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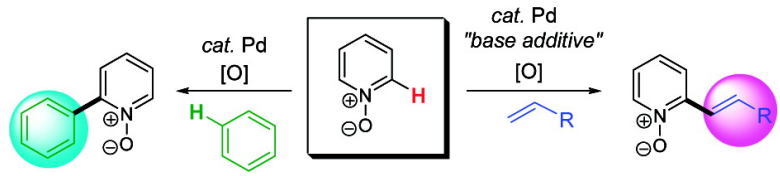

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Palladium-Catalyzed C−H Functionalization of Pyridine *N*-Oxides: Highly Selective Alkenylation and Direct Arylation with Unactivated Arenes

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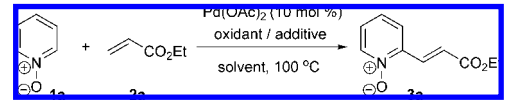
Transition metal-catalyzed C−H bond functionalization for the C−C bond formation has emerged as a promising area in organic synthesis.[1] In particular, reactions involving Pd-catalyzed activation of sp^2 or sp^3 C−H bonds of arenes or alkanes have been extensively investigated.[2] Successful applications of the C−H activation strategy on readily available substrates have been also reported using various metals other than Pd catalysts.[3,4]

Pyridine moiety is a key component of pharmacophores, natural products, and synthetic building blocks.[5] Substituted pyridines are usually prepared starting from halo- or metallated pyridyl compounds. However, this "*prefunctionalization*" route is inevitably accompanied with problems such as the need of extra preparation steps for the frequently unstable precursors and the formation of byproducts. Inspired by the key contributions from Fagnou[6a–d] and Hiyama group,[6e] we envisioned that the C−H bond activation approach using pyridine *N*-oxides would serve as an attractive platform for the 2-functionalization of pyridine species.[7] Described herein are two new protocols for the oxidative C−C bond formation of pyridine *N*-oxides; selective alkenylation and direct cross-coupling with unactivated arenes.

At the outset on the alkenylation of *N*-oxides based on the Fujiwara−Moritani approach,[8] we tried to optimize the reaction conditions using pyridine *N*-oxide (**1a**) and ethyl acrylate (Table 1).[9] It was found that the nature of oxidants, additives, and solvent play a critical role on the reaction efficiency. While no reaction took place without oxidants and additives in acidic solvent (entry 1), the addition of AgF (3.0 equiv) produced noticeable yield that was further increased in 1,4-dioxane alone (entries 2 and 3). We subsequently found that the addition of certain bases provided more significant improvement (entry 5). Finally, the reaction proceeded highly efficiently when 10 mol % of $Pd(OAc)_2$ was used in combination with Ag_2CO_3 (1.5 equiv) and pyridine (1.0 equiv, entry 8).[10] *This transformation is highly site-selective at the 2-position and no regioisomeric products of* **3a** were observed. In addition, it proceeds with complete stereoselectivity to generate (*E*)-**3a** exclusively. Moreover, the chemoseletivity was remarkably high since it did not suffer from double alkenylation at all.

As shown in Scheme 1, a palladium complex (**A**) bound to the *N*-oxide oxygen was isolated by the treatment of **1a** with $PdCl_2(PPh_3)_2$ which showed a moderate catalytic activity giving **3a** in 66% yield under the optimized conditions.[9] When **A** was submitted to various reaction conditions with **2a**, no alkenylated product **3a** was obtained, suggesting that the *N*-oxide-bound Pd complex **A** is probably a resting species positioned outside the catalytic cycle. In fact, Hiyama proposed that the C−H activation of pyridine *N*-oxides[6e] or their equivalents[7d] proceeds via the direct oxidative addition of Ni(0) center to the acidic C2−H bond. On the other hand, Kiplinger suggested that *N*-oxide-bound actinide species serve as distinct precursors for the subsequent ortho C−H bond activation of bound pyridine *N*-oxide.[11]

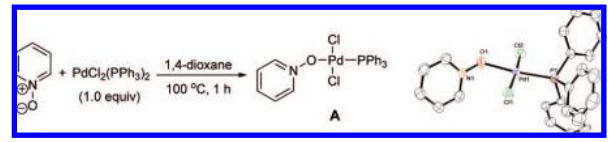
Table 1. Optimization for the Alkenylation of Pyridine *N*-Oxide[a]



