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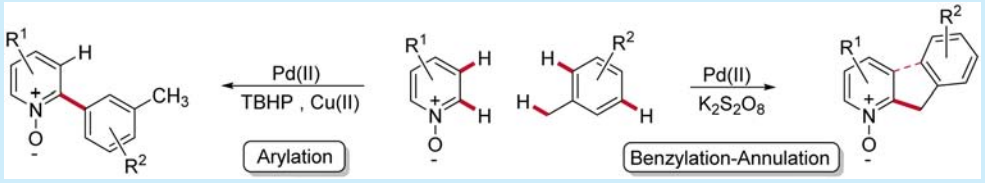
Palladium-Catalyzed Regioselective Benzylation–Annulation of Pyridine *N*-Oxides with Toluene Derivatives via Multiple C–H Bond Activations: Benzylation versus Arylation

Ebrahim Kianmehr,*[,†] Nasser Faghih,[†] and Khalid Mohammed Khan[‡]

[†]School of Chemistry, College of Science, University of Tehran, Tehran 1417614411, Iran

[‡]H. E. J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi 75270, Pakistan

Supporting Information



ABSTRACT: A palladium-catalyzed cross-dehydrogenative coupling (CDC) reaction of pyridine *N*-oxides with toluenes has been developed that operates under mild conditions. 2-Benzylpyridines can be obtained directly by this method via a CDC reaction between unactivated toluenes and pyridine *N*-oxides. In addition, azafluorene *N*-oxides, of value for future medicinal chemistry applications, can be obtained successfully by this procedure via four tandem C–H bond activations.

Transition-metal-catalyzed cross-coupling reactions have emerged as powerful tools for the construction of carbon–carbon and carbon–heteroatom bonds in the key step of many natural, unnatural and biologically active products syntheses. It is a reaction that has become even more applicable now that C–H bond activation has been developed.[1] Recently C–C bond forming reactions from two C–H bonds, under oxidative conditions (cross-dehydrogenative coupling, CDC), have gained considerable attention. Tandem oxidation of C–H bonds allows the use of simple (i.e., less functionalized) reagents and often reduces the number of steps to the target molecule.[2] Despite a number of reports concerning oxidative coupling between Csp–H and Csp–H,[3] Csp–H and Csp^2–H,[4] Csp–H and Csp^3–H,[5] Csp^2–H and Csp^2–H bonds,[6] there are few examples of the construction of C–C bonds between Csp^3–H and Csp^2–H bonds via a CDC reaction.[7]

The 2-benzylpyridine core structure is present as a key structural unit in many biologically active compounds possessing insecticidal, phosphodiesterase inhibiting, antifungal, antispermatogenic, antifertility, antagonistic, and antiarrhythmic activities.[8] For example, compound **1** has been reported as P2 × 3 and P2 × 2/3 receptor antagonist, and derivatives of **2** are known as antiarrhythmic drugs (Figure 1).[9] Benzylation of pyridine and pyridine *N*-oxide derivatives to construct the 2-benzylpyridine structural motif has been reported rarely. Although this class of compounds can be accessed through addition of benzyl Grignard reagents to suitable pyridyl compounds, there are only a few new synthetic methodologies available for construction of 2-benzylpyridines. 2-(2-Pyridyl)-ethanol derivatives can serve as the starting materials in a palladium-catalyzed reaction with aryl halides for the synthesis of the title compounds.[10]

Figure 1. Examples of bioactive 2-benzylpyridines.

2-Methylpyridine *N*-oxides were used by Fagnou for the synthesis of 2-benzylpyridines via direct arylation of benzylic Csp^3–H bond (Scheme 1) in 2008.[11] Decarboxylative cross-coupling of 2-(2-pyridyl)acetates with aryl halides, for the synthesis of 2-benzylpyridine derivatives, was reported by Liu[12] in 2010, and palladium-catalyzed arylation of 2-methylpyridine with aryl halides is another approach for the synthesis of 2-benzylpyridines developed by Knochel in 2011.[13] Palladium-catalyzed C–H couplings of pyridine *N*-oxides with benzyl chloride derivatives were reported by Mai in 2012.[14] (Scheme 1) In all of the above-mentioned methods, prefunctionalization of at least one of the starting materials was necessary.

Recently, due to low toxicity, stability, and commercially availability, toluene and its derivatives have been used in CDC reactions as ArCOO– and ArCO– surrogates.[15]

There are only a few examples in which toluene has been used as a benzyl source and remains intact under the reaction

