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Graphical Abstract

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Safa Azzouni[a,b], Anne Gaucher[a], Damien Prim[a] and Mohamed Lotfi Efrit[b]

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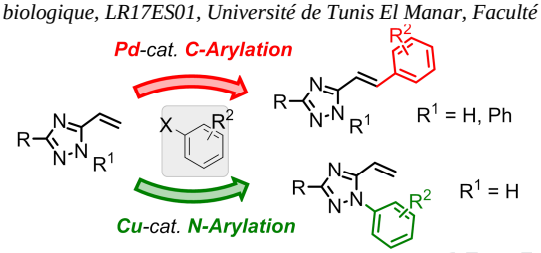

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ABSTRACT

The preparation of 1,3,5-trisubstituted 1,2,4-triazoles is described using selective orthogonal arylation sequences. Ligand free Pd-catalyzed arylation allowed installing various (het)aryl units exclusively at the vinyl fragment of N1 substituted or N1-H precursors. Successful double arylations starting from *ortho*, *meta* and *para* bisiodobenzenes led to extended bistriazolyl derivatives. In contrast, Cu-catalyzed arylation using pyridylmethylamine as the ligand, led to N1-arylated triazoles keeping intact the vinyl moiety. Arylation process was compatible with electron donating groups in *ortho*, *meta* and *para* positions and tolerated electron withdrawing groups with a lesser extent. The strategy is general and spread the molecular diversity at the triazole core.

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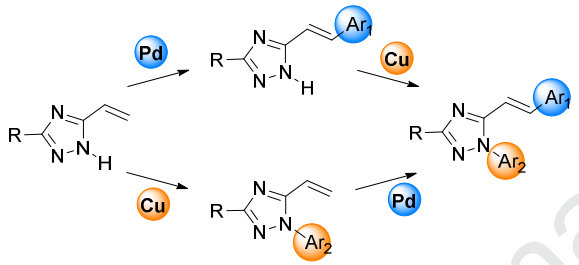
1. Introduction

The joint presence of three nitrogen and two carbon atoms in a five-membered ring confers triazoles unique properties combining different weak interactions, a characteristic basicity and several coordination modes.[1] Among them, 1,2,4-triazoles hold a unique place in the broad class of heterocyclic compounds. Indeed, the 1,2,4-triazole scaffold displays wide applications in pharmaceutical,[2] agricultural[3] and material sciences fields.[4] Moreover triazole derivatives exhibit corrosion inhibition[5] properties and serves as ligand in catalytic transformations.[6] Due to the lasting interest of the scientific community for such heterocycles and their properties, selective access to polyfunctional triazoles remains a major challenge. In this context, the 1,3,5-trisubstituted 1,2,4-triazole scaffold is of special interest because modulation of properties mandatorily arises from selective modification of the substitution pattern.

Although appealing preparation methods have been reported,[7] effective control of the substitution pattern may represent a hurdle especially when the triazole platform is substituted by several transition metal reactive fragments. In this paper, we describe the selective Pd- and Cu-catalyzed functionalization of vinyl-triazoles. Our strategy allows installing aryl fragments at the vinyl fragment and at the N1-H position. In addition, both sites can be iteratively arylated spreading thus the molecular diversity at the triazole core (Scheme 1).



Scheme 1. Selective Pd- and Cu-arylation of 5-vinyl-1,2,4-triazoles.

2. Results and discussion

Vinyltriazole precursors used in the arylation sequences were first prepared from imidate starting material according to our recent publication.[8] As shown in figure 1, triazoles **1**-**3** display a substitution pattern including phenyl or isopropyl groups located at position 3. N1 is substituted either by a phenyl group in substrate **1** or remains unsubstituted in compounds **2** and **3**.

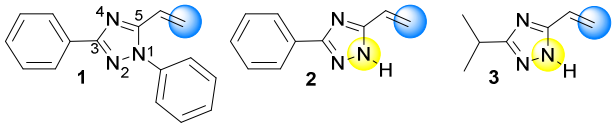
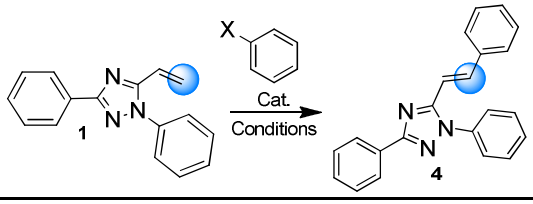


Figure 1. 5-vinyl-1,2,4-triazole precursors.

We first experimented the arylation of triazole precursor **1**, in order to set suitable conditions (Table 1). We started to test bromobenzene as the coupling partner. In this case, using $Pd(OAc)_2$ (5%) as the catalyst, K_3PO_4 (2 eq.) as the base in DMF at 110 °C led to partial conversion even after 24h reaction course (see ESI and preliminary result[8]). This prompted us to switch to iodobenzene. Several catalytic systems and conditions were tested in order improve the conversion. Condition B (Et_3N (2 eq), MeCN at 80°C) in the presence or absence of tetrabutylammonium iodide (TBAI) led to disappointing results even using 10% of $Pd(OAc)_2$ (entries 2, 3).

