylene. For HMBC, there was a correlation between the methylene hydrogen and carbon 1, but not carbon 2. This suggests that the organotellurium group was at position 5 of triazole (see Supporting Information).

With the starting materials at hand, the next step was the functionalization of 5-telluro-1,2,3-triazoles via the tellurium/lithium<sup>14</sup> exchange reaction with *n*-BuLi, followed by trapping the lithium intermediate with different electrophiles. Initially, we tested the solvent to be used in the reaction and found that THF was the most optimal. We employed a temperature of -78 °C.

We focused on evaluating the generality of the reaction. Product structures, yields and reaction times are summarized in Table 1.

**Table 1.** Products of the tellurium/lithium exchange of 5-telluro-1,2,3-triazoles.



Entry	Electrophiles	Product	Yield (%)
1			61
2			91
3			84
4			70

5			58
6			67
7			47
8			57
9	$\text{I}-\text{CH}_3$		89
10	$\text{TMS}-\text{Cl}$		31
11			89

Looking at Table 1, it can be seen that the reaction worked well for aromatic aldehydes, with yields ranging from 61 to 91% (Table 1, entries 1-4 and 6). Aldehydes with electron donor groups such as MeO and Me gave high yields (Table 1, entries 2 and 3, 91% and 84%, respectively). In aldehydes with electron-withdrawing groups such as Cl and NO<sub>2</sub>, the yields were moderate, generating products with a yield of 70% and 67%, respectively (Table 1, entries 4 and 6, respectively). Meanwhile, alkyl aldehyde gave a moderate yield (Table 1, entry 5, 58%).

On the other hand, aromatic ketones with electron-withdrawing substituents, such as Cl and Br, exhibited low yields (47 and 57%, respectively) (Table 1, entries 7 and 8, respectively).

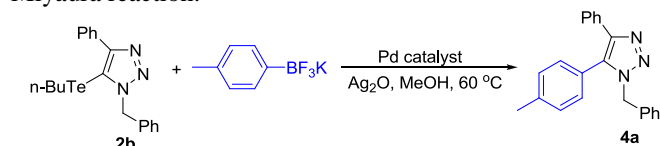
Reaction with alkyl halide generated a high yield (Table 3, entry 9, 89% yield), while those using TMS-Cl gave a yield of 31% and chlorodiphenylphosphine as the electrophile, 89% (Table 1, entries 10 and 11, respectively).

Functionalization was also possible through the Suzuki-Miyaura cross-coupling reaction using potassium aryltrifluoroborate salts catalyzed by palladium complexes. Initially, we focused our attention on the optimization of the reaction conditions. Therefore, we investigated some

parameters, such as different palladium catalysts, additives and solvents (Table 2).

We employed 5-telluro-1,2,3-triazole (**2b**) and the potassium *p*-tolyltrifluoroborate salt as standard reagents. In the first test, a mixture of **2b** (0.5 mmol), potassium *p*-tolyltrifluoroborate (0.6 mmol), palladium catalyst (10 mol %) and Ag<sub>2</sub>O (1 eq.) in MeOH was reacted at 60 °C for 1-3 h in the absence of a base to obtain the product (see Table 2).

**Table 2.** Optimization of the palladium-catalyzed Suzuki-Miyaura reaction.

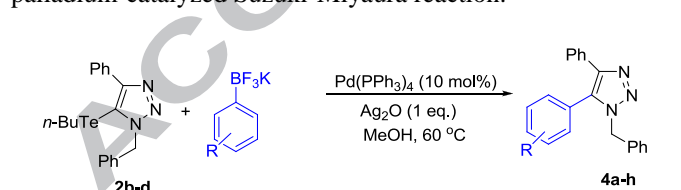


Entry	Catalyst (10mol%)	Reaction Time (h)	Yield (%)
1	Pd(OAc) <sub>2</sub>	1	nr <sup>a</sup>
2	PdCl <sub>2</sub>	2	nr <sup>a</sup>
3	Pd <sub>2</sub> (dba) <sub>3</sub>	1	28
4	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	2	traces
5	Pd(PPh <sub>3</sub> ) <sub>4</sub>	2	42 <sup>b</sup>
6	Pd(PPh <sub>3</sub> ) <sub>4</sub>	2	54
7	Pd(PPh <sub>3</sub> ) <sub>4</sub>	1	nr <sup>c</sup>
8	Pd(PPh <sub>3</sub> ) <sub>4</sub>	3	37
9	Pd(PPh <sub>3</sub> ) <sub>4</sub>	1	nr <sup>a</sup>