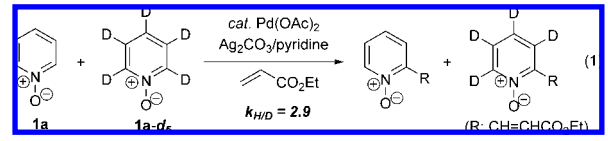
entry	oxidant (equiv)	solvent	additive	yield (%)[b]
1	none	AcOH/1,4-dioxane[c]	none	<1
2	AgF (3.0)	AcOH/1,4-dioxane[c]	none	15
3	AgF (3.0)	1,4-dioxane	none	28
4	AgF (3.0)	DMF	none	5
5	AgF (3.0)	1,4-dioxane	K_2CO_3	54
6	Ag_2O (1.5)	1,4-dioxane	K_2CO_3	60
7	Ag_2CO_3 (1.5)	1,4-dioxane	K_2CO_3	72
8	Ag_2CO_3 (1.5)	1,4-dioxane	pyridine	96 (91)

[a] Conditions: **1a** (4 equiv), ethyl acrylate (0.3 mmol), $Pd(OAc)_2$ (10 mol %), oxidant (1.5∼3.0 equiv), additive (1.0 equiv), and solvent (0.6 mL) at 100 °C for 12 h. [b] NMR yield (isolated yield in parenthesis). [c] Volume ratio of 1:3 (AcOH/1,4-dioxane).

Scheme 1. Preparation and Molecular Structure of a Complex **A**



Kinetic isotope competition experiments were also carried out under the reaction conditions to reveal the intermolecular kinetic isotope effects ($k_{H/D}$) being 2.9 (eq 1).[12] In addition, when proto- (**1a**) and deutero- (**1a-*d*$_5$**) substrates were run side by side in separate flasks, a significant rate difference was observed.[9]



The scope of the alkenylation reaction was broad as shown in Table 2. Olefins conjugated with ester, amide, or ketone groups were all smoothly alkenylated at the 2-position of **1a** (entries 1−3). Diethyl vinylphosphonate also participated in the reaction (entry 4). We were pleased to observe that aliphatic olefins were readily reacted with **1a** in modest yield (entry 5). Moreover, (*E*)-2-styrylpyridine *N*-oxide was efficiently obtained by the reaction with styrene at higher temperatures (entry 6).

Pyridine *N*-oxides substituted with a phenyl group at the para or ortho position were readily alkenylated with satisfactory yields (entries 7 and 8). Interestingly, 3-phenylpyridine *N*-oxide underwent the alkenylation with excellent selectivity at the less bulky site (entry 9). Furthermore, other types of *N*-oxides derived from pyrazine,

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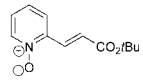
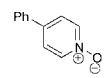
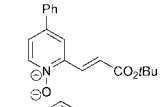
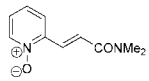
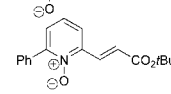
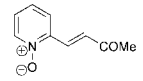
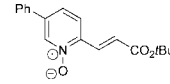
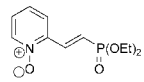
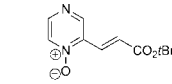
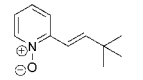
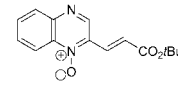
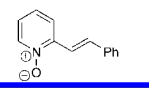
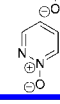
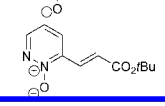
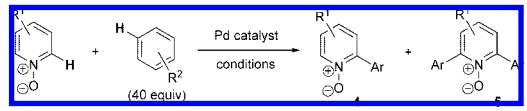
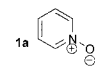
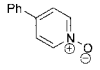
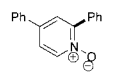
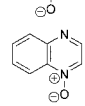
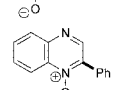
Table 2. Highly Selective Alkenylation of Various *N*-Oxides[a]

entry	*N*-oxide	olefin	product	yield(%)[b]	entry	*N*-oxide	olefin	product	yield(%)[b]
1	 **1a**	 **2b**		91	7		**2b**		68
2	**1a**			87	8		**2b**		73
3	**1a**			62	9		**2b**		88
4	**1a**			70	10		**2b**		69
5	**1a**			53	11		**2b**		63
6[c]	**1a**			64	12		**2b**		76

[a] Reaction conditions: olefin (0.3 mmol), *N*-oxide (4 equiv), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (1.5 equiv) in 1,4-dioxane (0.6 mL) at 100 °C for 12 h. [b] Isolated yield. [c] At 120 °C for 16 h.

