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Direct C−H Functionalization of Pyridine via a Transient Activator Strategy: Synthesis of 2,6-Diarylpyridines

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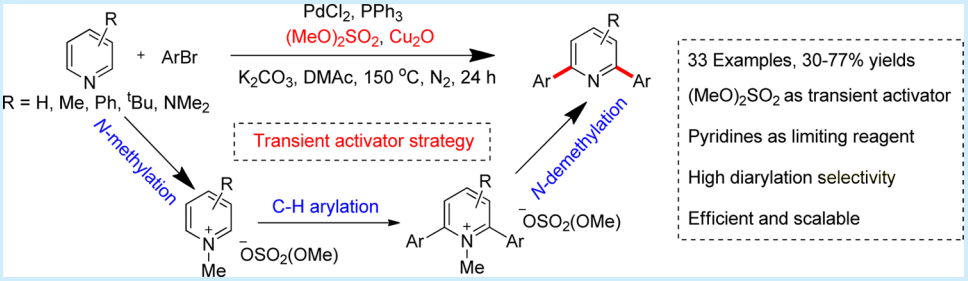
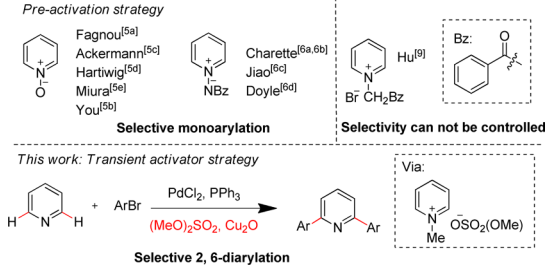
Supporting Information



ABSTRACT: A Pd-catalyzed highly selective direct diarylation of pyridines has been developed using a transient activator strategy. Both $(MeO)_2SO_2$ and Cu_2O are required for this transformation. The in situ generated *N*-methylpyridinium salt can be arylated at both 2- and 6-positions under the cooperative Pd/Cu catalysis. A subsequent *N*-demethylation then gives the 2,6-diarylpyridines. This protocol provides a novel synthetic route for the symmetric 2,6-diarylpyridines.

The transition-metal-catalyzed direct C−H arylation of pyridine is of great interest to the chemical community due to the presence of arylpyridines in natural products, pharmaceutical agents, and other organic materials.[1] The pyridine ring suffers from low reactivity due to its electronically deficient nature and strong Lewis basicity; thus, direct pyridine C−H functionalization is particularly challenging.[2] Although significant progress has been made in the development of methodologies for direct arylation on the pyridine ring,[3] a large excess of pyridine is often required.[4] A pyridine preactivation strategy has been widely applied in pyridine arylation reactions. Pioneering work in this field has been reported by Fagnou, Hiyama, Hartwig, Charette, and other groups, who have demonstrated a selective direct *ortho*-monoarylation of pyridine using *N*-oxides[5] or *N*-imino-pyridiniumylides[6] (Scheme 1). However, these preactivation strategies have a major limitation in that an additional step is required for installation and removal of the activating group. Therefore, the direct C−H arylation of a stoichiometric amount of unmasked pyridine without using a preactivation strategy is especially appealing. Additionally, symmetric 2,6-diarylpyridines are very important structural motifs and are found in many biologically active compounds and functional materials;[7] however, a highly selective synthesis of 2,6-diarylpyridines via a double C−H functionalization remains, to the best of our knowledge, undocumented.

Scheme 1. Activation Strategies for Pyridine Arylation



Recently, traceless or transient directing group strategies have attracted much attention.[8] Such approaches allow for sequential installation of the directing group, C−H bond functionalization of the substrate, and removal of the directing group in one reaction. These protocols not only avoid additional steps to remove the undesired directing group but also offer unique positional selectivity. Inspired by these strategies, a transient activator strategy has been proposed to activate the unmasked pyridine substrates. In this strategy, the pyridine would be activated by in situ formation of the *N*-alkylpyridinium salt in the presence of an alkylating reagent, which may facilitate C−H arylation at both the C-2 and C-6 positions of pyridine. Subsequent dealkylation of the resulting pyridinium salt would give the 2,6-diarylpyridines. In 2009, Hu reported a direct Pd-catalyzed *ortho*-arylation of pyridine by using a pre-alkylated pyridine (*N*-phenacylpyridinium

