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Palladium-catalyzed *ortho*-C-H Alkenylation of 2-benzyl-1,2,3-triazoles

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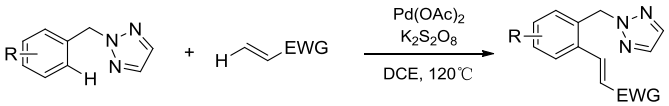
A mild and efficient method for the direct alkenylation of 2-benzyl-1, 2, 3-triazoles via Pd-catalyzed C–H bond activation was developed. This protocol was compatible with various substrates and gave the corresponding products in good to excellent yields. Thus, the present work provides a novel and valuable method for the synthesis of 2-benzyl-1, 2, 3-triazole derivatives.

Since Fujiwara and Moritani reported the pioneering work on Palladium-catalyzed oxidative coupling between arenes and olefins in 1967, [1] C-H alkenylation has emerged as a powerful tool for the synthesis of natural product and pharmaceutical precursors.[2] However, low selectivity has restricted the practicality of this transformation. In order to achieve regioselective C-H bond functionalization, a large number of directing groups have been reported. For instance, in 2011, the Yu group reported Pd-catalyzed olefination of aromatic C-H bond using urea as a directing group.[3a] In 2012, Zhang et al. reported Pd-catalyzed C-H alkenylation using thioether as directing groups.[3b] Later, the Shi group described a Pd-catalyzed oxidative olefination of phenol derivatives.[3c] More recently, Pd-catalyzed *ortho*-C-H alkenylation of phenylalanine derivatives has been developed by Carretero group.[3d] Despite these significant progress achieved, those employing 1,2,3-triazoles as directing groups remain underdeveloped.[4]

1,2,3-triazoles have widespread applications in diverse fields such as material chemistry and medicinal chemistry.[5] Over the last decades, a large volume of research has been carried out on 1,2,3-triazoles and their derivatives, which are present as core structural components in an array of drug categories such as anticancer,[6a] antibacterials[6b] and HIV Protease Inhibitors.[6c] The great medicinal significance and broad applications of 1,2,3-triazoles prompted us to develop new strategies to the access of various derivatives containing this moiety. Recently, the Ackermann group reported a Ru-catalyzed C–H cross-dehydrogenative alkenylation using 1,2,3-triazole derivatives as versatile directing groups.[7] However, the substrates have only been limited to 1-substituted-1,2,3-triazoles. So far, no example of the alkenylation of 2-substituted-1,2,3-triazoles has been reported. Considering the important application of 2-substituted-1, 2, 3-triazoles as pharmacophore and motivated by our continuous interest in the C-H activation,[8] herein we developed a novel method to alkenylation of 2-benzyl-1,2,3-triazoles. (Scheme 1).



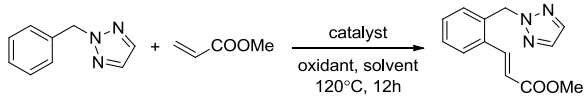
Scheme 1. C-H alkenylation of 2-benzyl-1,2,3-triazoles **1**

We initiated our studies by exploring reactions between 2-benzyl-1,2,3-triazole (**1a**) and alkene (**2a**) to identify suitable reaction conditions (Table 1). First, the reaction was conducted with $Pd(OAc)_2$ as a catalyst, BQ as oxidant in DCE at 120 ℃ for 12h. To our delight, the desired product **3a** was generated in 21% yield. To increase the yield of this reaction, some other generally used oxidants, such as AgOAc, $Cu(OAc)_2$, $PhI(OAc)_2$, MnO_2, and $K_2S_2O_8$ were tested, in which $K_2S_2O_8$ was found to be the most effective which gives a yield of 83% (entries 2−6). Subsequently, we investigated the effect of palladium catalysts on this reaction. The results showed that $PdCl_2$ and $PdCl_2(PPh_3)_2$ could also prompt this reaction but with relatively low yield (entries 8-9). No desired product was observed when $Pd(PPh_3)_4$ was chosen as catalyst (entry 7). When the loading of $Pd(OAc)_2$ was decreased to 5%, the yield of **3a** also decreased synchronously to 59% (entry 12). An attempt to increase the loading of $Pd(OAc)_2$ to 20% did not give a significant improvement on the yield. Moreover, the change of temperature to 80 ℃ and 140 ℃ let to 68% and 84% yield respectively (entries 10-11). While a variety of other solvents such as DMSO, DMF, and CH_3CN were screened, DCE still appeared to be the best solvent (entries 14-16). Thus, 10 mol% of $Pd(OAc)_2$, 2.0 equiv. of $K_2S_2O_8$ and DCE as solvent were chosen as the optimized conditions for the Pd-catalyzed reaction of **1a** with **2a**.

