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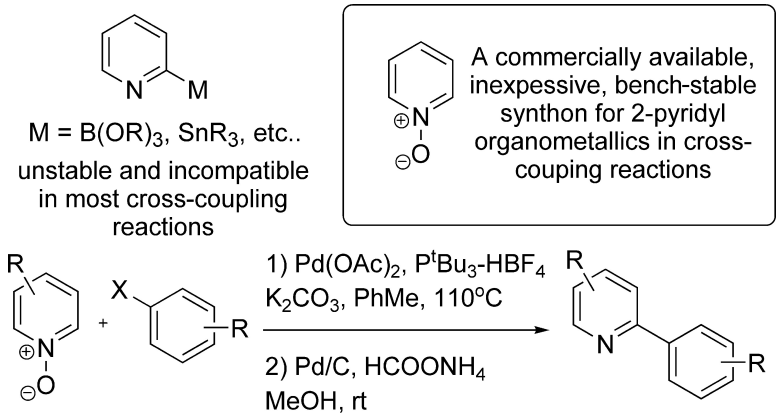

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A Solution to the 2-Pyridyl Organometallic Cross-Coupling Problem: Regioselective Catalytic Direct Arylation of Pyridine *N*-Oxides

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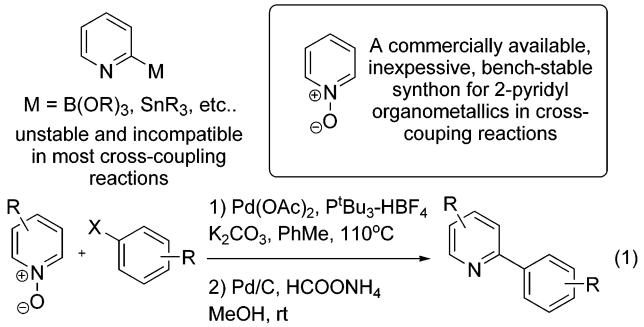
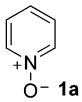
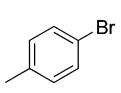
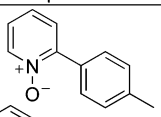
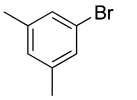
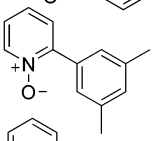
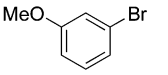
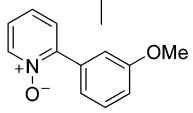
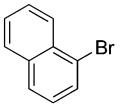
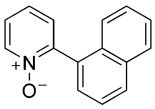
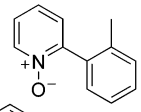
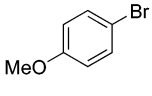
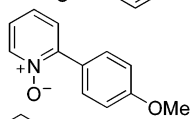
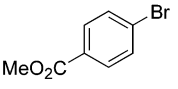
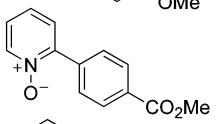
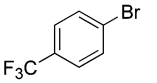
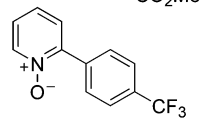
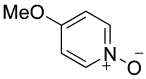
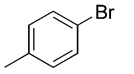
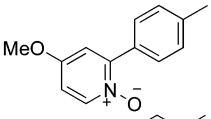
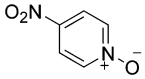
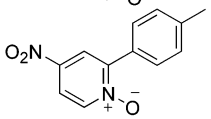
While transition metal catalyzed cross-couplings have been successfully employed with a wide range of halides and organometallics,[1] some substrate classes still pose significant challenges. This is the case with 2-pyridyl organometallics, whose frequent instability and difficult synthesis severely limits their application. For example, while the coupling of 2-halopyridines with aryl boronic acids is well precedented,[2] the inherent instability of 2-pyridyl boronic acid makes successful cross-couplings with this nucleophile rare.[3] Given the importance of 2-arylpyridines in materials[4] and medicinal chemistry,[5] the development of a readily available, bench-stable replacement for 2-pyridyl organometallics in cross-coupling reactions would find significant use in the preparation of this class of molecule.