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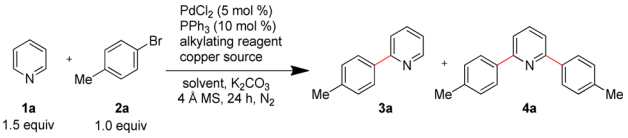
Table 1. Identification of the Transient Activator[a]



entry	alkylating reagent	copper source	solvent	yield (%) 3a+4a	ratio 4a/3a
1	MeI	Cu_2O	DMAc	trace	–
2	*p*-$MeC_6H_4SO_3Me$	Cu_2O	DMAc	11	–
3	BnBr	Cu_2O	DMAc	6.4	–
4	$PhCOCH_2Br$	Cu_2O	DMAc	trace	–
5	$(MeO)_2SO_2$	Cu_2O	DMAc	46	10:1
6	$(MeO)_2SO_2$	CuCl	DMAc	43	6:1
7	$(MeO)_2SO_2$	$CuCl_2$	DMAc	36	1:1
8	$(MeO)_2SO_2$	$CuSO_4$	DMAc	15	2:1
9	$(MeO)_2SO_2$	CuO	DMAc	38	3:1
10	none	Cu_2O	DMAc	NR	–
11	$(MeO)_2SO_2$	Cu_2O	DMF	43	2:1
12	$(MeO)_2SO_2$	Cu_2O	Diglyme	44	8:1
13	$(MeO)_2SO_2$	Cu_2O	NMP	8	–
14[b]	**$(MeO)_2SO_2$**	**Cu_2O**	**DMAc**	**62**	**8:1**

[a]Reaction conditions: **1a** (0.75 mmol), **2a** (0.5 mmol), $PdCl_2$ (5 mol %), PPh_3 (10 mol %), K_2CO_3 (2.0 equiv), copper source (0.75 equiv), alkylating reagent (0.8 equiv), solvent (2.5 mL), 4 Å MS (100 mg), 120 °C, 24 h, nitrogen atmosphere. Yield was determined by ^1H NMR analysis of a crude product with CH_2Br_2 as an internal standard. [b]Reaction run at 150 °C.

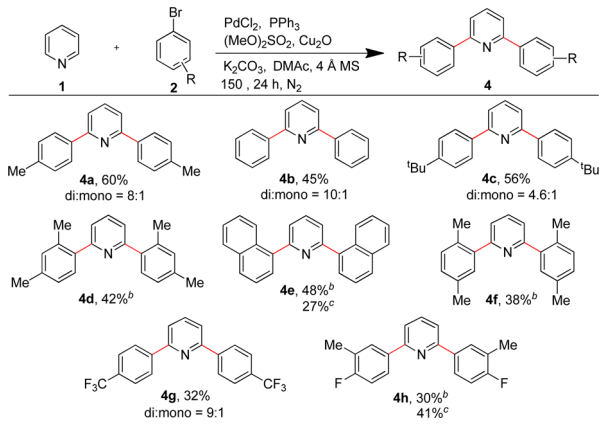
bromide) as a substrate; however, the di-/monoarylation selectivity could not be controlled[9] (Scheme 1). We anticipated that a proper alkylating reagent could be adopted as a transient activator, which can be installed and removed in situ, as well as serve as a directing group to control the selectivity. Herein, we report that a combination of the *N*-alkylating reagent dimethyl sulfate $(MeO)_2SO_2$ with Cu_2O allows for the activation of both the C_2–H and C_6–H bonds of pyridine for a highly selective diarylation in the presence of a Pd(II) catalyst (Scheme 1).