With the optimized reaction conditions in hand, we further investigated the scope of substrates. As shown in Table 2, the reaction tolerated a range of different electron-donating and electron-withdrawing functional groups, including Me, F, Cl and MeO. The corresponding *ortho*-alkenyl 2-benzyl-1, 2, 3-triazoles were obtained in moderate to good yields. The substrates with a *para*-electron-donating group (4-H, 4-MeO, and 4-Me) on the benzene rings afforded the desired products in good yields (**3a**, **3e**, **3j**). On the contrast, the reaction of **1** bearing a strong electron-withdrawing NO_2, CF_3, or CN group at the *para* position provided the corresponding product with slightly moderate yield (**3i**, **3k**, **3l**). The regioselectivity of alkenylation with *meta*-substituted substrates may be attributed to steric effects, delivering the product alkenylated at

the less hindered *ortho* position (**3f**, **3h**). The use of arenes bearing a halogen group also provided good yields (**3b, 3c, 3g**). Moreover, the present procedure was successfully extended to other acrylates. Ethyl acrylate, butyl acrylate and methyl acrylate was all compatible with this optimized conditions, which give the corresponding products in good yields (**3n**, **3p**). Besides, we found that when acrylonitrile was subjected to the reaction, it afforded the product **3o** in 50% yield. Notably, N-tert-Butylacrylamide also underwent this reaction in 53% yield. Interestingly, an attempt to use 2-benzyl-pyrazole as directing group failed to deliver the corresponding product 3q. The tolerance of this reaction to substrates with these functional groups indicated that it can be used for further transformation of the products.

Table 1. Optimization of reaction conditions.[a]



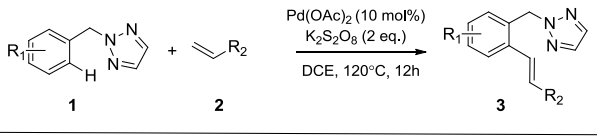
1a 2a 3a

Entry	Catalyst (mol %)	Oxidant	Solvent	Yield(%)[b]
1	$Pd(OAc)_2$(10)	BQ	DCE	21
2	$Pd(OAc)_2$(10)	AgOAc	DCE	17
3	$Pd(OAc)_2$(10)	$Cu(OAc)_2$	DCE	0
4	$Pd(OAc)_2$(10)	$PhI(OAc)_2$	DCE	18
5	$Pd(OAc)_2$(10)	MnO_2	DCE	0
6	**$Pd(OAc)_2$(10)**	**$K_2S_2O_8$**	**DCE**	**83**
7	$Pd(PPh_3)_4$(10)	$K_2S_2O_8$	DCE	0
8	$PdCl_2(PPh_3)_2$(10)	$K_2S_2O_8$	DCE	26
9	$PdCl_2$(10)	$K_2S_2O_8$	DCE	30
10[c]	$Pd(OAc)_2$(10)	$K_2S_2O_8$	DCE	68
11[d]	$Pd(OAc)_2$(10)	$K_2S_2O_8$	DCE	84
12	$Pd(OAc)_2$(5)	$K_2S_2O_8$	DCE	59
13	$Pd(OAc)_2$(20)	$K_2S_2O_8$	DCE	85
14	$Pd(OAc)_2$(10)	$K_2S_2O_8$	DMSO	42
15	$Pd(OAc)_2$(10)	$K_2S_2O_8$	DMF	55
16	$Pd(OAc)_2$(10)	$K_2S_2O_8$	CH_3CN	70

