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Ligand-Promoted C3-Selective Arylation of Pyridines with Pd Catalysts: Gram-Scale Synthesis of (±)-Preclamol

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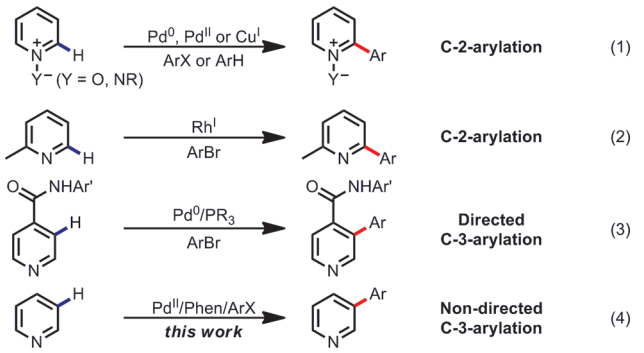
Supporting Information

ABSTRACT: The first example of Pd-catalyzed, C3-selective arylation of unprotected pyridines has been developed by employing a catalytic system consisting of $Pd(OAc)_2$ and 1,10-phenanthroline. This protocol provides an expeditious route to an important class of 3-arylpyridines and 3-arylpiperidines frequently found in bioactive compounds. A brief synthesis of the drug molecule (±)-preclamol is also reported.

Transition-metal-catalyzed C−H arylation of heteroarenes has recently emerged as a promising strategy for the construction of various biologically important heterobiaryls.[1] While a range of heteroarenes have been shown to be suitable substrates for these processes,[1,2] arylation of pyridines has remained an outstanding challenge because they are electron-poor and have a tendency to adopt a nonproductive N-bound coordination mode with metal centers.[3,4] Protection of the nitrogen via conversion to *N*-oxides and *N*-iminopyridinium ylides has allowed for the development of several C2-selective arylation reactions of pyridines (eq 1).[5] Significant work on the C2-selective arylation of unprotected 2-methylpyridine has also been reported (eq 2).[6−8] In sharp contrast, intermolecular C3- and C4-selective arylation reactions of pyridines have been achieved only with perfluoropyridines,[9,10] pyridines containing a directing group[11] (eq 3), or pyridines with a strong electron-withdrawing group at the C4 position.[12] Herein we report the first C3-selective arylation of pyridines using a catalyst generated in situ from $Pd(OAc)_2$ and 1,10-phenanthroline (Phen) (eq 4), wherein no additional substituents are required for the reactivity or selectivity.



We recently reported a C3-selective olefination reaction of pyridines using a $Pd(OAc)_2$/Phen catalytic system.[13] Our working hypothesis was that the unexpectedly high levels of reactivity with this catalyst could be a result of the strong bidentate coordination of the Phen ligand, which would destabilize the N-bound coordination mode of the pyridine substrates with Pd. The enhanced dissociation rate would increase the local concentration of the pyridine substrate around the Pd catalyst with various orientations with respect to the Pd center. Under these circumstances, it is possible that C3-selective C−H cleavage could take place when the appropriate orientation between the π system of the pyridine and Pd is assembled. Since the C3-selective arylation of pyridines has long been identified as a significant challenge by the medicinal chemistry community, we directed our efforts toward exploiting this newly observed reactivity to develop a C3-selective arylation of pyridines.

Although important advances in C3- and C4-selective arylation of pyridines have been made using $Pd(0)/PR_3$/ArX systems combined with substrate control,[11,12] we decided to focus on Pd(II)/ligand systems because of the long-term potential for developing a broader range of transformations. Guided by the previous conditions developed in our C3-selective olefination reaction, we investigated the arylation of pyridine (**1a**) with 4-iodotoluene (**2a**). We initially found that the arylated product could be obtained in 11% yield under conditions analogous to those for our olefination reaction. However, to our disappointment, a 12/1/6 (C3/C4/C2) mixture of isomers was found (Table 1, entry 1). During exploratory studies, we found that silver salts, which are commonly used as halide scavengers, were unnecessary. Inorganic bases had a dramatic effect; among those tested, only K_2CO_3, K_3PO_4, CsF, and Cs_2CO_3 were effective, and 3 equiv of Cs_2CO_3 improved the yield to 74% with excellent C3 selectivity (C3/C4/C2 ratio = 25/1/1, entry 2), demonstrating that external oxidants are not needed for this reaction. Importantly, we found that increasing the ligand loading from 13 to 30 mol % significantly improved the yields and selectivities (entries 3−8). When a Pd/ligand ratio of 1/3 was maintained, the Pd loading could be reduced to 5 mol % without a significant reduction in the yield (entry 9). Arylation with 2 mol % $Pd(OAc)_2$ afforded a lower yield (50%, entry 10). Other ligands, such as bipyridines, substituted phenanthrolines, and triphenylphosphine gave either poor yields or no product (entries 11−16). Under the best conditions, excess pyridine substrate was still