Table 1. Determination of suitable arylation conditions of vinyltriazole **1**.



Entry	Cat. Syst.	Cond.	TBAI (Y/N)	Time (h)	X	**1/4**	Yield (%)
1	$Pd(OAc)_2$ (5%)	A	N	24	Br	1/4.3	62[a]
2	$Pd(OAc)_2$ (10%)	B	N	24	I	1/1.7	
3	$Pd(OAc)_2$ (10%)	B	Y	24	I	1/0.9	
4	$Pd(OAc)_2$ (5%), PPh_3(40%)	B	N	24	I	1/0.4	
5	$Pd(OAc)_2$ (10%), PPh_3 (40%)	B	N	24	I	1/1	
6	PdCl2(dppf) (5%)	B	N	24	I	1/0.2	
7	$Pd(OAc)_2$ (5%)	C	Y	24	I	0/1	
8	$Pd(OAc)_2$ (5%)	C	Y	3	I	1/2.4	
9	$Pd(OAc)_2$ (5%)	A	N	24	I	0/1	
10	**$Pd(OAc)_2$ (5%)**	**A**	**N**	**4**	**I**	**0/1**	**78**

Condition A: K_3PO_4 (2 eq.), DMF, 110°C. B: Et_3N (2 eq.), MeCN, 80°C. C: NaOAc (2.5 eq.), DMF 110°C.

$Pd(OAc)_2$, PPh_3 combinations as well as $PdCl_2$(dppf) under condition B, similarly afforded poor conversions (entries 4-6). In contrast, under condition C in the presence of TBAI, using NaOAc (2.5 eq) as the base at 110°C in DMF for 24h allowed full conversion of the starting material (entry 7). Unfortunately, under these conditions, the reaction time could not be reduced as lower conversions were observed (compare entries 7 and 8). Fortunately, $Pd(OAc)_2$ (5%), K_3PO_4 (2 eq.) in DMF at 110 °C revealed the most efficient conditions even in the absence of TBAI (entry 9). Indeed, under these conditions a full conversion of the starting material was observed in 24h. The reaction time could be further reduced to 4h without any loss of conversion and target triazole **4** could be isolated in 78% yield.

With these conditions in hands, we further explored the installation of various aryl groups at the vinyl fragment of triazole **1** (figure 2).

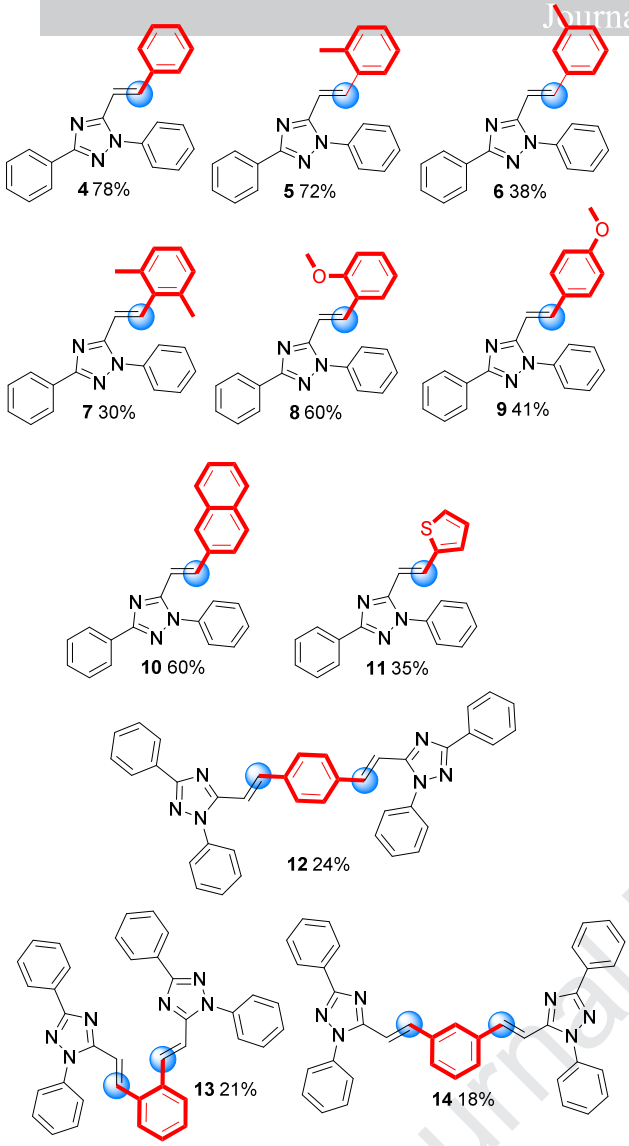


Figure 2. Access to variously substituted triazoles **4-14.**

O- and *m*-iodotoluenes as well as 2-iodo-1,3-dimethylbenzene were efficiently coupled to triazole **1** affording products **5-7** in 30 to 72 **%** yields. Similarly, triazoles **8** and **9** bearing *o*- and *p*-methoxy groups could be obtained in 60 and 41% yields respectively. Finally, triazoles **10** and **11** substitued by naphthyl and thienyl groups were synthesized in yields in 60 and 35% yields respectively. Precursor **1** was further reacted with bisiodobenzenes under the aforementioned conditions. Gratifyingly double coupling process afforded extended architectures **12-14** based on a central benzene core and two triazole units lying in *ortho*, *meta* and *para* fashion.

