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Palladium-Catalyzed C-H Alkenylation of *C*-Aryl Nitrones

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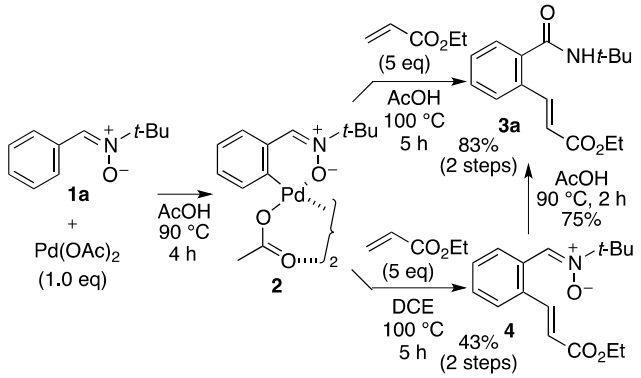
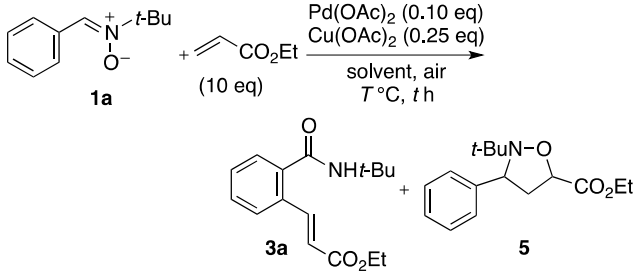
Palladium-catalyzed C-H alkenylation of *C*-aryl *N*-*t*-butyl nitrones with ethyl acrylate produced *ortho*-alkenylated benzamide derivatives via isomerization of the nitrone moiety. The use of 1,1,1,3,3,3-hexafluoro-2-propanol/acetic acid as a solvent resulted in effective C-H alkenylation, while competitive 1,3-dipolar cycloaddition was completely suppressed.

Transition-metal-catalyzed direct C-H functionalization is a successful and widely used strategy for various C-C bond formation reactions. There has recently been extensive study of directing-group-assisted cleavage of C-H bonds with the use of transition metal catalysts.[1,2] Although various types of nitrogen- and oxygen-based directing group, including amines, amides, carboxylic acids, esters, and heterocycles such as pyridines, have been intensively investigated, nitrones have seldom been employed in this field. One reason for this is their high reactivity toward 1,3-dipolar cycloaddition[3] and toward oxidation of unsaturated compounds in the presence of transition metal catalysts.[4] As a matter of fact, the examples of nitrone-directed C-H functionalization have been limited to several Rh and Ir catalyzed reactions.[5,6,7] With respect to Pd, *C*-aryl nitrones have been reported to generate the palladacyclic intermediates via C-H bond activation.[8] However, these Pd complexes were tested as catalysts, rather than substrates, for coupling reactions[8b–d] because of the inert and stable carbenoid-like nature of their Pd-C bonds. Herein, we report a palladium-catalyzed direct coupling reaction between *C*-aryl nitrones and acrylates to afford *ortho*-alkenylated benzamide derivatives via cascade C-H functionalization and isomerization of the nitrone moiety, circumventing the problem of undesired side-reactions of nitrones and the relatively low reactivity of the Pd-C bond of the palladacyclic intermediates.



Scheme 1. Potential Mizoroki-Heck-type coupling using palladacyclic intermediate **2**

Table 1. Reaction of nitrone **1a** with ethyl acrylate in the presence of $Pd(OAc)_2$ and $Cu(OAc)_2$