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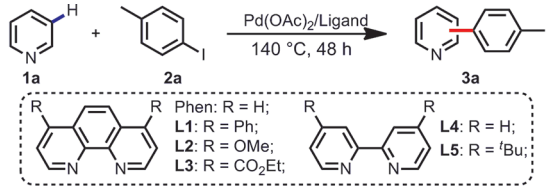
Table 1. Optimization of Conditions[a]



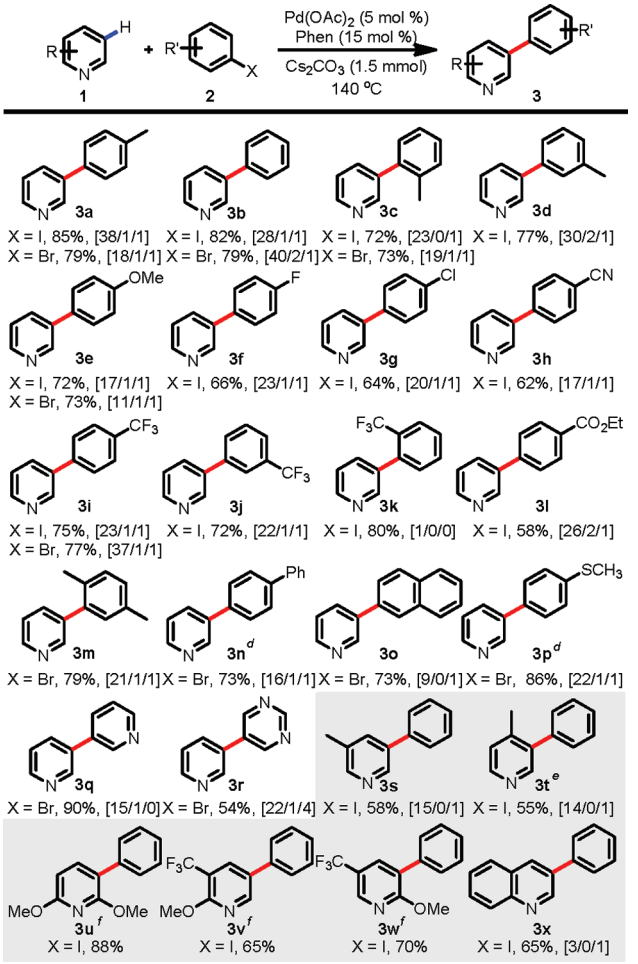
entry	$Pd(OAc)_2$ (mol %)	ligand (mol %)	additive (equiv)	yield (%)[b]
1	10	Phen (13)	Ag_2CO_3 (1.0)	11 [c]
2	10	Phen (13)	Cs_2CO_3 (3.0)	74 [d]
3	0	Phen (13)	Cs_2CO_3 (3.0)	0
4	10	Phen (0)	Cs_2CO_3 (3.0)	4
5	10	Phen (5)	Cs_2CO_3 (3.0)	40
6	10	Phen (20)	Cs_2CO_3 (3.0)	89
7	10	Phen (30)	Cs_2CO_3 (3.0)	93 [e]
8	10	Phen (40)	Cs_2CO_3 (3.0)	90
9	5	Phen (15)	Cs_2CO_3 (3.0)	92 (85) [e]
10	2	Phen (6)	Cs_2CO_3 (3.0)	50
11	5	**L1** (15)	Cs_2CO_3 (3.0)	41
12	5	**L2** (15)	Cs_2CO_3 (3.0)	0
13	5	**L3** (15)	Cs_2CO_3 (3.0)	28
14	5	**L4** (15)	Cs_2CO_3 (3.0)	0
15	5	**L5** (15)	Cs_2CO_3 (3.0)	8
16	5	Ph_3P (15)	Cs_2CO_3 (3.0)	8
17	5	Phen (15)	Cs_2CO_3 (3.0)	18 [f]
18	5	Phen (15)	Cs_2CO_3 (3.0)	81 [g]