The installation of aryl groups bearing electron withdrawing substituents was next envisioned. Disappointingly, the use of the aforementioned conditions A or B remained unsuccessful. Indeed, under these conditions, no conversion was observed (figure 3). Conditions C led to poor conversion and afforded mainly degradation side products. In contrast, modified conditions D using 3 eq. of TBAI as an additive allowed minimizing the formation of unidentified degradation products and finally isolating target triazoles **15-18**. The latter comprise nitrobenzene, trifluoromethylbenzene or cyanobenzene as well as pyridyl fragments and were obtained in modest to low yields ranging from 11 to 48%.

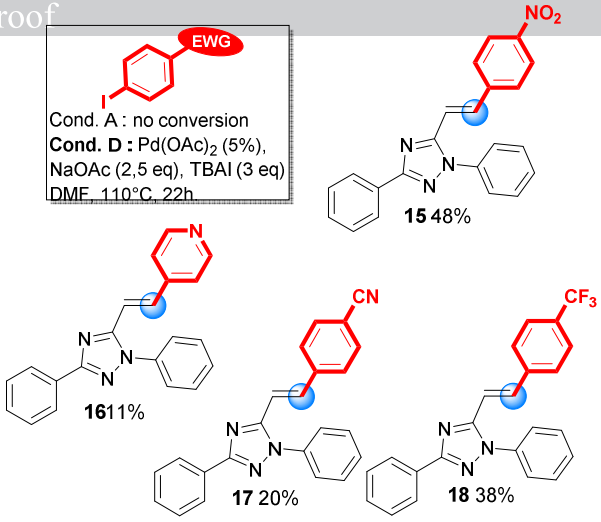


Figure 3. Catalytic conditions suitable for the installation of EWG groups

We next envisioned the arylation of the vinyl fragment of triazoles **2** and **3**. In the latter compounds, the N1 atom remains unsubstituted which may represent a challenging hurdle to overcome for selective arylation. Indeed, in these cases, both vinyl and N1 sites might be arylated under Pd-catalysis[9] and lead to mixtures of mono- and bis-arylated products (figure 4). Further, the absence of substituent at the N 1 site could favor the formation of Pd-triazole complexes and thus poison the catalytic system.

First attempts were realized using conditions A, B, C and D. Unfortunately, we were not able to isolate any of the potential products, crude products mainly affording intractable mixtures. However catalytic systems combining $Pd(OAc)_2$ and XPhos, afforded the expected compound **19** from triazole **2** and iodobenzene. The latter could be isolated in a fair 51 % yield using a Pd/L ratio of 1:2. Although *N*-arylated and bis-arylated products cannot be ruled out, we were not able to evidence their presence in the crude material. Triazoles **20-22** were obtained using identical reaction condition E. The latter targets arose from the reaction of precursor **2** and **3** and iodobenzene or *o*-iodotoluene.

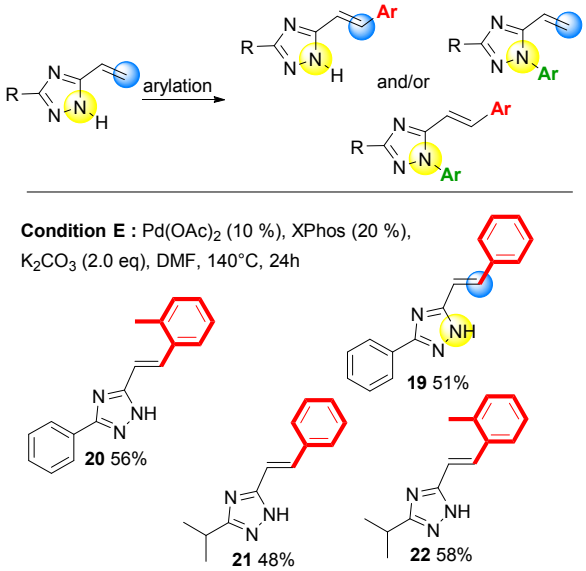


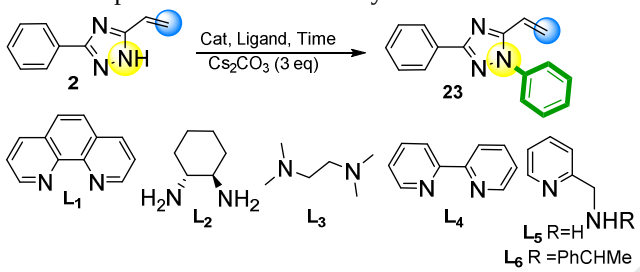
Figure4. Selective Pd-catalyzed arylation at the vinyl site of triazole **2** and **3**.

Our next objective was the selective arylation of the N1 site of triazoles **2** and **3**. To this end precursor **2** and iodobenzene were choosen as model reaction and reacted under various catalytic conditions.

As conditions A-E did not allow installing aryl groups at the N1 reactive site, we moved to Cu- and Fe-catalyzed process. Based on Buchwald, Bolm and Taillefer recent protocols,[10] several Cu or Fe-based catalytic conditions were tested.