<sup>a</sup>Byproduct was formed (detellurated triazole). <sup>b</sup>Using ultrasound bath. <sup>c</sup>1.2 equiv. Et<sub>3</sub>N.

Exchanging MeOH for other solvents such as toluene or DMF generated lower yields or no product at all (Table 2, entries 8 and 9). Detellurated product was observed in the conditions 1, 2 and 9, but when Et<sub>3</sub>N was used, the detellurated product was formed immediately (Table 2, entry 7). The optimized condition (Table 2, entry 6) was then extended to a range of substituted potassium aryltrifluoroborate salts. In all cases, the reactions were conducted in MeOH under a nitrogen atmosphere at 60 °C (Table 3).

**Table 3.** 5-Aryl-1,2,3-triazole functionalization by a palladium-catalyzed Suzuki-Miyaura reaction.



Entry	R-BF <sub>3</sub> K	Product	Time (h)	Yield (%)
1			4	54
2			3	40

3			1.5	74
4			1.0	54
5			1.0	52
6			1.0	46
7			1.5	27
8			-	-

The cross-coupling reaction worked well for aryltrifluoroborates containing substituted aryl rings with electron-donating groups (-Me, -SC<sub>2</sub>H<sub>5</sub> and HOCH<sub>2</sub>-), giving moderate to good yields. Aryltrifluoroborates with electron-withdrawing (Cbz, entry 5) and neutral (C<sub>6</sub>H<sub>5</sub>-, entry 2) groups obtained the coupled product at moderate yields (see Table 3). In the case of compounds 6 and 7 with alkyl groups at positions 1 and 4 of the heterocyclic ring, the yields were poor (46 and 27%, respectively). For the 1,4-diaryl-5-telluro-1,2,3-triazole, no coupled product was observed, probably due to the steric hindrance of aryl substituents at positions 1 and 4.

## Conclusions

In summary, functionalization of 5-telluro-1,2,3-triazoles through the Te/Li exchange or cross-coupling Suzuki-Miyaura reaction obtained moderate to good yields of the corresponding products. These transformations could be used in the synthesis of products with biological applications, such as those shown above. Other possible applications are in progress and will be reported in due time.

**Supporting Information:** Experimental details and analytical data for all new compounds, as well as the <sup>1</sup>H and <sup>13</sup>C NMR