In recent years, direct arylation has emerged as an attractive alternative to typical cross-coupling reactions.[6] In direct arylation, one of the preactivated cross-coupling partners (typically the organometallic species) is replaced by an unfunctionalized arene. Consistent with an electrophilic aromatic substitution (S_EAr) pathway, electron-rich heterocyclic arenes have been featured prominently in recent developments.[7] While some simple arenes can now be used,[8,9] direct arylation reactions with π-electron-deficient heteroarenes, such as pyridine, remain a challenging goal.[10] Herein we report the use of pyridine *N*-oxides as commercially available (or easily prepared),[11] inexpensive, bench-stable replacements for problematic 2-metallapyridines. Direct arylation reactions of pyridine *N*-oxides occur in excellent yield with complete selectivity for the 2-position with a wide range of aryl bromides (eq 1).



Reaction development was carried out with pyridine *N*-oxide and 4-bromotoluene. From these studies, palladium acetate in combination with tri-*tert*-butylphosphine (added to the reaction mixture as the commercially available and air-stable HBF_4 salt) emerged as the optimal metal−ligand combination. Potassium carbonate was deemed the optimal base, and toluene the optimal solvent.[12] The reactions are run under quite concentrated conditions (0.3 M), with 2−4 equiv of pyridine *N*-oxide. Under these conditions (4-bromotoluene, 2−4 equiv of pyridine *N*-oxide, 5 mol % of $Pd(OAc)_2$, 15 mol % of $P^tBu_3{\cdot}HBF_4$, 2 equiv of K_2CO_3 in toluene at 110 °C), 2-tolylpyridine *N*-oxide is obtained in 91% isolated yield exclusively as one regioisomer (Table 1, entry 1).[13] While 4 equiv of the *N*-oxide are not required, under the present conditions, a decrease to 1 equiv leads to diminished yields (entries 2−8). Importantly, when 1 equiv of **1a** is employed, greater than 95% of

Table 1. Regioselective Direct Arylation of Pyridine *N*-Oxides[a]

entry	*N*-oxide	aryl halide	product	yield[b]
1	 **1a**			91
2	**1a**			95
3	**1a**			89[c]
4	**1a**			76[d]
5	**1a**			45[e]
6	**1a**			97
7	**1a**			93[c]
8	**1a**			75[d]
9	**1a**			88
10	**1a**			87
11	**1a**			80
12	**1a**			74
13	**1a**			76
14	 **2a**			80
15	 **2a**			78

[a] Conditions: aryl halide (1 equiv), pyridine *N*-oxide (4 equiv), K_2CO_3 (2 equiv), $Pd(OAc)_2$ (0.05 equiv), and $P^tBu_3-HBF_4$ (0.15 equiv) in toluene (0.3 M) at 110 °C overnight. [b] Isolated yields. [c] With 3 equiv of **1a**. [d] With 2 equiv of **1a**. [e] With 1 equiv of **1a**.

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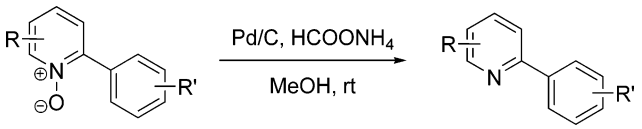
Table 2. Deoxygenation of 2-Arylpyridine *N*-Oxides[a]



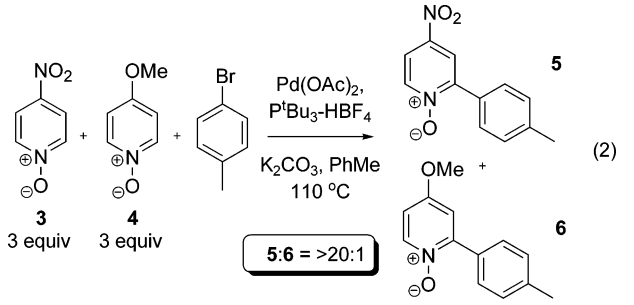
R	R′	yield (%)	R	R′	yield (%)
H	4-CH_3	95	4-OMe	4-CH_3	84
H	3-OMe	87	H	4-CO_2CH_3	87