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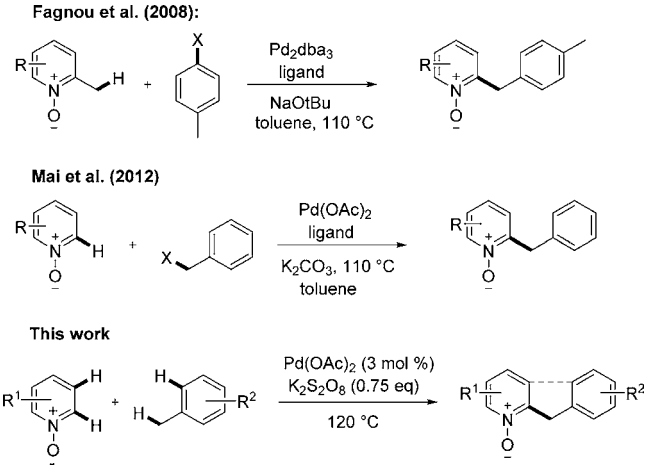
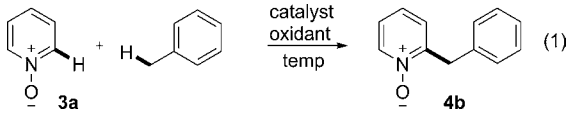
Scheme 1. Selected Approaches to Synthesis of 2-Benzylpyridine Derivatives



conditions without further oxidation.[16] To the best of our knowledge, the synthesis of 2-benzylpyridines via a CDC reaction, using two unfunctionalized starting materials, has not been reported. We herein present a simple and practical palladium-catalyzed CDC process for the direct benzylation of pyridine *N*-oxides using nonprefunctionalized and inexpensive toluene derivatives as the benzyl source and $K_2S_2O_8$ as the oxidant. At the outset of our study, we investigated the reaction of pyridine *N*-oxide and toluene as a model (eq 1, Table 1). To

Table 1. Optimization of the Reaction Conditions for Palladium-Catalyzed Coupling of Pyridine *N*-Oxide with Toluene

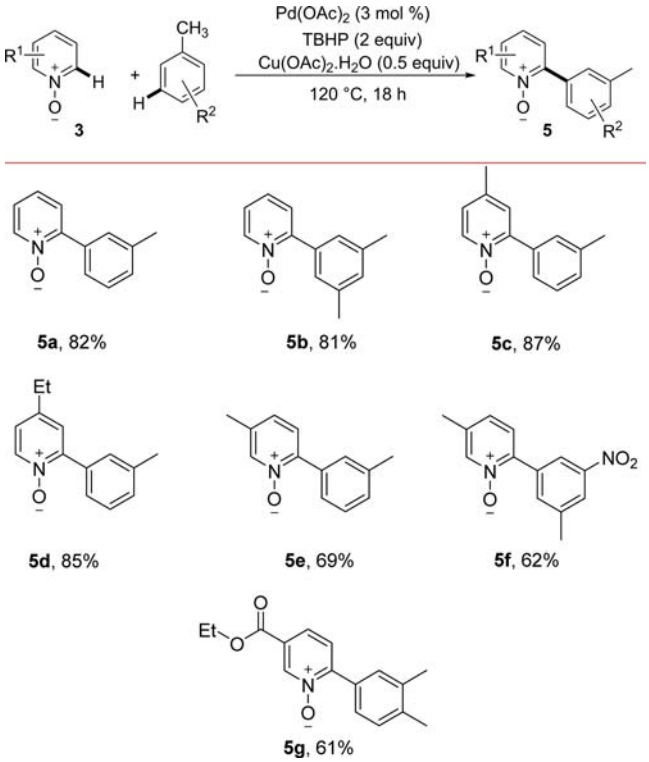


entry	catalyst (mol %)	oxidant (equiv)	temp (°C)	yield (%)
1	$Pd(OAc)_2$ (3)	$Na_2S_2O_8$ (1)	120	63
2	$Pd(OAc)_2$ (3)	$(NH_4)_2S_2O_8$ (1)	120	51
3	$Pd(OAc)_2$ (3)	TBHP (1)	120	trace
4	$Pd(OAc)_2$ (3)	$K_2S_2O_8$ (1)	120	75
5	$Pd(OAc)_2$ (3)	Ag_2CO_3 (0.75)	120	0
6	$Pd(OAc)_2$ (3)	DDQ (0.75)	120	0
7	**$Pd(OAc)_2$ (3)**	**$K_2S_2O_8$ (0.75)**	**120**	**83**
8	$Pd(OAc)_2$ (3)	$K_2S_2O_8$ (0.75)	100	56
9	$Pd(OAc)_2$ (3)	$K_2S_2O_8$ (0.75)	80	21
10	$Pd(OAc)_2$ (3)	$K_2S_2O_8$ (0.75)	120	61
11		$K_2S_2O_8$ (0.75)	120	0
12	$Pd(Cl)_2$ (3)	$K_2S_2O_8$ (0.75)	120	42
13	$Cu(Cl)_2$ (10)	$K_2S_2O_8$ (0.75)	120	38
14	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (0.75)	120	79

optimize the reaction conditions, various catalysts, oxidants, and temperatures of the reaction were investigated. As shown in Table 1, a variety of common oxidants were screened in the reaction, and the best results were obtained with $K_2S_2O_8$ (0.75 equiv). Under the optimized conditions, 3 mol % of Pd was sufficient to achieve 83% yield of 2-benzylpyridine *N*-oxide (Table1, entry 7). No reaction occurred in the absence of each catalyst and oxidant. Finally, the reaction temperature was also varied, and 120 °C gave the best results (Table 1, entries 7−9). The yield of the reaction was not improved by increasing the reaction time beyond 18 h. Remarkably, the reaction occurred in the absence of any additive or ligand.

