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Palladium-Catalyzed Olefination and Arylation of 2-Substituted 1,2,3-Triazole *N*-Oxides

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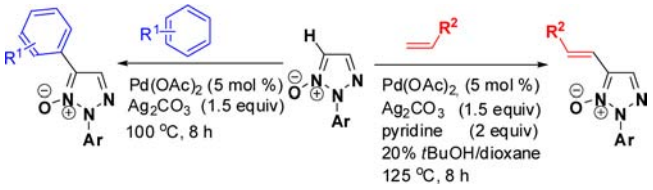
ABSTRACT



Two highly efficient protocols for the regioselective synthesis of 2-substituted 4-alkenyl- and 4-aryl-1,2,3-triazoles by the palladium-catalyzed C−H functionalization of 1,2,3-triazole *N*-oxides are reported. A possible pathway of direct alkenylation with 1-octene and vinyl acetate is discussed.

Transition-metal-catalyzed C−H bond activation for C−C bond formation is attracting considerable attention as a valuable tool in organic synthesis.[1] The Pd-catalyzed activation of the C−H bonds of arenes or alkanes has been widely explored.[2] Recently, the C−H bond activation of pyridine *N*-oxides has been found to serve as a typical platform for the 2-functionalization of the pyridine species.[3] Additionally, Fagnou et al.[4] found that higher reactivity was observed for *N*-oxides of electron-deficient six-membered heterocycles and for *N*-oxides derived from electron-rich five-membered heteroarenes.

Given the unique chemical and structural properties of 1,2,3-triazoles, they have been extensively investigated and applied in material science and medicinal chemistry (Figure 1).[5] Recently described methods for the direct catalytic functionalization of triazole and its derivatives have also been proven attractive but are mainly limited to the N-1 position.[6] To our knowledge, a few methods have been reported for the direct functionalization of

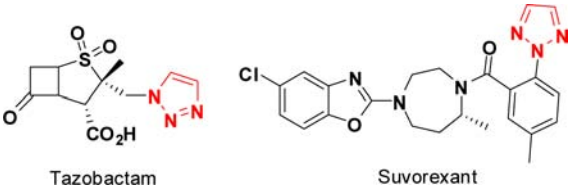


Figure 1. Present medicines containing 1,2,3-triazole.

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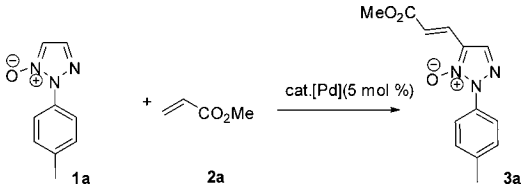
2-substituted 1,2,3-triazole.[7] Based on the key contributions of Fagnou,[3a−c,4a] we propose the 4-functionalization of 2-substituted 1,2,3-triazole species using the highly regioselective C−H bond activation approach and 2-substituted 1,2,3-triazole *N*-oxides. In this paper, we report two new protocols for C−C formation at the 5-position of 2-substituted 1,2,3-triazole *N*-oxides, namely, site-selective alkenylation and direct cross-coupling with inactivated arenes.

Based on the Fujiwara−Moritani approach,[8] we first optimized the reaction conditions using 2-substituted 1,2,3-triazole *N*-oxide (**1a**) and methyl acrylate (Table 1). The nature of oxidants, additives, and solvent play critical roles in the reaction efficiency. No reaction occurred in dioxane when no additive was used (entry 1). Pyridine produced a higher yield than K_2CO_3, Et_3N, and DBU (entries 2−5). Among the oxidants screened (entries 5−7), Ag_2CO_3 was selected as the most effective one. Furthermore, the addition of *t*-BuOH with dioxane significantly improved the **3a** yield (entries 8−12). Finally, the reaction very efficiently proceeded when 5 mol % of $Pd(OAc)_2$ was used in combination with Ag_2CO_3 (1.5 equiv.) and pyridine (2.0 equiv) (entry 9). This method is highly site selective at the 5-position, and no regioisomeric products of **3a** were observed. Additionally, the reaction proceeded with complete stereoselectivity and generated (*E*)-**3a** exclusively. The chemoselectivity was also remarkably high because double alkenylation did not occur at all.