Our initial studies began by testing different alkylating reagents using the following reaction conditions: pyridine **1a** (0.75 mmol), 1-bromo-4-methylbenzene **2a** (0.5 mmol), $PdCl_2$ (5.0 mol %), PPh_3 (10 mol %), and K_2CO_3 (2.0 equiv) in *N*,*N*-dimethylacetamide (DMAc) at 120 °C under a nitrogen atmosphere. Unfortunately, commonly used alkylating reagents such as MeI, $(MeO)_2SO_2$, *p*-$MeC_6H_4SO_3Me$, BnBr, and $PhCOCH_2Br$ were all inefficient, and no desired diarylation product was detected (see the Supporting Information (SI) Table 1). However, the diarylation was able to proceed in the presence of both an alkylating reagent and a copper source (Table 1, entries 1–5 and SI Table 1). The optimal combination was found to be Cu_2O and $(MeO)_2SO_2$, wherein the arylation products could be obtained in 46% yield with a di/mono ratio of 10:1 (Table 1, entry 5). Cu(II) sources including $CuCl_2$, $CuSO_4$, and CuO gave lower yields, with poor di/mono selectivity ranging from 1:1 to 3:1 (Table 1, entries 7–9). CuCl was found to be as active as Cu_2O, affording the arylation product in comparable yield but with lower selectivity (Table 1, entry 6). No product was produced in the absence of either Cu_2O or $(MeO)_2SO_2$ (Table 1, entry 10, and SI Table 1, entry 5). It appears that some cooperative effect exists between the Cu species and $(MeO)_2SO_2$,[10] which is important for the double C–H arylation process.

Solvent screening showed that *N*,*N*-dimethylformamide (DMF), Diglyme, and DMAc afforded the arylation product in comparable yield, while the highest diselectivity was obtained in DMAc (Table 1, entries 5, 11–13). Elevation of the temperature to 150 °C increased the yield markedly to 62% (Table 1, entry 14). However, altering other reaction parameters at this stage failed to further improve the yield (see SI Tables 1 and 2). Although the diarylation of pyridine provided only a moderate yield of the desired product, it still represents remarkable progress, since it avoids the use of a large excess of pyridine.

With the optimal reaction conditions in hand, we subsequently examined the substrate scope and the limitations of the reaction by employing a variety of pyridines and aryl halides as coupling partners (Schemes 2 and 3). Various aryl bromides could couple with pyridine (Scheme 2), giving the corresponding diarylation product **4a–h** in synthetically useful yields with high di/mono selectivity. Of note is that 2,4- or 2,5-dimethylbromobenzene could also be coupled with pyridine to give **4d** and **4f** in 42% and 38% yields, respectively, regardless of the steric hindrance. It

Scheme 2. Scope of the Arylation of Pyridine with Bromoarenes[a]



[a]Reaction conditions: $(MeO)_2SO_2$ (0.8 equiv), Cu_2O (0.75 equiv), 150 °C; the others are the same as those described in Table 1; isolated yields reported as the average of two experiments. [b]Only trace amount of monoarylation product was detected. [c]**1** (0.5 mmol), **2** (1.5 mmol); the other conditions are the same as those described in Table 1

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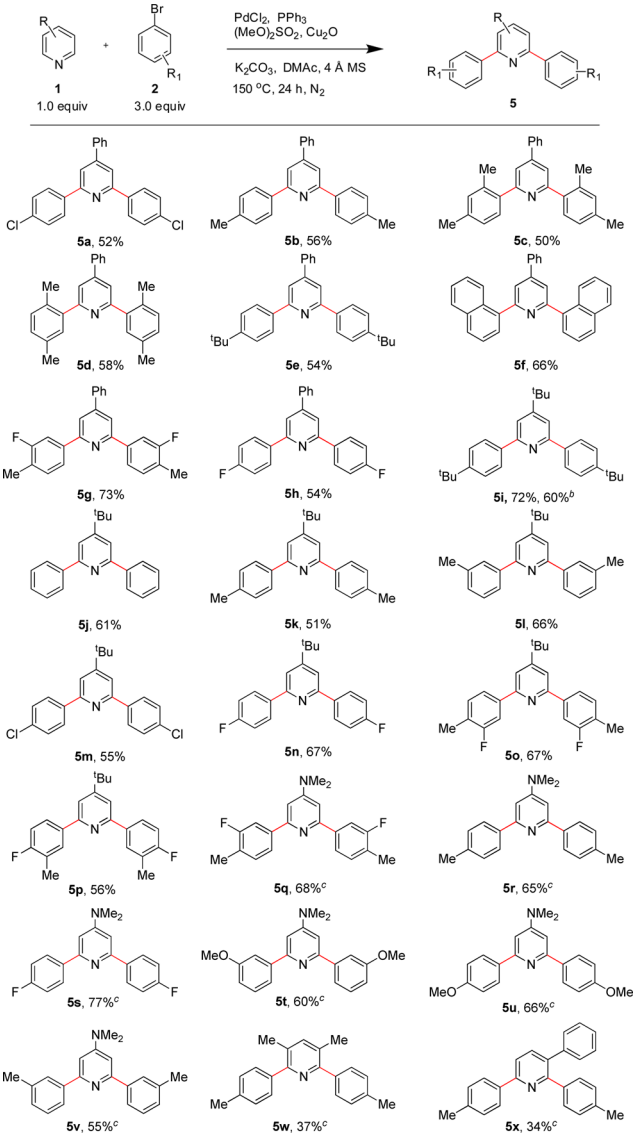
Scheme 3. Scope of the Arylation of Substituted Pyridine with Bromoarenes[a]