spectra data associated with this article can be found, in the online version

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19. **General procedure for the [3+2]-cycloaddition reaction:** To a two-necked 25-mL round-bottom flask under a nitrogen atmosphere containing CuI (0.190 g, 1 mmol), THF (4 mL), organic azide (1.1 mmol) and acetylene (1 mmol), PMDETA (0.21 mL, 1 mmol) was added and the reaction mixture stirred at room temperature. The reaction time was determined by monitoring TLC. The reaction mixture was then diluted with ethyl acetate and washed with aqueous NH<sub>4</sub>Cl. The organic phase was collected, dried with MgSO<sub>4</sub>, filtered and the solvent removed under vacuum. Purification was undertaken by silica gel chromatography (eluting with ethyl acetate/ hexane 1:9). **5-(butyltellanyl)-1,4-diphenyl-1H-1,2,3-triazole (2a).** The product was obtained as a white solid at a yield of 71%. mp 104 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ (ppm): 7.94 (d, *J* = 1.5 Hz, 1H); 7.91 (t, *J* = 1.5 Hz, 1H); 7.47-7.31 (m, 8H); 2.37 (t, *J* = 7.5 Hz, 2H) 1.27 (qn, *J* = 7.5 Hz, 2H); 0.98 (sx, *J* = 7.5 Hz, 2H) 0.60 (t, *J* = 7.5 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ (ppm): 154.0; 138.0; 131.4; 129.7; 129.1 (2C); 128.4 (5C); 126.4 (2C); 99.7; 32.9; 24.5; 13.0; 11.2. <sup>125</sup>Te NMR (CDCl<sub>3</sub>, 94.69 MHz) δ (ppm): 268.4. HRMS calcd for C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>Te + H<sup>+</sup>: 408.0719. Found: 408.0717. IR (cm<sup>-1</sup>): 3011, 2413, 1524, 1219, 767.
20. **General procedure for the Te/Li exchange reaction:** To a two-necked 50-mL round-bottom flask under a nitrogen atmosphere, *n*-BuLi (0.22 mL, 0.5 mmol, 2.2728 mol/L) was added to a solution of **2a** (0.20 g, 0.5 mmol) in THF (10 mL) at -78 °C. After 60 min of stirring at -78 °C, anisaldehyde (0.068 g, 0.5 mmol) was added and the mixture stirred for 12 h at room temperature, before being diluted with ethyl acetate and washed with aqueous NH<sub>4</sub>Cl. The organic phase was collected, dried with MgSO<sub>4</sub>, filtered and the solvent removed under vacuum. Purification was performed by silica gel chromatography, eluting with ethyl acetate / hexane.<sup>22,23</sup> **1,2,3-triazol-5-yl(4-methoxyphenyl)methanol (3b):** The product was obtained as a white solid at a yield of 91%. mp 114°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ (ppm): 7.69-7.65 (*m*, 2H); 7.37-7.25 (*m*, 8H); 6.90 (d, *J* = 8.6 Hz, 2H); 6.63 (d, *J* = 8.6 Hz, 2H); 6.16 (*s*, 1H); 3.68 (*s*, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ (ppm): 158.9; 146.0; 136.6; 135.7; 132.2; 130.5; 129.5; 128.8 (2C); 128.5 (2C); 128.5 (2C); 128.2; 127.0 (2C); 128.2 (2C); 113.6 (2C); 65.6; 55.2; HRMS calcd for C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub> + H<sup>+</sup>:



358.1556. Found: 358.1561. IR (cm<sup>-1</sup>): 3005, 2418, 1603, 1508, 1224, 1033, 770, 692.

**21. General procedure for the Suzuki-Miyaura cross-coupling reaction:** To a two-necked 25-mL round-bottom flask under a nitrogen atmosphere, Pd(PPh<sub>3</sub>)<sub>4</sub> (0.057 g, 10 mol%), Ag<sub>2</sub>O (0.231 g, 1.0 mmol), MeOH (5 mL), **2b** (0.209 g, 0.5 mmol) and potassium aryltrifluoroborate (0.118 g, 0.6 mmol) were added. The reaction mixture was stirred and heated at 60 °C. The reaction time was determined by monitoring TLC. Then the reaction mixture was diluted with ethyl acetate and washed with a saturated solution of NH<sub>4</sub>Cl. The organic phase was collected, dried with MgSO<sub>4</sub>, filtered and the solvent removed under vacuum. Purification was performed by silica gel chromatography (eluting with ethyl acetate/hexane).

**1-benzyl-4-phenyl-5-p-tolyl-1H-1,2,3-triazole (4a).** The product was obtained as a white solid at a yield of 54%. mp 111 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ (ppm): 7.50-7.47 (m, 2H); 7.17-7.11 (m, 8H); 6.97-6.92 (m, 4H); 5.29 (s, 2H); 2.32 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ (ppm): 144.4; 139.7; 135.5; 134.0; 131.1; 129.96 (2C); 129.90 (2C); 128.6 (2C); 128.4 (2C); 128.1; 127.6; 127.5 (2C); 126.7 (2C); 124.7; 51.8; 21.4. HRMS (ESI-TOF) *m/z* calcd for C<sub>22</sub>H<sub>19</sub>N<sub>3</sub> + H<sup>+</sup>: 326.1651. Found: 326.1661. IR (cm<sup>-1</sup>): 2982, 1444, 1219, 1038, 768.

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