[a] Conditions: pyridine *N*-oxide (1 equiv), Pd/C (0.1 equiv), $HCOONH_4$ (10 equiv), MeOH (0.2 M), room temperature.

the unreacted *N*-oxide can be recovered by silica gel chromatography, demonstrating that oxide decomposition is not occurring.

Illustrative examples of the reaction scope are included in Table 1. (Caution: Pyridine *N*-oxides have been shown to exothermically decompose at very high temperature.[14] Uncontrolled heating of the reaction media should be avoided.) A variety of substitution types and positions can be employed in these transformations. Both electron-rich (entries 6−8 and 11) and electron-poor (entries 12 and 13) aryl bromides are compatible, as are more sterically encumbered *ortho*-substituted arenes (entries 9 and 10).[15] The effect of substitution on the pyridine *N*-oxide has also been examined. The presence of both electron-donating and -withdrawing groups is tolerated, as exemplified by the successful coupling of both 4-methoxy and 4-nitropyridine *N*-oxide (entries 14 and 15). In contrast to reactions performed with many types of organometallics, these reactions are completely insensitive to the presence of water since 5 equiv of water added at the reaction outset has no deleterious impact on the reaction outcome. The 2-arylpyridine *N*-oxide products can easily be converted to the corresponding 2-aryl pyridines under mild conditions and in high yield via palladium-catalyzed reduction with ammonium formate (Table 2).[16]

The S_EAr mechanism has the strongest experimental support in direct arylation reactions.[7] Since pyridine *N*-oxides are known to react via S_EAr in other reactions,[17] a competition experiment was performed to determine if this pathway was operative. Under the standard conditions, 4-bromotoluene was reacted in the presence of both electron-deficient 4-nitropyridine *N*-oxide **3** and electron-rich 4-methoxypyridine *N*-oxide **4** (eq 2). In stark contrast to direct arylation reactions, which typically react preferentially with the more electron-rich substrate,[7] the only product detected by ^1H NMR analysis of the crude reaction mixture was **5**, arising from reaction of the more electron-deficient pyridine *N*-oxide. In another reaction, 3 equiv of pyridine and pyridine-d_5 *N*-oxides was reacted in one pot, revealing an intermolecular primary KIE of 4.7. These results are incompatible with an S_EAr mechanism, and we are currently working to elucidate the mode of direct arylation of these molecules.



(2)

In conclusion, palladium-catalyzed regioselective direct arylation of pyridine *N*-oxides occurs in high yield with a wide range of aryl bromides. The resulting 2-arylpyridine *N*-oxides can be easily reduced to the free pyridine via palladium-catalyzed hydrogenolysis. Preliminary mechanistic probes indicate that an S_EAr mechanism is not operative. Given the ready availability and low cost associated with the use of pyridine *N*-oxides, these reactions should find significant use in the preparation of these types of molecules and provide a useful alternative to the problematic use of 2-pyridyl organometallics in cross-coupling reactions.

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Supporting Information Available: Experimental procedures and spectroscopic characterization of all new products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Other solvents, such as dioxane, mesitylene, and *N*,*N*-dimethylacetamide, can also be employed.

(13) Free pyridine is unreactive under these conditions.

(14) Examples of exothermic onset temperatures (T_o) for pyridine *N*-oxide, 288 °C; 2,6-lutidine *N*-oxide, 288 °C; nicotinic acid *N*-oxide, 302 °C; γ-picoline *N*-oxide, 285 °C; picolinic acid *N*-oxide, 307 °C, from: Ando, T.; Fujimoto, Y.; Morisaki, S. *J. Haz. Mater.* **1991**, *28*, 251.

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