First CuI was experimented without ligand (Table 2, entry 1). In this case the starting triazole **2** was recovered unchanged. Combinations of CuI with various ligands were next tested. Using **L1** to **L5** with Cs_2CO_3 in DMF at 130°C afforded various ratio of the starting material **2** and the expected N-arylated product **23** (entries 2-7). Similarly, to N-ligands, XPhos afforded poor conversion (entry 8). Fe-based catalytic systems such as $Fe(acac)_2$/CuO or $FeCl_2$ were found ineffective (entries 10-11). Finally, Cu_2O was tested in combination with **L1** or **L5** in the presence of PEG-400 and Cs_2CO_3 (entries 12-14).

Table 2. Optimization of the N1 arylation reaction.



Entry	Cat.[a]	Ligand (20%)	Time (h)	**2/23**	Yield (%)
1	CuI (3%)	---	24	1/0	
2	CuI (3%)	**L_1**	24	0.5/0.4	
3	CuI (3%)	**L_1**	24	0.8/0.3	
4	CuI (3%)	**L_2**	30	1/1	
5	CuI (3%)	**L_3**	30	1/0	
6	CuI (3%)	**L_4**	30	0.6/0.2	
7	CuI (3%)	**L_5**	24	1/0.3	
8	CuI (3%)	XPhos	48	1/0.6	
9	$Fe(acac)_2$ (30%) CuO(10%)[11]	---	30	1/0	
10	$FeCl_2.4H_2O$ (30%)[11]	---	48	1/0	
11	Cu_2O (20%)	**L_1**/PEG	20	1/0.9	
12	Cu_2O (20%)	---	18	1/0	
13	**Cu_2O (20%)**	**L_6/PEG**	**48**	**0.6/1**	**51**

[a] Realized in DMF at 130°C.

Although complete conversions could not be reached, best ratio **2**/**23** of 0.6/1 was observed using pyridylmethylamine[12] **L5**/Cu_2O/PEG-400 in the presence of Cs_2CO_3 (entry 14). Control experiment showed that both L6 and PEG-400 were required (entry 13). From the 0.6/1 ratio observed in the crude material, the expected triazole **23** arising from a selective N-arylation process could be isolated in 51% yield.

Selective N1 arylation sequence was successfully realized with *o*-bromoiodobenzene affording triazole **25** in 57% yield. Further, the procedure was extended to triazole **3** from which targets **24** and **26** bearing a phenyl and a CF_3 substituted phenyl fragment have been isolated in 44 and 43% yield respectively. Finally, N1-arylation was also successful when applied to triazole **19**.

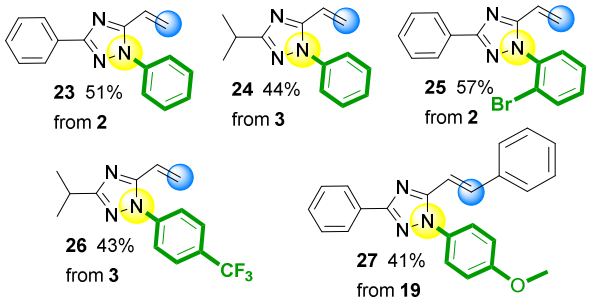


Figure 5. Selective Cu-catalyzed N-arylation of triazoles.

3. Conclusion

We succeeded in the preparation of 1,3,5-trisubstituted 1,2,4-triazoles. Selective orthogonal Pd- and Cu-catalyzed sequences are described allowing the installation of aryl groups at the vinyl substituent or at the N1-site of triazole precursors. Precisely, various (het)aryl units have been exclusively incorporated at the triazole core using ligand free Pd-catalyzed process. Double arylations starting from *ortho*, *meta* and *para* bisiodobenzenes led to extended bistriazolyl derivatives. The N1 arylation was realized using orthogonal Cu-catalysis. Combination of pyridylmethylamine as the ligand and Cu_2O led to N1-arylated triazoles keeping intact the vinyl moiety. The strategy is general and spread the molecular diversity at the triazole core.

4. Experimental section

General information

Unless otherwise specified, reagents were obtained from commercial sources and used without further purification. Solvents were obtained from Fisher Scientific and dried by standard methods. Reactions were monitored by thin-layer chromatography (TLC) using ALUGRAM®Xtra SIL GUR Silica Gel 60 F254 plates and visualized using UV light (254 nm). Melting points were determined on a Kofler hotstaged apparatus and were uncorrected. NMR spectra were recorded in CDCl3 as the solvent with TMS as the internal standard on a Bruker-300 spectrometer. Chemical shifts are reported in ppm (δ) downfield relative to TMS. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet), coupling constants (Hz), integration. High resolution mass spectra (HRMS) were performed on a BrukermaXis Q-TOF spectrometer by electron spray ionization (ESI) operating in positive mode. Triazoles **1-3** were prepared according to literature.[8]

General procedure for the Pd-catalyzed arylation of 5-vinyl triazole (4-13)

A 10 mL 2 dram screwed tube equipped with a magnetic stirring bar was charged with 5-vinyl-1,2,4-triazole (0.17 mmol, 1.0 equiv), an organic halide (0.17 mmol, 1.0 equiv), and K_3PO_4 (108 mg, 0.32 mmol, 2.0 equiv); then $Pd(OAc)_2$ (1.7 mg, 0.008 mmol) were added, followed by DMF (1.0 mL), which was added to the mixture via syringe at r.t. under argon. The tube was sealed and put into a preheated oil bath at 110 °C for 4 h. The

mixture was cooled to r.t quenched with H_2O (20 mL). The layers were separated and the aqueous layer was extracted with Diethyl Ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was then purified by preparative TLC (silica gel, EtOAc–PE, 3/7).