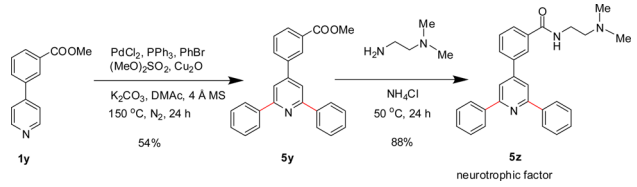
[a]Reaction conditions: **1** (0.125 mmol), **2** (0.375 mmol), $PdCl_2$ (10 mol %), PPh_3 (20 mol %), K_2CO_3 (2.0 equiv), $(MeO)_2SO_2$ (1.6 equiv), Cu_2O (1.5 equiv), DMAc (2.5 mL), 150 °C, 4 Å MS (50 mg), 24 h, N_2 atmosphere. Isolated yields reported as the average of two experiments. [b]The reaction was scaled up to 32-fold. [c]Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), $PdCl_2$ (5 mol %), PPh_3 (10 mol %), K_2CO_3 (4.0 equiv), $(MeO)_2SO_2$ (0.8 equiv), Cu_2O (0.5 equiv), DMAc (2.5 mL), 150 °C, 4 Å MS (100 mg), 72 h, N_2 atmosphere.

should be mentioned that even using pyridine as the limiting reagent (**1**/**2e** or **2h** = 1:3) also successfully afforded diarylation products (**4e** or **4h**).

Next the substituted pyridines, used as the limiting reagent, were investigated under slightly modified reaction conditions (Scheme 3). Gratifyingly, the coupling of symmetrically substituted pyridines with aryl bromides bearing various substitution patterns afforded the expected products **5a**–**w** in moderate to good yields. In all cases, the 2,6-diarylpyridine was almost exclusively formed, with only a trace amount of monoarylation product being detected. It should also be noted that the Cl atom was also tolerated (**5a** and **5m**), serving as a potential handle for further transformations. Furthermore, the reaction could be easily scaled up: 4-*tert*-butylpyridine reacted with 4-*tert*-butylbromobenzene smoothly by 32-fold to give product **5i** in 60% isolated yield. In the case of 4-dimethylamino-pyridine, which contains the strong electron-donating group $-NMe_2$ at the 4-position, a longer reaction time was required to achieve comparable yields. This might be attributed in part to the relatively low demethylation reactivity of the corresponding *N*-methyl diarylpyridinium salt.[11] Significantly, the unsymmetrically substituted pyridine, 3-phenylpyridine with a congested 2-position, also afforded its corresponding diarylation product **5x** with high selectivity, albeit in only 34% isolated yield.

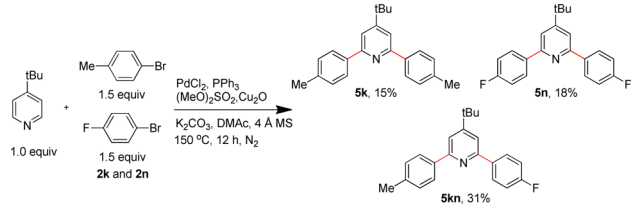
This high-level site-selective C–H arylation method would greatly improve its applicability in the late stages of synthesis of biologically active compounds. For example, by employing our methodology, a neurotrophic factor **5z** could be synthesized from **1y** in only two steps with a 48% overall isolated yield (Scheme 4), demonstrating the efficiency of this approach.