[a] Reaction conditions: pyridine (3.0 mL) and **2a** (0.5 mmol) at 140 °C for 48 h. [b] Total yields of all isomers, as determined by ^1H NMR analysis of the reaction mixtures. [c] C3/C4/C2 isomer ratio calculated from the isolated yields was 12/1/6. [d] C3/C4/C2 isomer ratio was 25/1/1. [e] The isolated yield is given in parentheses; the C3/C4/C2 ratio was 38/1/1. [f] Pyridine (0.24 mL, 3.0 mmol) with DMF (1 mL) was used. [g] Pyridine (2.0 mL, 25 mmol) with DMF (1 mL) was used.

needed to obtain synthetically useful yields. The yield was found to decrease significantly from 92 to 18% when pyridine was reduced to 6 equiv in 1 mL of *N*,*N*-dimethylformamide (DMF) (entry 17). The use of 50 equiv of pyridine in 1 mL of DMF, however, afforded the arylated product in 81% yield (entry 18). The compatibility of this catalytic reaction with DMF solvent is important for further development of more efficient catalysts to reduce the stoichiometry of the pyridine substrate to 1 equiv.

With the optimized conditions in hand, we next examined the scope of aryl halide coupling partners using simple pyridine **1a** as the substrate (unshaded entries in Table 2). Excellent functional group compatibility was found among the aryl iodides that were tested. Both electron-donating (**3a**−**e**) and electron-withdrawing (**3f**−**l**) substituents at the para, meta, or ortho position were tolerated, giving the corresponding arylated products in good yields with high levels of C3 selectivity. Importantly, readily available aryl bromides also proved to be suitable coupling partners (**3a**−**c**, **3e**, **3i**, and **3m**−**r**). We were pleased to find that an aryl bromide containing a sulfur atom (**3p**) worked in this reaction to give a yield of 86% with high C3 selectivity. Unfortunately, aryl chlorides were found to be unreactive under these conditions. Next, we examined the reactivity of nitrogen-containing heteroaryl bromides. Gratifyingly, these reactions proceeded smoothly, providing an attractive route for the synthesis

Table 2. C3-Selective Arylation of Pyridines [a,b,c]



[a] Reaction conditions: **1** (3.0 mL), **2** (0.5 mmol), $Pd(OAc)_2$ (5 mol %), ligand (15 mol %), and Cs_2CO_3 (1.5 mmol) at 140 °C for 48 h. [b] Isolated yields are given. [c] C3/C4/C2 isomer ratios were calculated from the isolated yields. [d] Run for 96 h. [e] $Pd(OAc)_2$ (15 mol %) and ligand (45 mol %) were used. [f] **1** (30 mmol) with 1 mL of DMF was used.

of biologically important heterobiaryls (**3q** and **3r**). It is worth noting that these C3-arylated biaryls prepared from simple pyridine are highly desirable building blocks for the synthesis of diverse heterobiaryls using the known C2- and C4-selective C−H functionalization reactions.[3−10]

The scope of pyridine substrates was also briefly surveyed (shaded entries in Table 2). 3-Picoline (**3s**) gave a yield of 58% with high C3 selectivity, but 4-picoline (**3t**) was less reactive, possibly because of steric hindrance; 15 mol % $Pd(OAc)_2$ was used to give a 55% yield. Electron-withdrawing groups on the pyridine ring significantly reduced the reactivity. However, the introduction of a methoxy group at C2 was found to restore the reactivity in the presence of an electron-withdrawing CF_3 group (**3u**−**w**). Quinoline could also be arylated in 65% yield, albeit with lower C3 selectivity (**3x**).

3-Arylpyridines and 3-arylpiperidines are important classes of bioactive heterocycles that are difficult to access.[14] To demonstrate the applicability of this method in the synthesis of these types of molecules, we prepared C3-arylated pyridine **3y** on a gram scale under the optimized conditions (Scheme 1).