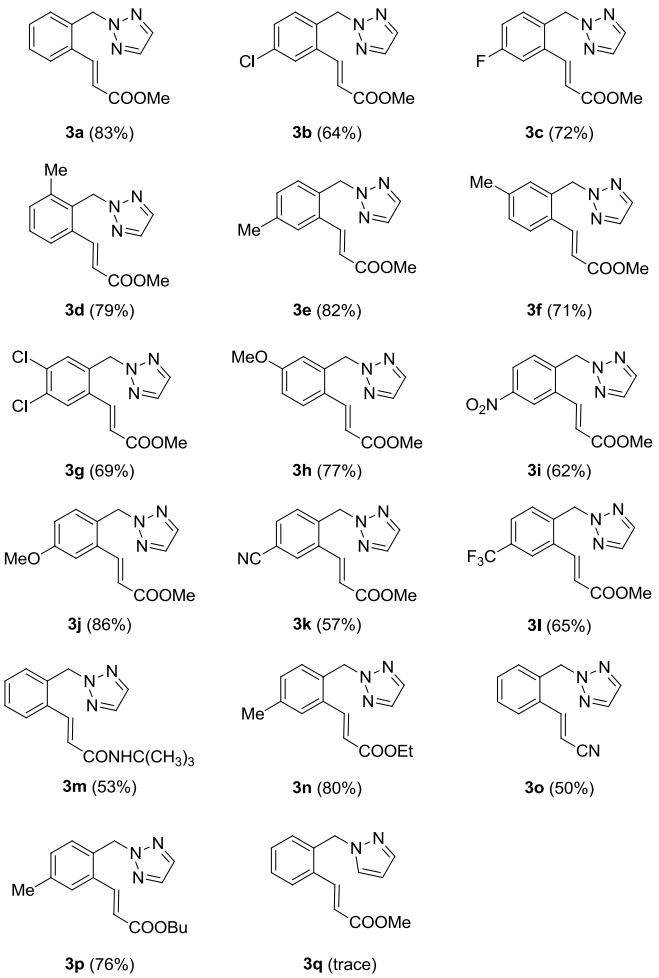
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), palladium catalyst (0.02 mmol) and oxidant (0.4 mmol) in solvent (2.0 mL), stirred at 120 ℃ for 12 h. [b] Isolated yields. [c] Reaction temperature: 80 ℃. [d] Reaction temperature: 140 ℃.

On the basis of these results we obtained and found in the previous reports, [9] a plausible reaction mechanism that was proposed and is shown in Scheme 2. First, coordination of 2-benzyl-1, 2, 3-triazole to palladium acetate is followed by C−H activation to form a five-membered cyclopalladated intermediate **A**, which has been confirmed by previous research. Subsequently, olefin insertion takes place followed by β-hydride elimination of the intermediate **B**, furnishing the E-olefinated products **C** and liberate Pd(0). The Pd(II) is regenerated from the oxidation of Pd(0) by $K_2S_2O_8$.

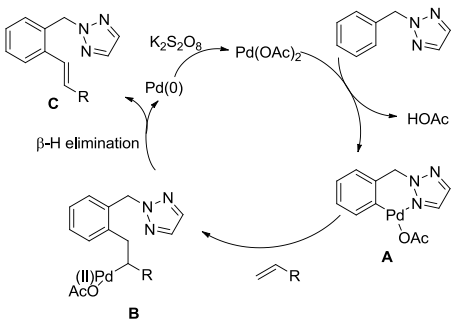
Table 2. Palladium-catalyzed alkenylation of 2-benzyl-1,2,3-triazoles with alkenes.[a]



1 2 3



[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol) and $K_2S_2O_8$ (0.4 mmol) in DCE (2.0 mL), stirred at 120 ℃ for 12 h. Isolated yields are given.



Scheme 2. Plausible Reaction Mechanism.

In conclusion, we have described a mild and efficient alkenylation of 2-benzyl-1,2,3-triazoles. This reaction occurs through *ortho*-C-H alkenylation under Pd-catalyzed using $K_2S_2O_8$ as an oxidant. This approach provides a complementary method for the synthesis of 2-benzyl-1,2,3-triazole derivatives which are important building blocks in medicine and materials.

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Notes and references

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