We then tested the protocol for the Pd-catalyzed alkenylation of **3a** on the alkenylation of other 2-substituted-1,2,3-triazole *N*-oxides and alkenes (Table 2). Diverse decorated products **3b**−**j** formed in high yields, and regioisomeric products were not observed.

Interestingly, high yields of 1-octene and vinyl acetate were also obtained under the same reaction conditions, as shown in Table 3. However, the isomer distribution of the products considerably differed from those of the alkenes in Table 2. 1-Octene produced three isomers **3ka**, **3kb**, and **3kc**; vinyl acetate produced a mixture of **3la** and **3lb** (Table 3).

Table 1. Optimization of Typical Reaction Conditions[a]



entry	oxidant (1.5 equiv)	additive (2 equiv)	solvent (v/v)	yield of **3a**[c] (%)
1	Ag_2CO_3	none	dioxane	trace
2	Ag_2CO_3	K_2CO_3	dioxane	45
3	Ag_2CO_3	EtN_3	dioxane	5
4	Ag_2CO_3	DBU	dioxane	12
5	Ag_2CO_3	pyridine	dioxane	68
6	Ag_2O	pyridine	dioxane	43
7	AgAcO	pyridine	dioxane	37
8	Ag_2CO_3	pyridine	10% *t*-BuOH/dioxane	76
9	Ag_2CO_3	pyridine	20% *t*-BuOH/dioxane	**92**
10	Ag_2CO_3	pyridine	30% *t*-BuOH/dioxane	81
11	Ag_2CO_3	pyridine	*t*-BuOH	55
12[b]	Ag_2CO_3	pyridine	*t*-BuOH	trace

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (1.2 mmol), $Pd(OAc)_2$ (5 mol %), 125 °C, and 8 h (unless otherwise noted). [b] Reaction at 100 °C for 8 h, after which the rest of the catalyst (0.12 mmol, 20 mol %) and Ag_2CO_3 (2 equiv) were added and the reaction proceeded for another 24 h. [c] Yield of isolated product.

The Pd-catalyzed direct cross-coupling reactions between 1-octene and vinyl acetate as coupling partners have been reported.[9] However, the direct alkenylation of triazole derivatives is rarely reported. We propose that the Pd-catalyzed vinylation proceeds through a pathway different from the typical mechanism of the Heck reaction. In path A, the resulting Pd−C bond of **A** adds to the carbon−carbon double bond of 1-octene to form the Pd complexes **B** and **C**. The β-H elimination of **B** to reverse carbon occurred, resulting in the formation of **3ka** and **3kb**. For complex **C**, **3kc** was obtained because β-H elimination only occurred at one carbon.[9c] In path B, complexes **E** and **F** formed similar to 1-octene. The β-H elimination of **E** and β-OAc elimination of **F** resulted in the formation of **3la** and **3 lb**, respectively (Scheme 1).[9d]

Surprisely, we found that 2-substituted 5-aryl-1,2,3-triazole *N*-oxide was produced as a side product **3m** in addition to the desired alkenylated compound (**3a**) when the alkenylation reaction was carried out in benzene. Based on the various conditions screened using **1a** and benzene, the optimal conditions for the arylation of *N*-oxides were as follows: benzene (40 equiv), $Pd(OAc)_2$ (5 mol %), Ag_2CO_3 (1.5 equiv), and 100 °C. Using the optimized protocol, **3m**−**r** formed in high yields. This system was also applied to other arenes such as *p*-xylene, *m*-xylene, and

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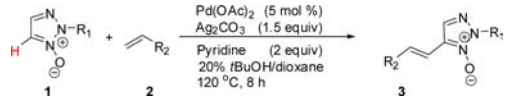
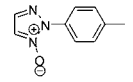
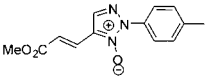
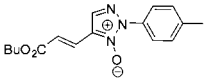
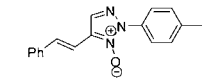
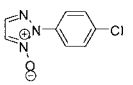
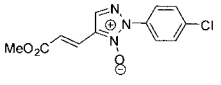
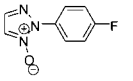
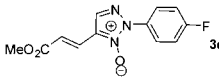
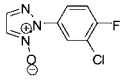
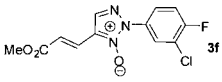
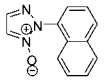
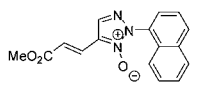
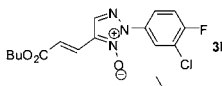
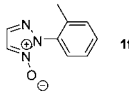
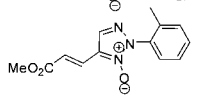
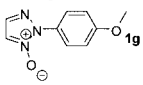
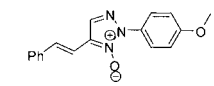
Table 2. Reactions of 2-Substituted 1,2,3-Triazole *N*-Oxides and Alkenes[a]