(*E*)-1,3-diphenyl-5-styryl-1H-1,2,4-triazole (4): Yellow powder (78%), m.p. 132 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 – 8.07 (m, 2H), 7.82 (d, *J* = 16.0 Hz, 1H), 7.52 – 7.17 (m, 13H), 6.82 (d, *J* = 16.0 Hz, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 153.4, 137.9, 137.3, 135.6, 130.8, 129.6, 129.4, 129.3, 129.1, 128.8, 128.6, 127.4, 126.7, 125.5, 111.9. HRMS (ESI): m/z calcd for $C_{22}H_{18}N_3$ $[M+H]^+$: 324.1501, found : 324.1510.

(*E*)-5-(2-methylstyryl)-1,3-diphenyl-1H-1,2,4-triazole (5): Brown powder (72%), m.p. 152 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 – 8.08 (m, 2H), 8.04 (d, *J* = 15.8 Hz, 1H), 7.59 – 7.23 (m, 9H), 7.29 – 7.01 (m, 3H), 6.75 (d, *J* = 15.8 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162, 153.5, 137.1, 135.7, 134.7, 130.8, 130.7, 129.6, 129.4, 129.1, 129.0, 128.6, 126.6, 126.2, 125.7, 125.5, 113.2, 20.0. HRMS (ESI): m/z calcd for $C_{23}H_{20}N_3$ $[M+H]^+$: 338.1657, found: 338.1665.

(*E*)-5-(3-methylstyryl)-1,3-diphenyl-1H-1,2,4-triazole (6): Brown powder (38%), m.p. 117 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.92 (d, *J* = 16.0 Hz, 1H), 7.65 – 7.25 (m, 11H), 7.20 (d, *J* = 7.3 Hz, 1H), 6.95 (d, *J* = 16.0 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 153.4, 138.5, 138.1, 137.3, 135.5, 130.8, 130.1, 129.6, 129.4, 129.0, 128.7, 128.6, 128.0, 126.6, 125.5, 124.6, 111.7, 21.4. HRMS (ESI): calcd for $C_{23}H_{20}N_3$ $[M+H]^+$: 338.1657, found: 338.1648.

(*E*)-5-(2,6-dimethylstyryl)-1,3-diphenyl-1H-1,2,4-triazole (7): Brown powder (30%), m.p. 126 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.6 Hz, 2H), 8.02 (d, *J* = 16.3 Hz, 1H), 7.59 – 7.45 (m, 8H), 7.19 – 7.10 (m, 3H), 6.58 (d, *J* = 16.3 Hz, 1H), 2.42 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 153.2, 137.2, 136.5, 136.4, 135.3, 130.8, 129.5, 129.4, 129.1, 128.6, 128.2, 127.8, 126.7, 125.4, 117.9, 21.2. HRMS (ESI): calcd for $C_{24}H_{22}N_3$ $[M+H]^+$: 352.1814, found : 352.1812.

(*E*)-5-(2-methoxystyryl)-1,3-diphenyl-1H-1,2,4-triazole (8): Yellow powder (60%), m.p. 120 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 7.8, 1.8 Hz, 2H), 8.18 (d, *J* = 16.1 Hz, 1H), 7.67 – 7.22 (m, 10H), 7.12 (d, *J* = 16.1 Hz, 1H), 7.02 – 6.82 (m, 2H), 3.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 158.0, 154.0, 137.5, 133.6, 131.0, 130.3, 129.4, 129.4, 128.9, 128.6, 126.7, 125.4, 125.4, 124.6, 120.7, 113.0, 111.1, 55.4. HRMS: (ESI : calcd for $C_{23}H_{20}N_3O$ $[M+H]^+$: 354.1616, found : 354.1606.

(*E*)-5-(4-methoxystyryl)-1,3-diphenyl-1H-1,2,4-triazole (9): White powder (41%), m.p. 149 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.91 (d, *J* = 15.9 Hz, 1H), 7.69 – 7.41 (m, 10H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 15.9 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 160.6, 153.7, 137.5, 137.4, 130.9, 129.5, 129.0, 128.9, 128.6, 126.6, 125.5, 114.3, 109.6, 55.3. HRMS (ESI): m/z calcd for $C_{23}H_{20}N_3O$ $[M+H]^+$: 354.1616, found : 354.1601.

