

Published on Web 11/30/2005

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 materials⁴ 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 HBF₄ 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-



^{*a*} Conditions: aryl halide (1 equiv), pyridine *N*-oxide (4 equiv), K_2CO_3 (2 equiv), $Pd(OAc)_2$ (0.05 equiv), and $P'Bu_3$ -HBF₄ (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**.

 $(OAc)_2$, 15 mol % of P'Bu₃·HBF₄, 2 equiv of K₂CO₃ 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



^{*a*} Conditions: pyridine *N*-oxide (1 equiv), Pd/C (0.1 equiv), HCOONH₄ (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 palladiumcatalyzed 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 electronrich 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, 3 equiv of pyridine and pyridine *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.



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.

Acknowledgment. We thank NSERC, the Canada Foundation for Innovation, the Ontario Innovation Trust, and the University of Ottawa, the Ontario government (PREA, K.F.), and the Research Corporation (Cottrell Scholar Award, K.F.) for support of this work. L.-C.C. thanks the Canadian government for a NSERC-PGS D scholarship. S.R. thanks NSERC for a summer undergraduate scholarship.

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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