1 2 3

entry	*N*-oxides **1**	**2**	product **3**	yield of **3** (%)[b]
1	 **1a**	 **2a**		**3a** 92
2	**1a**	 **2b**		**3b** 81
3	**1a**	 **2c**		**3c** 82
4	 **1b**	**2a**		**3d** 89
5	 **1c**	**2a**		**3e** 81
6	 **1d**	**2a**		**3f** 91
7	 **1e**	**2a**		**3g** 88
8	**1d**	**2b**		**3h** 90
9	 **1f**	**2a**		**3i** 83
10	 **1g**	**2c**		**3j** 89

[a] Reaction conditions: **1** (0.3 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (0.015 mmol, 5 mol %), Ag_2CO_3 (1.5 equiv), pyridine (2 equiv), 125 °C, and 8 h. [b] Isolated yield.

1,2-dichlorobenzene, and **3p**–**r** were obtained in moderate yields (Table 4). However, isomers were obtained which are difficult to separate when toluene and iodobenzene was applied to this catalytic system.

The resultant alkenylated and arylated *N*-oxides (e.g., **3e** and **3m**) were readily deoxygenated and produced 2-substituted 4-alkenyl and 4-aryl-1,2,3-triazoles using typical methods in high yields (Scheme 2).[10] To the best of our knowledge, a few methods for the synthesis of 2-substituted 4-alkenyl-1,2,3-triazoles have been reported. Although a few reports have described the synthesis of 2-substituted 4-phenyl-1,2,3-triazoles,[11,7d] Pd-catalyzed direct arylation method still remains a challenge. As shown

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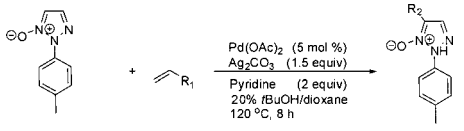
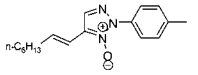
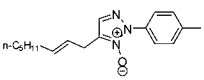
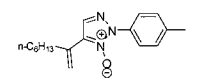
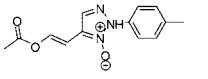
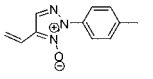
Table 3. Reactions of **3a** with 1-Octene and Vinyl Acetate[a]

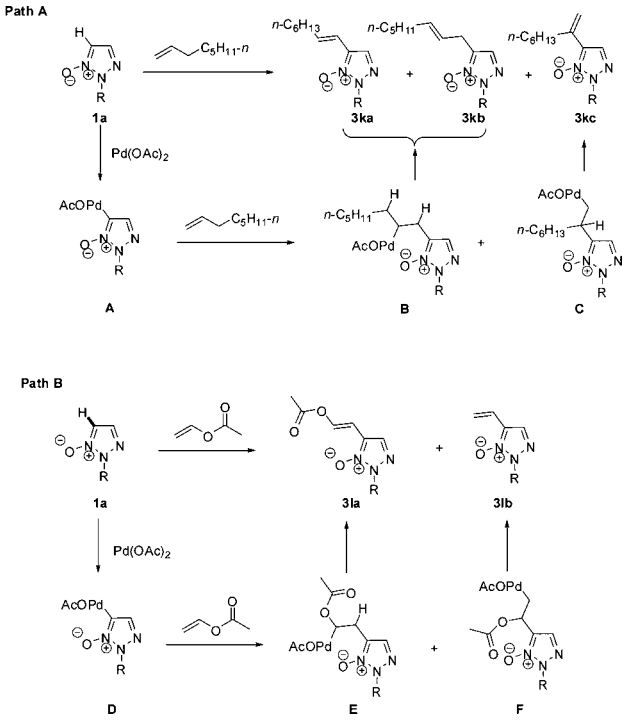


1a 2 3

entry	*N*-oxides **1**	**2**	product **3**	yield of **3** (%)[b]
1	**1a**	**2d**		**3ka** 38
				**3kb** 27
				**3kc** 31
2	**1a**	 **2e**		**3la** 36
				**3lb** 55