(*E*)-5-(2-(naphthalen-2-yl)vinyl)-1,3-diphenyl-1H-1,2,4-triazole (10): Yellow powder (60%), m.p. 203 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 8.0, 1.4 Hz, 2H), 8.13 (d, *J* = 15.9 Hz, 1H), 8.03 – 7.78 (m, 4H), 7.74 – 7.45 (m, 11H), 7.08 (d, *J* = 15.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 153.4, 138.0, 137.3, 133.7, 133.4, 133.1, 130.8, 129.6, 129.4, 129.1, 128.7, 128.6, 128.5, 128.4, 127.7, 126.8, 126.6, 125.5, 123.3, 112.0. HRMS (ESI): m/z calcd for $C_{26}H_{20}N_3$ $[M+H]^+$: 374.1657, found : 374.1656.

(*E*)-1,3-diphenyl-5-(2-(thiophen-2-yl)vinyl)-1H-1,2,4-triazole (11): Yellow oil (35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 7.9, 1.6 Hz, 2H), 8.06 (d, *J* = 15.7 Hz, 1H), 7.72 – 7.21 (m, 10H), 7.17 – 6.98 (m, 1H), 6.75 (d, *J* = 15.7 Hz, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 140.8, 137.2, 129.6, 129.4, 129.2, 129.0, 128.6, 128.0, 126.8, 126.6, 125.4, 110.9. HRMS (ESI): m/z calcd for $C_{20}H_{16}N_3S$ $[M+H]^+$: 330.1065, found : 330.1074.

1,4-bis((*E*)-2-(1,3-diphenyl-1H-1,2,4-triazol-5-yl)vinyl)benzene (12): Yellow powder (24%), m.p. 194 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.23 (ddd, *J* = 7.6, 5.9, 2.0 Hz, 4H), 8.03 – 7.79 (m, 2H), 7.70 – 7.37 (m, 20H), 6.97 (t, *J* = 10.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 160.0, 153.0, 136.0, 135.3, 129.6, 129,5, 129.2, 129.1, 128.8, 128.6, 128.0, 126.7, 125.5. HRMS (ESI): m/z calcd for $C_{38}H_{29}N_6$ $[M+H]^+$: 569.2454, found : 569.2463.

1,2-bis((*E*)-2-(1,3-diphenyl-1H-1,2,4-triazol-5-yl)vinyl)benzene (13): Yellow powder (21%), m.p. 195 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (t, *J* = 10.5 Hz, 4H), 7.57 – 7.47 (m, 2H), 7.48 – 7.22 (m, 10H), 6.74 (d, *J* = 15.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 159.7, 153.0, 144.6, 137.1, 136.2, 129.7, 129.6, 129.2, 128.6, 127.9, 126.7, 125.4, 112.4. HRMS (ESI): m/z calcd for $C_{38}H_{29}N_6$ $[M+H]^+$: 569.2454, found: 569.2463.

1,3-bis((*E*)-2-(1,3-diphenyl-1H-1,2,4-triazol-5-yl)vinyl)benzene (14): Yellow powder (18%), m.p. 202 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.9 Hz, 4H), 7.86 (t, *J* = 14.7 Hz, 2H), 7.61 – 7.26 (m, 20H), 6.87 (d, *J* = 15.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 137.2, 137.1, 136.2, 129.7, 129.6, 129.3, 129.2, 128.6, 127.9, 127.8, 126.7, 126.7, 125.4. HRMS (ESI): m/z calcd for $C_{38}H_{29}N_6$ $[M+H]^+$: 569.2454, found: 569.2465.

General procedure for the Pd-catalyzed arylation of 5-vinyl triazole (15-18)

A 10 mL 2 dram screwed tube equipped with a magnetic stirring bar was charged with 5-vinyl-1,2,4-triazole (0.17 mmol, 1.0 equiv), an organic halide (0.17 mmol, 1.0 equiv), and NaOAc (26.24 mg, 0.32 mmol, 2.0 equiv); TBAI (0.017 mmol, 6.27 mg); then $Pd(OAc)_2$ (1.7 mg, 0.008 mmol) were added, followed by DMF (1.0 mL), which was added to the mixture via syringe at r.t. under argon. The tube was sealed and put into a preheated oil bath at 110 °C for 22 h. The mixture was cooled to r.t quenched with H_2O (20 mL). The layers were separated and the aqueous layer was extracted with Diethyl Ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was then purified by preparative TLC (silica gel, EtOAc–PE, 3/7).

(*E*)-5-(4-nitrostyryl)-1,3-diphenyl-1H-1,2,4-triazole (15): Yellow powder (48%), m.p. 182 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 – 8.23 (m, 4H), 8.00 (d, *J* = 16.0 Hz, 1H), 7.73 – 7.44 (m, 10H), 7.09 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 152.3, 141.8, 136.9, 135, 130.4, 129.7, 129.6, 129.4, 128.6, 127.8, 126.5, 125.4, 124.1, 115.9. HRMS (ESI): m/z calcd for $C_{22}H_{17}N_4O_2$ $[M+H]^+$: 369.1352, found: 369.1360.