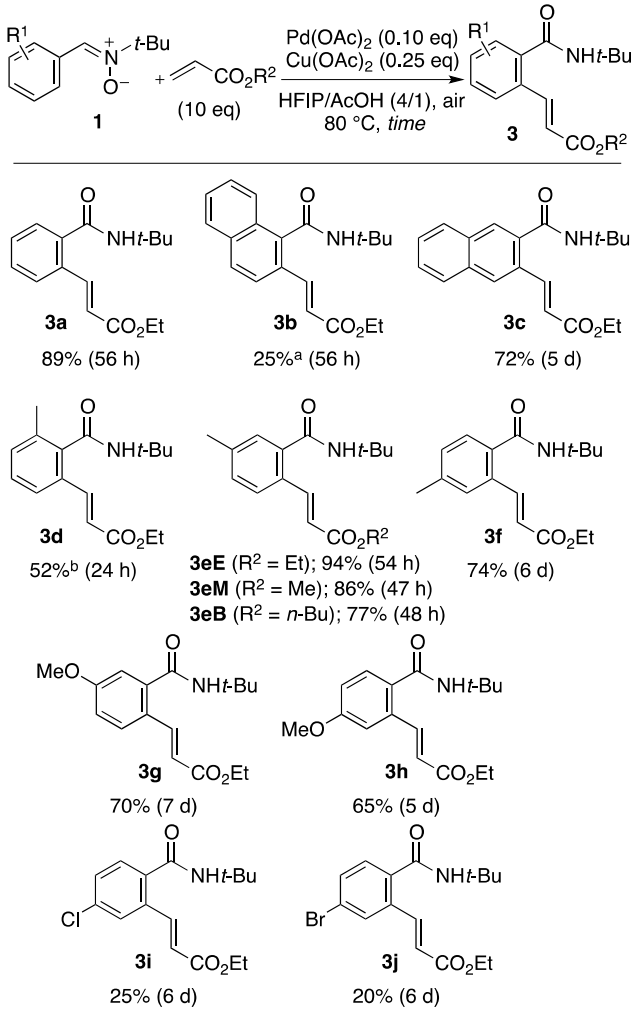
Entry	Solvent[a]	*T*/°C	*t*/h	Product	Yield/%
1	AcOH	90	24	**3a**	53
2	DCE	90	66	**5**	83[b]
3	DCE/AcOH (1/1)	90	49	**3a**	24
4	TFE/AcOH(4/1)	90	47	**3a**	73
5	HFIP/AcOH (2/1)	80	43	**3a**	78
6	HFIP/AcOH (4/1)	80	56	**3a**	89
7	HFIP/AcOH (9/1)	80	138	**3a**	75
8	HFIP	50	174	**3a**	18

[a]DCE = $ClCH_2CH_2Cl$. TFE = CF_3CH_2OH. HFIP = $(CF_3)_2CHOH$. [b]*trans*/*cis* = 3/1.

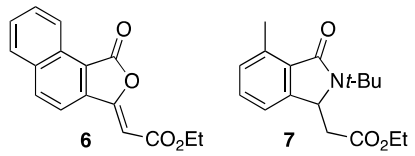
Firstly, we examined the stoichiometric reactivity of the reported palladacyclic intermediate **2**, which was obtained from *N*-*t*-butyl nitrone **1a** and $Pd(OAc)_2$ in AcOH[8b] as shown in Scheme 1. When the palladium intermediate **2** was treated with ethyl acrylate in AcOH at 100 °C, an oxidative Mizoroki-Heck-type coupling reaction took place. To our surprise, the nitrone moiety was isomerized to give *N*-*t*-butyl benzamide **3a** in good yield. After several attempts, an alkenylated nitrone **4** was isolated using dichloroethane (DCE) as a solvent.[2d] It was confirmed that **4** was readily isomerized to *N*-*t*-butyl amide **3a** under reflux conditions in AcOH.[9] Based on these observations, it was suggested that the palladacyclic intermediate **2** reacted first with ethyl acrylate to afford **4**, as expected, followed by isomerization of the nitrone moiety in AcOH.

Encouraged by these results, the catalytic reaction between *N*-*t*-butyl nitrone **1a** and ethyl acrylate was investigated. When a mixture of nitrone **1a** and ethyl acrylate was heated in the presence of $Pd(OAc)_2$ (0.10 eq) and $Cu(OAc)_2$ (0.25 eq) in AcOH at 90 °C under air, *ortho*-alkenylation proceeded to afford the isomerized *N*-*t*-butyl benzamide **3a** in 53% yield (Table 1, Entry 1). In this case, the undesired 1,3-dipolar adduct **5** was fortunately not detected by ^1H NMR analysis of the crude products. In contrast, isoxazolidine **5** (*trans*/*cis* = 3/1),[10] rather than *ortho*-alkenylated amide **3a** or nitrone **4**, was obtained in 83% yield when DCE was used as a solvent (Entry 2). In the absence of