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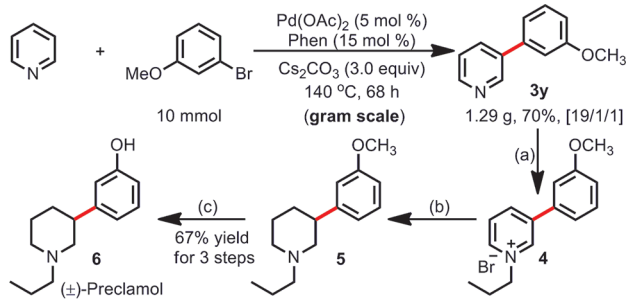
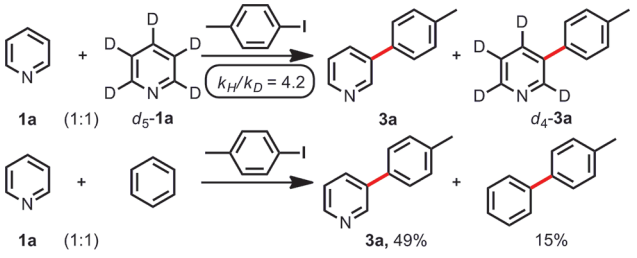
Scheme 1. Synthesis of (±)-Preclamol[a]



[a] Reagents and conditions: (a) 1-bromopropane, CH_3CN, 110 °C; (b) PtO_2, MeOH, H_2 (60 psi), room temperature; (c) HBr in HOAc (33%), reflux.

Scheme 2. Kinetic Isotope Effects and Competition Reactions[a]



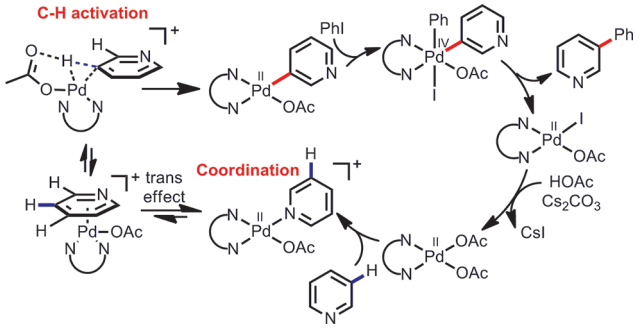
[a] Reagents and conditions: $Pd(OAc)_2$ (5 mol %), Phen (15 mol %), 4-iodotoluene (0.5 mmol), Cs_2CO_3 (1.5 mmol), substrates [37.5 equiv, 37.5 equiv (1:1)], 140 °C, 48 h.

Propylation of the nitrogen atom of the pyridine ring followed by chemoselective hydrogenation and demethylation afforded the racemic form of the preclinical drug preclamol[15] in 67% yield over three steps. In comparison with previous approaches requiring expensive air- or moisture-sensitive organometallic reagents,[16] the current method is advantageous for rapid library synthesis in drug discovery because of its operational simplicity and broad availability of starting materials.

During our mechanistic investigation, we found that two preliminary observations warrant discussion. A significant isotope effect was observed ($k_H/k_D = 4.2$, Scheme 2), indicating that classical Fujiwara-type electrophilic palladation may not be operative. A concerted metalation/deprotonation (Martinez pathway) to form the C−Pd bond at the C3 position is a plausible mechanistic pathway.[17] At this stage, the S_EAr mechanism involving a rate-limiting deprotonation cannot be ruled out. The decrease in reactivity with electron-deficient 3-nicotinate (15% yield) and sterically hindered 2-picoline (38% yield, C3/C5 = 1/2) suggests that coordination of the π ring with the Pd(II) center is required. Intriguingly, competition experiments between pyridine and electron-rich benzene (both in one pot and in separate parallel reactions) showed that pyridine is significantly more reactive than benzene (Scheme 2). At this stage, we attribute the superior reactivity of pyridine to its initial coordination to the Pd center via the nitrogen and subsequent dissociation into the vicinity, allowing it to achieve a higher effective molarity than benzene.

On the basis of the above observations, a plausible mechanism for this reaction is proposed in Scheme 3. The N-bound pyridine

Scheme 3. Plausible Mechanism



substrate dissociates from Pd, assisted by the ligand. Pyridine subsequently reorients itself to bind to Pd through the π system, which triggers C3−H activation to form the aryl−Pd(II) species. Oxidative addition of iodobenzene to this intermediate followed by reductive elimination furnishes the desired 3-phenylpyridine.

In summary, non-directed C3-selective arylation of unprotected pyridines has been developed for the first time using a catalyst generated in situ from $Pd(OAc)_2$ and Phen. The utility of this methodology has been demonstrated in a concise synthesis of the drug molecule (±)-preclamol.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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