(*E*)-4-(2-(1,3-diphenyl-1H-1,2,4-triazol-5-yl)vinyl)pyridine (16): Yellow powder (11%), m.p. 211 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J* = 5.9 Hz, 2H), 8.21 – 8.13 (m, 2H), 7.77 (d, *J* = 16.0 Hz, 1H), 7.59 – 7.35 (m, 8H), 7.29 (d, *J* = 5.9 Hz, 2H), 7.02 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 152.3, 150.4, 134.9, 130.5, 129.7, 129.6, 129.4, 128.6, 126.6,

125.4, 121.3, 116.1. HRMS (ESI): m/z calcd for $C_{21}H_{17}N_4$ [M+H]$^+$: 325.1453, found: 325.1459.

(*E*)-4-(2-(1,3-diphenyl-1H-1,2,4-triazol-5-yl)vinyl)benzonitrile (17): Yellow powder (20%), m.p. 174 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 – 8.25 (m, 2H), 7.95 (d, *J* = 16.0 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.67 (dt, *J* = 8.4, 6.6 Hz, 9H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.04 (d, *J* = 15.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 139.9, 137.0, 135.5, 132.9, 132.6, 129.7, 129.6, 129.4, 128.6, 127.9, 127.7, 126.6, 125.4, 118.7, 115.2. HRMS (ESI): calcd for $C_{23}H_{17}N_4$: 349.1453, found: 349.1451.

(*E*)-1,3-diphenyl-5-(4-(trifluoromethyl)styryl)-1H-1,2,4-triazole (18): Yellow powder (38%), m.p. 146 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.3 Hz, 2H), 7.93 (d, *J* = 16.0 Hz, 1H), 7.64 – 7.28 (m, 12H), 6.98 (d, *J* = 16.0 Hz, 1H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 152.7, 138.9, 137.1, 136.0, 130.9, 130.5, 129.7, 129.6, 129.5, 129.2, 128.6, 127.4, 126.6, 125.8, 125.7, 125.4, 122.1, 114.3. HRMS (ESI): m/z calcd for $C_{23}H_{17}N_3F_3$ [M+H]$^+$: 392.1375, found: 392.1384.

General procedure for the Pd-catalyzed arylation of 5-vinyl triazole (19-22)

A 10 mL 2 dram screwed tube equipped with a magnetic stirring bar was charged with 5-vinyl-1,2,4-triazole (0.17 mmol, 1.0 equiv), o-dihaloarene (0.17 mmol, 1.0 equiv), and K_2CO_3 (70 mg, 0.51 mmol, 3.0 equiv); then $Pd(OAc)_2$ (3.8 mg, 0.017 mmol) and XPhos (16mg, 0.034 mmol) were added, followed by DMF (1.0 mL), which was added to the mixture via syringe at r.t. under argon. The tube was sealed and put into a preheated oil bath at 160 °C for 24 h. The mixture was cooled to r.t., quenched with H_2O (20 mL). The layers were separated and the aqueous layer was extracted with Diethyl Ether (3 × 20 mL). The combined organic extracts were dried (MgSO4), filtered, and concentrated in vacuo. The crude product was then purified by preparatory TLC (silica gel, Ether–PE, 7/3).

3-Phenyl-5-styryl-1H-1,2,4-triazole (19): White solid (51%), m.p. 110 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (m, *J* = 6.6, 2H), 7.61 (d, *J* = 16.3 Hz, 1H), 7.48 – 7.06 (m, 9H), 7.04 (d, *J* = 16.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160, 158.1, 135.8, 135.6, 129.9, 128.9, 128.8, 128.7, 128.7, 128.4, 128.3, 127.1, 126.5, 114.4. HRMS (ESI): m/z calcd for $C_{16}H_{14}N_3$ [M+H]$^+$: 248.1188, found: 248.1185.

(*E*)-5-(2-methylstyryl)-3-phenyl-1H-1,2,4-triazole (20): White solid (56%), m.p. 118 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (m, 2H), 7.93 (d, *J* = 16.2 Hz, 1H), 7.50 (m,1H), 7.42 (m, 3H), 7.18 (m, 4H), 6.95 (d, *J* = 16.2 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 136.7, 134.5, 133.6, 130.6, 129.9, 129.0, 128.8, 128.7, 126.5, 126.2, 125.5, 115.4, 19.8. HRMS (ESI): m/z calcd for $C_{17}H_{16}N_3$ [M+H]$^+$: 262.1344, found: 262.1345.

(*E*)-3-isopropyl-5-styryl-1H-1,2,4-triazole (21): Yellow oil (48%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 16.3 Hz, 1H), 7.53 (d, *J* = 7 Hz, 2H), 7.37 – 7.26 (m, 3H), 7.05 (d, *J* = 16.3 Hz, 1H), 3.22 – 3.13 (m, 1H), 1.40 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 134.6, 128.7, 128.5, 128.3, 126.9, 126.8, 116.3, 27.3, 21.3. HRMS (ESI): m/z calcd for $C_{13}H_{16}N_3$ [M+H]$^+$: 214.1344, found: 214.1346.

(*E*)-3-isopropyl-5-(2-methylstyryl)-1H-1,2,4-triazole (22): Yellow oil (58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 16.2 Hz, 1H), 7.55 (m, 1H), 7.19 (m, 3H), 6.95 (d, *J* = 16.2 Hz, 1H), 3.17 (m, 1H), 2.39 (s, 3H), 1.39 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 135.1, 132.3, 130.5, 128.4, 126.1, 125.5, 117.3, 27.3, 21.3, 19.8. HRMS (ESI): m/z calcd for $C_{14}H_{18}N_3$ [M+H]$^+$: 228.1501, found: 228.1496.