Table 2. C-H alkenylation of nitrones **1**



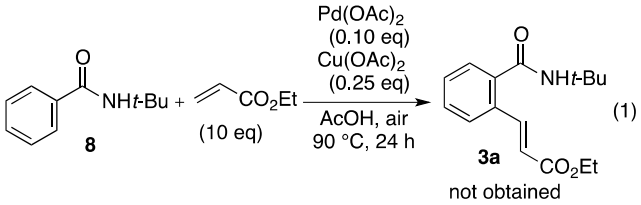
[a]By-product **6** (47%) was also obtained. [b]By-product **7** (23%) was also obtained.



$Pd(OAc)_2$ and $Cu(OAc)_2$ (in DCE at 80 °C for 3 d), the chemical yield of **5** decreased to 47%, which indicated that Pd and/or Cu salts promoted 1,3-dipolar cycloaddition as Lewis acids.[11] From the reaction in a mixture of DCE and AcOH as solvents, *ortho*-alkenylated amide **3a** was isolated (Entry 3). It was found that the chemical yield was enhanced when a fluorinated alcohol was added as a co-solvent with AcOH (Entries 4–8).[12] When the reaction was performed in a 4:1 mixture of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and AcOH, the product **3a** was obtained in 89% yield. Thus, the appropriate choice of solvent was decisive in preventing undesired side reactions and improving the yield.

Under the optimized conditions, direct C-H alkenylation reactions of various *C*-aryl nitrones **1** were carried out using ethyl acrylate as a coupling partner.[13] As shown in Table 2, the C-H alkenylation of *C*-naphthyl nitrones **1b** and **1c** and *C*-phenyl nitrones **1d**–**1h** with alkyl or alkoxy-substituent on aromatic ring proceeded to afford the corresponding amides **3b**–**3h** in good yields, although additional intramolecular cyclization of **3b** and **3d** occurred to produce **6** and **7**. In the case of the *m*-methyl-substituted substrate **1e**, the product **3eE** (R^2 = Et) was obtained in 94% yield. Instead of ethyl acrylate, methyl and butyl acrylates furnished the amides **3eM** and **3eB** in 86% and 77% yields, respectively. The reactions of nitrones **1i** and **1j** bearing electron-withdrawing chloro- and bromo-groups were so sluggish that the yields were not good and the corresponding hydrolyzed aldehydes were recovered.

In order to obtain further insight into the reaction, the following reactions were performed. When *N*-(*t*-butyl)benzamide (**8**) was treated with a stoichiometric amount of $Pd(OAc)_2$ in AcOH at 90 °C for 24 h, a small amount (around 30%) of a palladacyclic intermediate was presumed to be generated according to the analysis of the ^{1}H NMR spectrum[14] and the amide **8** was mainly recovered. Despite the observation of the palladium intermediate, none of the corresponding amide **3a** was produced when the reaction starting from benzamide **8** with ethyl acrylate was carried out under identical conditions (Eq. 1). Based on these results, the pathway via the initial isomerization from the nitrone **1** to the corresponding amide followed by C-H activation-alkenylation is not plausible.[15]



In summary, palladium-catalyzed *ortho*-C-H alkenylation of *C*-aryl *N*-*t*-butyl nitrones afforded the *ortho*-alkenylated benzamide derivatives. Based on the choice of the solvent used, the selectivity between C-H alkenylation and undesired 1,3-dipolar cycloaddition was fully controlled. By employing nitrones as substrates, the present reaction provides an easy access to *ortho*-alkenylated benzamide derivatives, which are difficult to prepare directly from the corresponding benzamides and alkenes by the conventional palladium-catalyzed C-H functionalization reactions.

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14 See Supporting Information for details.

15 The C-H alkenylation reaction of **1a** in CD_3COOD corresponding to Entry 1 in Table 1 provided the information to suggest that C-H activation step is not reversible, see: Supporting Information for details.