Table 3. Pd-Catalyzed Direct Arylation of Various *N*-Oxides Using Unactivated Arenes[a]



entry	*N*-oxide	arene	major product	yield(%, **4**+**5**)[b]	ratio(**4**/**5**)[c]	entry	*N*-oxide	arene	major product	yield(%, **4**+**5**)[b]	ratio(**4**/**5**)[c]
1[d]	**1a** 			79	3 : 1	7				40	5 : 1
2				76	3 : 1	8				74	–
3[e]				65	20 : 1	9	**1a**			53	10 : 1
4[f]				61	3 : 1	10	**1a**			68	2.5 :1
5				56	–	11	**1a**			42	20 : 1
6				58	–	12	**1a**			47	15 : 1

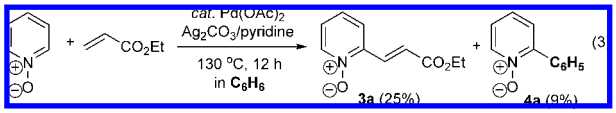
[a] Reaction conditions: *N*-oxide (0.6 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.2 equiv), and arene (40 equiv) at 130 °C for 16 h. [b] Isolated yield of product mixture. [c] Ratio of isolated products. [d] Run using 2 equiv of Ag_2CO_3. [e] $PdCl_2(dppe)$ (10 mol %) was used. [f] Run using 1 equiv of Ag_2CO_3.

quinoxaline, and pyridazine were also viable substrates for the ortho alkenylation reactions (entries 10−12).

The resultant alkenylated pyridine *N*-oxides (e.g., **3a**) were readily deoxygenated to give 2-alkenylpyridines (eq 2),[6e] making the present alkenylation route a highly attractive alternative for the 2-functionalization of pyridine derivatives.[7,13]

During the course of our studies on the alkenylation reaction, we observed that 2-phenylpyridine *N*-oxide (**4a**) was produced as a side product in addition to the desired alkenylated compound (**3a**) *when the reaction was carried out in benzene at 130 °C* (eq 3). Obviously, the ortho arylated product **4a** can be envisioned to generate oxidatively by the cross-coupling of simultaneously activated species of pyridine *N*-oxide and benzene by Pd catalyst.

Although a few reports have described the oxidative cross-coupling of (hetero)aryl species with arenes via the double C−H bond activation route,[14] convenient arylation of certain heteroaro-



matics such as pyridine still remains as a challenge to work with. This consideration made us to search for optimal conditions for the arylation of pyridine *N*-oxides with simple arenes since this approach was envisioned to serve as an efficient alternative way for the direct arylation of pyridines.

Among various conditions screened using **1a** and benzene,[9] we optimized the oxidative arylation of *N*-oxides as follows: arenes (40 equiv), $Pd(OAc)_2$ (10 mol %), and Ag_2CO_3 (2.2 equiv) at 130 °C.[15] The reaction scope was next explored, revealing that it proceeds with moderate to excellent selectivity for the formation of monoarylated adducts and the extent of which varies on the substrates employed (Table 3). For instance, reaction of **1a** or its para derivative with benzene afforded the corresponding ortho phenylated products with a 3:1 ratio (**4/5**) in high yields (entries 1 and 2). The ratio was increased up to 20:1 when 3-substitued pyridine *N*-oxide was employed (entry 3), indicating the importance of steric effects on the selectivity. Interestingly, phenylation of isoquinoline *N*-oxide with benzene provided 1-phenylisoquinoline 2-oxide as the major product (entry 4).

Interestingly, *N*-oxides of quinoline and benzo[*h*]quinoline were arylated selectively at the ortho-position in good yields (entries 5−6). It is noteworthy that since previous examples of the Pd-catalyzed direct coupling of benzo[*h*]quinoline are shown to proceed selectively at the C(10) position,[16] our present system offers a useful complementary route for the selective aryl introduction at the ortho position. Therefore, *this may serve as a notable example of controlling site-selectivity by the employment of different directing groups within the same molecular skeletons*. *N*-Oxides of pyrazine and quinoxaline were also readily cross coupled with benzene at the ortho position (entries 7 and 8).

It should be noted that homocoupling between employed arenes during the course of the direct arylation can be significantly reduced down to 5% based on the equivalent of pyridine *N*-oxide used, when the reaction was carried out in the presence of pyridine or its derivatives, without deteriorating the reaction efficiency and selectivity.[9]

Preliminary survey on the scope of arenes revealed that the arylations indeed take place with a range of unactivated arenes. Cross-coupling of **1a** with selected entries of 1,2-disubstituted arenes provides monoarylated products as major, and the reacting site on arenes was at the meta position relative to the 1,2-disubstituents of the arenes (entries 9−11). Likewise, when 1,3-xylene was employed, the reaction occurred at the meta position relative to the dimethyl substituents (entry 12).[17]

In summary, relying on the Pd-mediated C−H bond activation strategy, we have developed two highly promising oxidative protocols for the selective alkenylation and direct arylation of pyridine *N*-oxides using olefins and unactivated arenes, respectively. Mechanistic studies toward the detailed understanding of the activation pathways and synthetic applications based on the present approaches are under way.

Acknowledgment. Dedicated to Professor Kwan Soo Kim on the occasion of his 60th birthday. This research was supported by the Korea Research Foundation Grant (KRF-2006-312-C00587). We also thank Dr. Junseung Lee for the crystal structure analysis.

Supporting Information Available: Data and copies of ^1H and ^{13}C NMR spectra of new compounds and one CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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