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Palladium-Catalyzed Alkenylation of Quinoline-*N*-oxides via C−H Activation under External-Oxidant-Free Conditions

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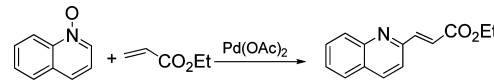
Selective activation of C−H bonds catalyzed by transition metals can assemble value-added molecules through C−C bond formation.[1] This synthetic strategy is intriguing for the chemical and pharmaceutical industries because it may not only significantly simplify and shorten the synthetic route for various types of organic compounds but also allow the utilization of readily available, cheap, and environmentally benign starting materials. Recently, there has been much progress in terms of synthesis efficiency and atom economy in direct C−C bond formation by aromatic compounds catalyzed by transition metals via activation of a normally unreactive C−H bond. The protocol has been developed for activating C−H bonds at the ortho position of inducing groups, such as hydroxyl,[2] carbonyl,[3] imino,[4] 2-substituted pyridyl,[5] oxazolyl, 2-imidazolyl,[6] amido,[7] and so on. Notably, cyclometalation plays a key role in these reactions, and the arylmetal intermediates react with a variety of substrates, such as aryl halides and olefins, to give the corresponding products.

Fagnou, Hiyama, and Chang[8] groups have independently developed cross-coupling reactions via the C−H activation of pyridine-*N*-oxides, in which the *N*-oxide group is a key element for introducing a functional group at the position ortho to the nitrogen atom. However, an additional ligand and oxidant were required to achieve the reaction, and reducing agents were needed to reduce the *N*-oxide products. On the other hand, *N*-oxides are prototypical oxidants that have been routinely used in some reactions.[9] We deduced that quinoline-*N*-oxides might serve as both an inducing platform and an oxidant in the Pd-catalyzed C−H activation reaction. Herein, we disclose our preliminary results on the Pd-catalyzed alkenylation of quinoline- and isoquinoline-*N*-oxides without external oxidants.

With palladium acetate as the catalyst, the condensation of quinoline-*N*-oxide **1a** and ethyl acrylate **2a** was initially chosen as a model reaction to examine the influence of solvents under aerobic atmosphere. As shown in Table 1, when quinoline-*N*-oxide **1a** was treated with an excess amount of ethyl acrylate **2a** in the presence of 5 mol % $Pd(OAc)_2$ in 1-methyl-2-pyrrolidinone (NMP) at 110 °C for 20 h, only monoalkenylated product **3a** was obtained as the main product in 86% isolated yield (Table 1, entry 5), whereas only moderate yields were obtained in toluene and DMF at 110 °C (Table 1, entries 2 and 7). Moreover, the addition of 4 Å molecular sieves (MS) as a desiccant and PPh_3 as the ligand did not improve the yields (Table 1, entry 8 vs entry 6 and entry 9 vs entry 5). The presence of Ag_2O as an oxidant also did not favor this reaction. An isolated yield of only 37% was obtained for **3a** when 1.2 equiv of Ag_2O was used (Table 1, entry 10).

Under the optimized conditions without an external oxidant, the scope of substrates was examined, and the results are summarized in Table 2. The quinoline-*N*-oxide and its derivatives with electron-donating methyl groups at the 3-, 4-, and 6-positions were smoothly alkenylated at the 2-position with acrylate in high yields (entries 1−8). In the case of acrylonitrile as a substrate, a moderate yield was obtained (entry 9). Isoquinoline-*N*-oxide also reacted smoothly to afford the corresponding α-alkenylated product (entry 10). A poor yield (27%) was obtained for 8-hydroxyl quinoline-*N*-oxide, which may have been caused by the deactivation of catalyst through coordination of the palladium atom with the two O oxygen atoms of the substrate. In contrast, electron-withdrawing groups passivated the reactions. No desired product was obtained when 4-nitroquinoline-*N*-oxide was used as the substrate. It is worth noting that quinazoline 1-*N*-oxide was also a suitable substrate to provide the 2-alkenylated quinazoline in 95% yield (entry 12), but no products were afforded when *N*-oxides derived from pyridine and its derivatives pyrazine, pyrimidine, and 1-methyl-imidazole were utilized as the substrate.

Table 1. Direct Coupling Reaction of Quinoline-*N*-oxide **1a** with Ethyl Acrylate **2a** Catalyzed by $Pd(OAc)_2$[a]



1a **2a** **3a**

Entry	Solvents	Temp (°C)	Additives	Yields (%)[b]
1	DMF	100	none	9
2	DMF	110	none	56
3	DMF	120	none	51
4	NMP	100	none	63
5	NMP	110	none	86
6	DMSO	110	none	79
7	toluene	110	none	55
8	DMSO	110	4 Å MS (100 mg)	79
9	NMP	110	PPh_3 (20 mol %)	63
10	NMP	110	Ag_2O (1.2 equiv)	37

[a] Reaction conditions: **1a** (1 mmol), **2a** (5 mmol), $Pd(OAc)_2$ (5 mol %), solvent (1 mL), 20 h. [b] Isolated yields.

To clarify the mechanism of the reaction, control experiments were carried out. When quinoline was treated with acrylate under the optimized conditions, no reaction occurred. Obviously, *N*-oxide in the substrate is the key functional group for activating the C−H bond at the position ortho to the N atom. On the other hand, it is well-known that an oxidant is necessary to regenerate Pd(II) from Pd(0) and complete the catalytic cycle in such reaction systems. When we treated a mixture of 2-alkenylated quinoline-*N*-oxide and quinoline-*N*-oxide with $Pd_2(dba)_3$, only 2-alkenylated quinoline was observed by HPLC. Additionally, no quinoline was observed by HPLC during the reaction process of Pd-catalyzed alkenylation of quinoline-*N*-oxide. These results might suggest that alkenylated quinoline-*N*-oxide can be reduced by Pd(0) but that the starting material, quinoline-*N*-oxide, does not work as an oxidant.

To further examine whether the alkenylated quinoline-*N*-oxides oxidize Pd(0) species to regenerate Pd(II) and the intramolecular redox reaction happens in the process, a competition experiment

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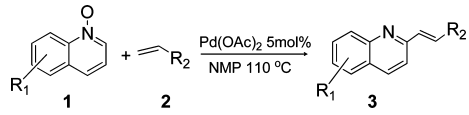
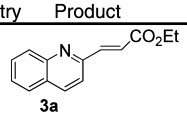
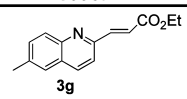
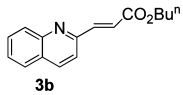
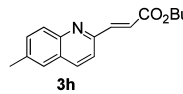
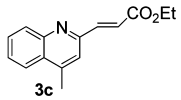
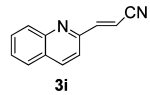
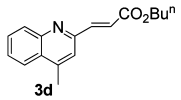
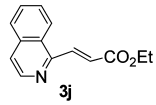
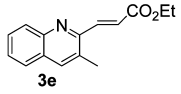
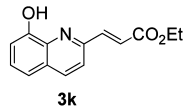
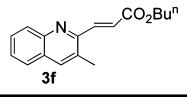
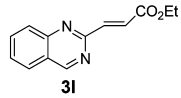
Table 2. Palladium-Catalyzed Alkenylation of Quinoline-*N*-oxides[a]

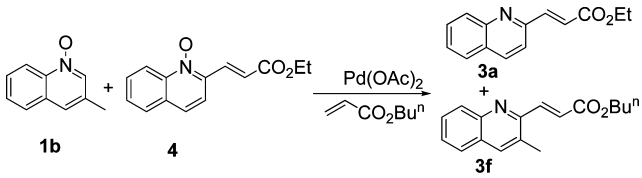


1 2 3

Entry	Product	Yields	Entry	Product	Yields[b]
1	 3a	86%	7	 3g	93%
2	 3b	85%	8	 3h	92%
3	 3c	85%	9	 3i	65%
4	 3d	80%	10	 3j	67%
5	 3e	82%	11	 3k	27%
6	 3f	90%	12	 3l	95%

[a] Reaction conditions: **1** (1 mmol), **2** (5 mmol), $Pd(OAc)_2$ (5 mol %), NMP (1 mL), 110 °C, 20 h. [b] Isolated yields.

Scheme 1



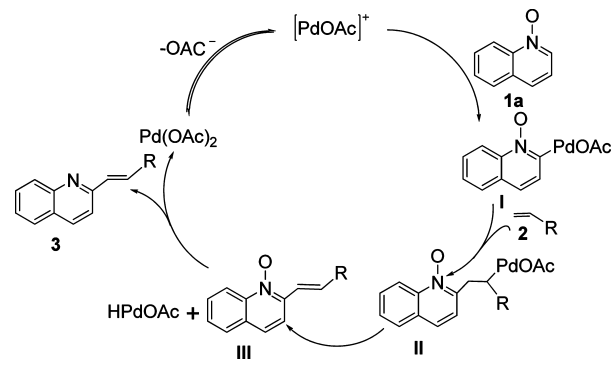
1b 4

was performed. One equivalent of *N*-oxide **4**, prepared using a slight modification of the protocol reported by Heimgärtner,[10] was added to a reaction system consisting of 1 equiv of 3-methylquinoline-*N*-oxide **1b** and 5 equiv of *n*-butyl acrylate under the optimized conditions. Products **3a** and **3f** were detected by HPLC analysis of the reaction mixture (Scheme 1). These results are incompatible with the intramolecular redox reaction and suggest that alkenylated quinoline-*N*-oxides act as the oxidant to convert Pd(0) into Pd(II), thus completing the catalytic cycle.

A plausible mechanism for the direct coupling of quinoline-*N*-oxides with acrylate is shown in Scheme 2. First, aryl−Pd complex **I** is formed via coordination of the palladium atom to the *N*-oxide and subsequent electrophilic attack at the 2-position carbon atom. Next, coordination of the palladium complex **I** with alkene substrate **2** followed by syn insertion gives intermediate **II**. β-Hydride elimination of **II** forms palladium hydride and intermediate **III**.[11] Oxidation of palladium hydride by intermediate **III** affords products **3** and palladium acetate to complete the catalytic cycle.

The present report reveals for the first time that quinoline-*N*-oxides serve as both the inducing platform and the oxidant in Pd-

Scheme 2. Plausible Mechanism for the Direct Coupling Reaction



catalyzed C−H bond activation, providing 2-alkenylated quinolines and 1-alkenylated isoquinolines in chemo- and regioselective manners under external-oxidant-free conditions. Investigations of the elucidation of the reaction pathway in detail and extending the scope of the reaction to other substrates are in process.

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Supporting Information Available: Detailed experimental procedures and spectroscopic characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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