Scheme 4. Synthesis of Neurotrophic Factor



An intermolecular competition experiment was conducted using 4-*tert*-butylpyridine with an equimolar ratio of 4-methyl and 4-fluorobromobenzene (Scheme 5). An unsymmetric diary-

Scheme 5. Intermolecular Competition Studies



lpyridine **5kn** was formed with a much higher ^1H NMR yield than both the symmetrical diarylpyridines **5k** and **5n** (31% versus 15% and 18%, respectively). Almost no monoarylation product was detected. This provides a potential opportunity for the synthesis of unsymmetrical diarylpyridines using a one-pot process. We reasoned that, in the presence of transient activator $(MeO)_2SO_2$, the pyridine reactivity was significantly enhanced via in situ formation of a *N*-methylpyridinium salt. The arylation process was so fast that once the monoarylation product of *N*-methylpyridinium salt was generated, the second arylation occurred to give the diarylated pyridinium compound, which was more prone to undergo the *N*-demethylation to give a final product. It was reported that *N*-methyl-pyridinium salt could be demethylated by heating in amide solvent under reflux.[11] Thereby, the strategy features high reactivity and exquisite di/mono selectivity. The existence of both the mono- and diarylated pyridinium compounds was evidenced by HRMS analysis of the crude reaction mixture at the initial stage of the reaction (see SI Figure 2). Indeed, the reaction of the prepared *N*-methyl 4-*tert*-butylpyridinium methyl sulfate with 1-bromo-4-methylbenzene could furnish the expected 2,6-diarylated product **5k** (see SI eq 1).

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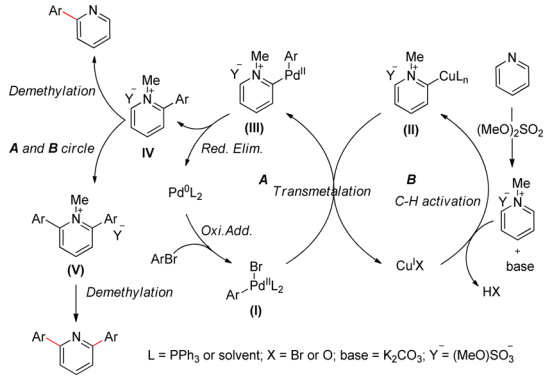
These results further proved that the *N*-methylpyridinium salt was an important intermediate.

However, when the reaction between the *N*-methylpyridinium methyl sulfate and the 1-bromo-4-methylbenzene was performed in the absence of Cu_2O, no 2,6-diarylated pyridine was detected (see SI eq 2). We supposed that the Cu_2O might play an important role in the *ortho* C−H bond cleavage of the pyridinium salt. Indeed, an HRMS spectrum of the reaction solution of *N*-methylpyridinium methyl sulfate with Cu_2O showed a peak at 212.0492 *m/z*, indicating the involvement of a Cu-pyridinium species in the reaction (see SI eq 3 and Figure 3). We also carried out the kinetic isotope effect (KIE) studies (see SI eq 4). A typical secondary KIE of 1.08 indicated that the C−H bond breaking of pyridine may not be related to the rate-limiting step.

On the basis of the above results, a possible reaction mechanism has been proposed (Scheme 6). First, oxidative addition of ArBr

Scheme 6. Proposed Catalytic Mechanism



to the *in situ* formed Pd(0) affords species **I**. The transmetalation of **I** with Cu^I pyridyl species **II**, most likely generated from the reaction of Cu_2O with the methylated pyridine, gives the Pd intermediate **III**. Reductive elimination of Pd(0) from **III** produces **IV**. Compound **IV** then either undergoes demethylation to afford the monoarylated pyridine or re-enters the catalytic cycle to give compound **V**, which is subsequently demethylated, furnishing the major product 2,6-diarylpyridine.

In summary, we have developed a simple protocol for the straightforward synthesis of 2,6-diarylpyridines by Pd-catalyzed one-pot double C−H arylation of pyridine using a transient activator strategy. The presence of $(MeO)_2SO_2$ as a transient activator reagent, in combination with Cu_2O as an additive, is essential for this transformation. A plausible catalytic mechanism involving *N*-methylation, C−H arylation, and demethylation has been tentatively proposed based on the experimental results

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00498.

Typical experimental procedures, characterization data, ^1H and ^{13}C NMR spectra for new compounds, and X-ray crystallographic analysis (PDF)

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Notes

The authors declare no competing financial interest.

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