General procedure for the Cu-catalyzed arylation of 5-vinyl triazole (23-27)

A 10 mL dram screwed tube equipped with a magnetic stirring bar was charged with 5-vinyl-1,2,4- triazole (0.17 mmol, 1.0 equiv), the aryl halide (0.17 mmol, 1.0 equiv), and Cs_2CO_3 (110 mg, 0.32 mmol, 2.0 equiv) followed by Cu_2O (4.8 mg, 0.034 mmol), 1,10-phenantroline (6,1 mg, 0.32 mmol) and DMF (1.0 mL). The tube was sealed and put into a preheated oil bath at 110 °C for 4 h under argon. The mixture was cooled to rt and quenched with H_2O (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3×20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was then purified by preparative TLC (silica gel, EtOAc–PE, 3/7).

1,3-diphenyl-5-vinyl-1H-1,2,4-triazole (23): Yellow powder (51%), m.p. 82 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (dt, *J* = 8.4, 2.2 Hz, 2H), 7.54 – 7.41 (m, 8H), 6.68 – 6.49 (m, 2H), 5.67 (dd, *J* = 10.3, 2.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 152.8, 137.0, 130.6, 129.4, 129.3, 129.0, 128.4, 126.5, 125.3, 123.6, 121.6. HRMS (ESI): m/z calcd for $C_{16}H_{14}N_3$ [M+H]$^+$: 248.1188, found: 248.1187.

3-isopropyl-1-phenyl-5-vinyl-1H-1,2,4-triazole (24): Yellow powder (44%), m.p 97°C . ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.37 (m, 5H), 6.78 (dd, *J* = 17.6, 11.0 Hz, 1H), 6.34 (d, *J* = 17.6 Hz, 1H), 5.55 (dd, *J* = 27.4, 11.0 Hz, 1H), 3.12 – 3.07 (m, 1H), 1.35 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 151.9, 137.0, 129.2, 128.6, 125.1, 122.9, 121.7, 28.2, 21.5. HRMS (ESI): m/z calcd for $C_{13}H_{16}N_3$ [M+H]$^+$: 214.1344, found : 214.1355.

1-(2-bromophenyl)-3-phenyl-5-vinyl-1H-1,2,4-triazole (25): Yellow powder, m.p 134°C yield: 47%. ^{1}H NMR (300 MHz, CDCl3) δ 8.38 – 8.15 (m, 2H), 7.66 (dd,*J* = 7.9, 1.4 Hz, 2H), 7.56 – 7.16 (m, 5H), 6.98 (dd, *J* = 19.6, 8.0 Hz, 2H), 6.76 (t, *J* = 7.6 Hz, 1H). 13C NMR (75 MHz, $CDCl_3$) δ 162.4, 155.8, 142.5, 130.6, 130.5, 130.1, 129.5, 128.8, 128.6, 128.5, 127.8, 127.6, 126.6, 125.0, 124.5, 118.6, 117.1. HRMS (ESI): m/z calculated for $C_{16}H_{13}N_3Br$ [M+H]+: 326.0293, found: 326.0298.

3-isopropyl-1-(4-(trifluoromethyl)phenyl)-5-vinyl-1H-1,2,4-triazole (26): Yellow powder (43%), m.p 88 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.3, 4.1 Hz, 2H), 7.63 (t, *J* = 8.6 Hz, 2H), 6.83 – 6.30 (m, 2H), 5.66 (ddd, *J* = 38.7, 10.8, 1.4 Hz, 1H), 3.17 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.39 (d, *J* = 7 Hz, 3H), 1.34 (d, *J* = 7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 161.7, 161.1, 152.5, 126.7, 126.6, 126.6, 126.3, 125.5, 125.2, 124.3, 121.3, 120 .3, 25.9, 21.6, 21.5. ^{9}F NMR (282 MHz, $CDCl_3$) δ -62.60, -62.62. HRMS (ESI): m/z calcd for $C_{14}H_{15}F_3N_3$ [M+H]$^+$: 282.1218, found: 282.1215.

(*E*)-1-(4-methoxyphenyl)-3-phenyl-5-styryl-1H-1,2,4-triazole (27): Brown powder (41%) m.p. 159 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (m, 2H), 7.92 (d, *J* = 16.0 Hz, 1H), 7.53 – 7.32 (m, 10H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 16.0 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 160.0, 153.3, 137.8, 135.5, 130.6, 130.0, 129.4, 129.2, 128.8, 128.5, 127.3, 126.9, 126.6, 114.6, 111.6, 55.6. HRMS (ESI): m/z calcd for $C_{23}H_{20}N_3O$ [M+H]$^+$: 354.1606, found : 354.1601.

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Highlights

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- Orthogonal arylations sequences lead to diversely substituted 1,2,4-triazoles
- Selective C-arylation is realized using ligand free Pd-catalytic system
- Cu/pyridylmethylamine catalytic system allow selective N-arylation of triazoles
- Extended bistriazolyl derivatives arise from double arylation process

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: