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Palladium-Catalyzed Oxidative Cross-Coupling between Pyridine *N*-Oxides and Indoles

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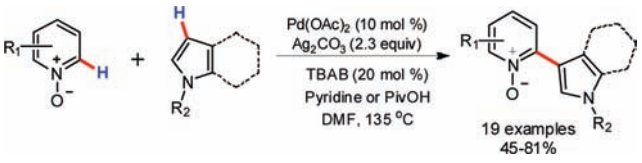
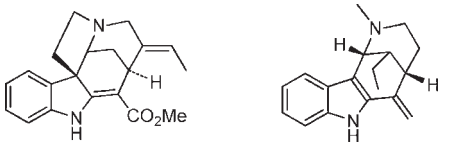
ABSTRACT



A Pd(II)-catalyzed oxidative coupling between pyridine *N*-oxides and *N*-substituted indoles via 2-fold C−H bond activation was achieved with high selectivity using Ag_2CO_3 as an oxidant.

Biaryls, including pyridylindoles, play an important and wide role in pharmaceuticals, fragrances, dyes, and agrochemicals.[1] For instance, 3-(2-pyridyl)-indoles are known to be useful synthetic precursors for indole alkaloids such as analogues of Akuammicine and Uleine (Chart 1).[2] Although several methods have been described for the preparation of 2-pyridyl-indoles,[2−5] most of them have used 2-pyridyl organometallics and have limitations. For example, a stoichiometric amount of zinc reagents and aryl halides were needed in Negishi coupling with decreased atom economy, and extensive prior functionalization of the starting materials is necessary.[2,3] The reaction of quinoline *N*-oxides and indoles, that gives 3-(2-quinolinyl)indoles is known, but it requires a stoichiometric amount of benzoyl chloride, and the reactivity is much decresed for pyridine *N*-oxides.[5] Therefore, it is necessary to develop a simple, general, and efficient method for the assembly of 3-(2-pyridyl)-indoles.

Chart 1



Palladium-catalyzed direct oxidative functionalization of C−H bonds of two (hetero)arene coupling partners constitutes an important and desirable process for the

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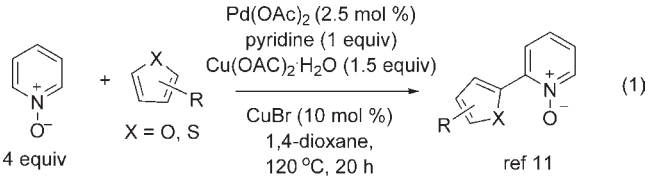
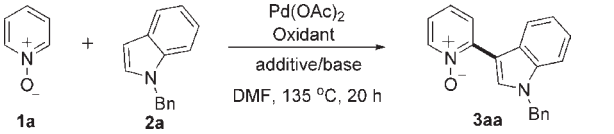
synthesis of biaryls.[6] Fagnou and DeBoef independently reported that Pd(II) can catalyze the oxidative cross-coupling between a heteroarene and a carbocyclic arene.[7] In particular, recent studies by the groups of Fagnou,[8] Hiyama,[9] Chang,[10] Hu and You,[11] and Cui and Wu[12] have shown that *N*-oxides of pyridines and quinolines can undergo C−H functionalization at the 2-position in a Pd- and Ni-catalyzed cross-coupling with arenes, heteroarenes, arylhalides, and olefins. Here bench-stable pyridine *N*-oxides can be regarded as a useful surrogate of 2-pyridyl organometallics and they function as an activated form of pyridine.[13] Given the significance of 2-aryl- and 2-vinylpyridines in material and medicinal chemistry, these processes represent powerful and atom-economic methods to access functionalized pyridines. Despite an increasing number of reports, 2-fold oxidative C−H functionalization remains a great challenge, especially when one of the coupling partners is an indole. This is because indoles are electron-rich heteroarenes that often undergo decomposition under oxidative conditions.[7d] In addition, azoles are also susceptible to oxidative homocoupling.[14] For example, DeBoef reported that the reaction conditions optimal for the Pd(II)-catalyzed oxidative coupling of benzofuran were inapplicable for indoles.[7d] We now report an oxidative cross-coupling between pyridine *N*-oxides and *N*-substituted indoles, where the functionalization occurred at the 3-position of indoles.



(1)

You, Hu, and co-workers recently reported a Pd(II)-catalyzed, copper(I)-promoted oxidative cross-coupling between pyridine *N*-oxides and electron-rich heteroarenes such as furans and thiophenes, where $Cu(OAc)_2 \cdot H_2O$ was used as an oxidant (eq 1).[11] When we applied these conditions and attempted to extend the heteroarene partners to indoles such as *N*-benzyl indole, the desired product **3aa** was obtained in only 12% NMR yield, together with decomposition products (Table 1, entry 1). Thus further screening of the reaction conditions is necessary. When $Pd(OAc)_2$ (10 mol %) was used as a catalyst and Ag_2CO_3 (2.3 equiv) as an oxidant (DMF, 135 °C), this reaction proceeded to give the coupled product in 35% NMR yield (entry 2, Table 1). The addition of 4 equiv of pyridine proved to be beneficial, and the yield was improved to 45%. Pyridine has been often used as an additive in palladium-catalyzed oxidation reactions,[15] and it likely serves to stabilize the palladium(II) catalyst.