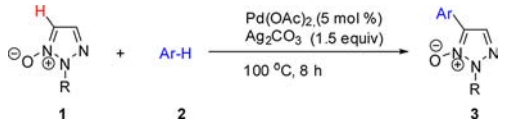
[a] Reaction conditions: **1a** (0.3 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (0.015 mmol, 5 mol %), Ag_2CO_3 (1.5 equiv), pyridine (2 equiv), 125 °C, and 8 h. [b] Isolated yield.

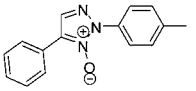
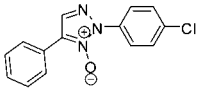
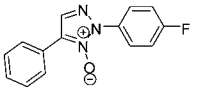
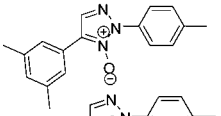
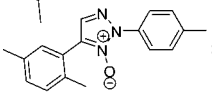
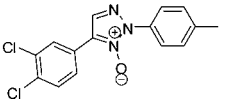
Scheme 1. Possible Reaction Pathways for the Reaction of **1a** with 1-Octene and Vinyl Acetate



in Scheme 3, no reaction occurred at the C4 or C5 sites under the same conditions when we explored if **1a** was deoxygenated. Obviously, our approach was an efficient

Table 4. Reactions of 2-Substituted-1,2,3-Triazole *N*-Oxides and Arenes[a]



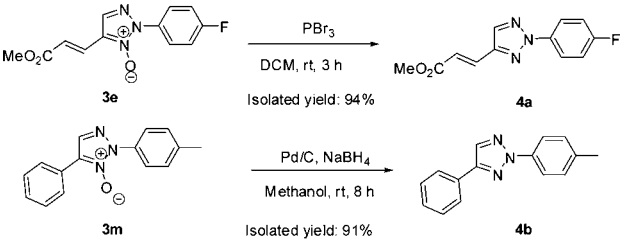
entry	*N*-oxides **1**	Ar-H **2**	product **3**	yield of **3** (%)[b]
1	**1a**		 **3m**	91
2	**1b**		 **3n**	85
3	**1c**		 **3o**	82
4	**1a**		 **3p**	62
5	**1a**		 **3q**	52
6	**1a**		 **3r**	57

[a] Reaction conditions: **1** (0.3 mmol), **2** (40 equiv), $Pd(OAc)_2$ (0.015 mmol, 5 mol %), Ag_2CO_3 (1.5 equiv), 100 °C, and 8 h (unless otherwise noted). [b] Yield of isolated product.

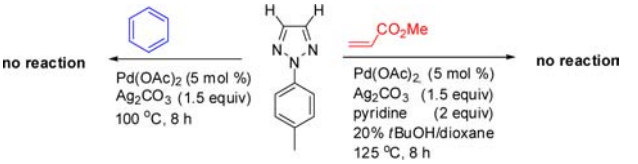
alternative to the 4-functionalization of 2-substituted 1,2,3-triazoles.

In summary, we report for the first time two novel protocols of the 4-C-alkylation and arylation of 2-substituted 1,2,3-triazoles by the Pd-catalyzed oxidative C−C bond formation of 2-substituted 1,2,3-triazole *N*-oxides with high regioselectivity. The reaction preferably occurred at C5 because of the activity of 2-substituted 1,2,3-triazole *N*-oxides at this site. This reactivity may have a wide

Scheme 2. Deoxygenation for 2-Substituted 1,2,3-Triazole *N*-Oxides



Scheme 3. Inert 4 and 5 Sites of 2-Substituted 1,2,3-Triazole



impact on direct functionalization and on the increasing number of metal-catalyzed heterocycle transformations that can utilize the *N*-oxide activation strategy in the rapid functionalization of these substrates.

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Supporting Information Available. Typical experimental procedures, characterization data, and ^1H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.