Table 1. Synthesis of a 3-(2-Pyridyl)-indole[a]



	oxidant	base	additive (mol %)[b]	yield (%)[c]
1[d]	$Cu(OAc)_2 \cdot H_2O$	pyridine	CuBr (10%)	12
2	Ag_2CO_3	none	none	35
3	Ag_2CO_3	pyridine	none	45
4	Ag_2CO_3	Cs_2CO_3	none	18
5	Ag_2CO_3	K_2CO_3	none	22
6	Ag_2CO_3	pyridine	TBAB (20%)	88 (83[e], 81[f])
7	Ag_2CO_3	pyridine	TBAF (20%)	<10
8	Ag_2CO_3	pyridine	TBAC (20%)	<10
9	Ag_2CO_3	pyridine	TBAB (10%)	48
10	Ag_2CO_3	pyridine	TBAB (40%)	54
11	Ag_2CO_3	none	PivOH (30%) TBAB (20%)	70

[a] Conditions: *N*-benzyl indole (0.5 mmol), pyridine *N*-oxides (4 equiv), $Pd(OAc)_2$ (10 mol %), oxidant (2.3 equiv), base (4 equiv), additive, DMF (3 mL), 135 °C, 20 h. [b] TBAB = tetrabutylammonium bromide, TBAF = tetrabutylammonium fluoride, TBAC = tetrabutylammonium chloride. [c] NMR yield using 1,3,5-trimethoxybenzene as a standard. [d] $Cu(OAc)_2 \cdot H_2O$ (2.5 equiv), CuBr (10 mol %), pyridine (1 equiv), 1,4-dioxane (3 mL). [e] 5 mol % $Pd(OAc)_2$. [f] Isolated yield using 5 mol % $Pd(OAc)_2$.

We noted that when pyridine was replaced with other basic additives such as K_2CO_3 and Cs_2CO_3, a lower yield of **3aa** was obtained (entries 4 and 5). Further improvement

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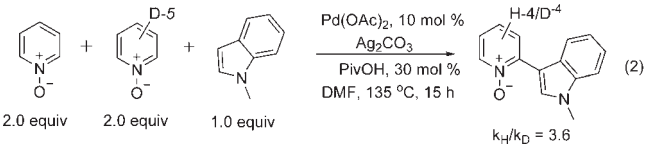
of the reaction efficiency was achieved when TBAB (20 mol %) was introduced as a coadditive, and **3a** was obtained in 88% NMR yield and 81% isolated yield (entry 6). Silver chunks or mirrors were observed after the reaction when TBAB was used. It is possible that this additive helps mediate or stabilize the Ag_2CO_3 oxidant. It should be mentioned that using other tetrabutylammonium salts such as TBAF, TBAC, and TBAI (20 mol %) or using a larger (40 mol %) or smaller (10 mol %) amount of TBAB all resulted in lower catalytic efficiency (entries 6−10). Screening of a few other silver oxidants such as AgOAc (3.0 equiv) and Ag_2O (2.3 equiv) revealed that Ag_2CO_3 was optimal (see Supporting Information). Under these optimized conditions (Conditions A), the loading of $Pd(OAc)_2$ can be reduced to 5 mol % without much loss of the catalytic activity (83% NMR yield of **3a**). In addition, further screening indicated that this reaction can be achieved with a slightly lower yield when the pyridine additive was replaced by 30 mol % PivOH (Conditions B, entry 11, Table 1). This transformation is high in site selectivity and chemoselectivity, and C−H functiozalization occurs at the 2-position of pyridine *N*-oxide and the 3-position of the indole, as evidenced by the NOE correlation between H(2) and NCH_2Ph protons in the indole ring. No double heteroarylation of pyridine *N*-oxides was observed.

The scope of this reaction is broad as given in Table 2. Pyridine *N*-oxide underwent smooth coupling with a variety of *N*-substituted indoles although the reaction for simple indole only gave decomposition products. The coupled products were isolated in high yields for the *N*-Me, -Bn, and -Ph substrates (entries 1−3). Various alkyl, halide, and alkoxyl substituents at the 2-, 5-, and 7-positions of indoles can be tolerated (entries 4−7), and the expected products were isolated in moderate to good yields. In contrast, no desired coupling was observed for 1,3-dimethylindole with the 3-position being blocked, which is consistent with selectivity for the C−H activation at the 3-position of indole. In addition to indoles, other heterocycles such as a pyrrole and an imidazole are also applicable (entries 8 and 10).



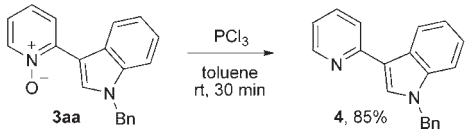
(2)

Intermolecular competition experiments between pyridine *N*-oxide and pyridine-d_5 *N*-oxide were carried out in the reaction with *N*-benzyl indole under the pyridine-free conditions (Conditions B). Under these conditions, intramolecular oxygen transfer from pyridine *N*-oxide or pyridine-d_5 *N*-oxide to pyridine, if any, can be avoided. A kinetic isotope effect of 3.6 was obtained (eq 2), which indicates that cleavage of the *N*-oxide C−H bond is involved in the rate-determining step.

The scope of the *N*-oxide substrate was further defined using *N*-benzyl and *N*-methyl indoles. Pyridine *N*-oxides with alkyl and aryl substituents at the 2-, 3-, and 4-positions all reacted smoothly (entries 11−15). In addition, *N*-oxides of pyrazine (entry 16), quinoline, and isoquinoline are also efficient substrates. In particular, the coupling of isoquinoline *N*-oxide is regioselective, and **3fa** was isolated in 70% as a single isomeric product, where the C−H bond at the (more hindered) 1-position undergoes cleavage (entry 15). This selectivity is consistent with that reported in the oxidative coupling of isoquinoline *N*-oxide with benzene,[10] and the observed selectivity is ascribed to electronic effects. Surprisingly, no coupling reaction occurred for 2,3-dimethylpyridine *N*-oxide under both Conditions A and B.

To our surprise, coupling reactions between 3-phenylpyridine *N*-oxide and indole **2b** performed under Conditions A afforded **3aa** as the major product, even though no simple pyridine *N*-oxide was provided. The more electron-poor, more oxidizing 3-phenylpyridine *N*-oxide likely undergoes oxygen atom transfer to pyridine (an additive in Conditions A) and in situ generated simple pyridine *N*-oxide. Thus it seems that conditions A are not applicable for pyridine *N*-oxides bearing electron-withdrawing groups. Under the pyridine-free Conditions B, this coupling proceeded smoothly and product **3hb** was isolated in 57% yield (entry 17); this coupling occurred at the *ortho* position that is less sterically hindered. Under Conditions B, Other pyridine *N*-oxides bearing withdrawing groups such 3-Br and 3-CN groups also smoothly coupled with indoles (entries 18−19), but ^{1}H NMR analysis of the coupled products **3ja** and **3ib** revealed that the selectivity is switched and the more hindered *ortho* C−H bond undergoes cleavage. Here the C−H activation is likely dominated by electronic effects when these 3-substituents are less bulky.

The coupled pyridine *N*-oxide products were easily deoxygenated to give the corresponding 2-heteroarylpyridines. Thus when **3aa** was treated with PCl_3 (rt, 30 min),[10] clean reduction occurred and **4** was obtained in 85% yield (eq 3). The combination of present C−H/C−H oxidative coupling and subsequent reduction constitutes an attractive synthetic route to access indole-functionalized pyridines. Although direct functionalization of pyridines at the 2-position is known,[16] the synthetic applications seem limited to pyridines that are substituted at one of the 2-positions. Furthermore, no direct heteroarylation of pyridines has been reported.



(3)

In summary, we have successfully developed a Pd(II)-catalyzed oxidative coupling between pyridine *N*-oxides (and analogues) and *N*-substituted indoles, a process that

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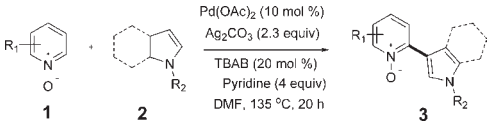
Table 2. Scope of the Pd-Catalyzed Indole/*N*-Oxides Cross-Coupling



entry	*N*-oxide	indole	product	yield (%)[b]	entry	*N*-oxide	indole	product	yield (%)[b]
1	1a	2a	3aa	81 (A)	11	1b	2a	3ba	74 (A)
2	1a	2b	3ab	76 (A)	12	1c	2a	3ca	72 (A)
3	1a	2c	3ac	72 (A)	13	1d	2a	3da	75 (A)
4	1a	2d	3ad	63 (A)	14	1e	2a	3ea	68 (A)
5	1a	2e	3ae	74 (A)	15	1f	2a	3fa	70 (A)
6	1a	2f	3af	58 (A)	16	1g	2a	3ga	62 (A)
7	1a	2g	3ag	60 (A)	17	1h	2b	3hb	57 (B)
8	1a	2h	3ah	67 (A)	18	1i	2b	3ib	45 (B)
9	1a	2i	3ai	56 (A)	19	1j	2a	3ja	52 (B)
10	1a	2j	3aj	54 (A)					

[a] Conditions A: indole (0.5 mmol), *N*-oxide (4equiv), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.3 equiv), pyridine (4 equiv), TBAB (20 mol %), DMF (3 mL), 135 °C, 20 h. Conditions B: indole (0.5 mmol), *N*-oxide (4 equiv), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.3 equiv), PivOH (30 mol %), TBAB (20 mol %), DMF (3 mL), 135 °C, 20 h. [b] Isolated yield, method after parentheses.

involves selective 2-fold activation of the C−H bond in both coupling partners. A broad scope of *N*-oxide and indole coupling partners has been defined. Mechanistic studies on the details of the C−H activation pathway are currently underway. Studies on oxidative C−H activation will be carried out using *N*-oxide compounds as built-in internal oxidants.[17]

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