In the optimization study, we found that the persulfate salts were of crucial importance for the benzylation reaction, and when the reaction was performed in the presence of TBHP and $Cu(OAc)_2$, the monoarylated adduct was obtained exclusively. Both oxidants, TBHP and $Cu(OAc)_2$, are very important for the arylation pathway. Omitting TBHP from the reaction conditions reduces the yield of the reaction to 12% and causes the lack of regioselectivity, and removing copper salt from the reaction conditions reduces the yield to 49% (Supporting Information). A series of 2-arylated pyridine *N*-oxides, prepared by this procedure, are shown in Scheme 2. In 2008, Chang et al.

Scheme 2. Palladium-Catalyzed Direct Arylation of Pyridine *N*-Oxides by Toluenes[a]



[a]Reaction conditions: pyridine *N*-oxides (1 mmol), $Pd(OAc)_2$ (3 mol %), TBHP (2 equiv), $Cu(OAc)_2.H_2O$ (0.5 equiv) in toluene derivatives (2 mL) at 120 °C for 18 h.

reported the palladium-catalyzed direct arylation of pyridine *N*-oxide derivatives with arenes in the presence of Ag_2CO_3 as the oxidant.[17] The reaction leads to mono- and diarylated adducts, the extent of which varies with the substrates employed.

Once the optimized conditions for the desired benzylation reaction were established, the scope of the reaction was investigated. A variety of combinations of substrates were examined, and the results are summarized in Scheme 3. Pyridine *N*-oxides with both electron-donating and electron-withdrawing groups such as methyl or methyl ketone groups reacted smoothly and resulted in the corresponding 2-benzylpyridine *N*-oxides **4a−l** in good yields. Pyridine *N*-oxide **4a** is a sterically disfavored product, but it is formed preferentially. C−H bond activation in pyridine *N*-oxides probably proceeds via a CMD mechanism, and the electronic

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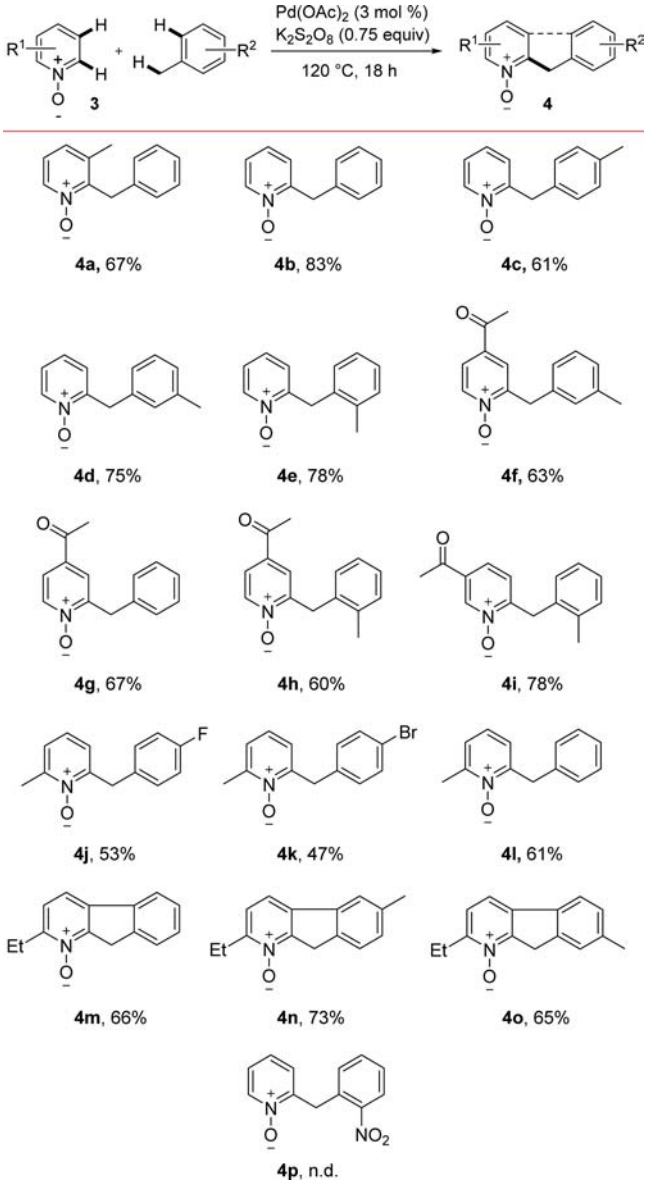
Scheme 3. Palladium-Catalyzed Direct Benzylations of Pyridine *N*-Oxides by Toluene[a]



[a]Reaction conditions: pyridine *N*-oxides (1 mmol), $Pd(OAc)_2$ (3 mol %), $K_2S_2O_8$ (0.75 equiv) in toluene derivatives (20 mmol) at 120 °C for 18 h.

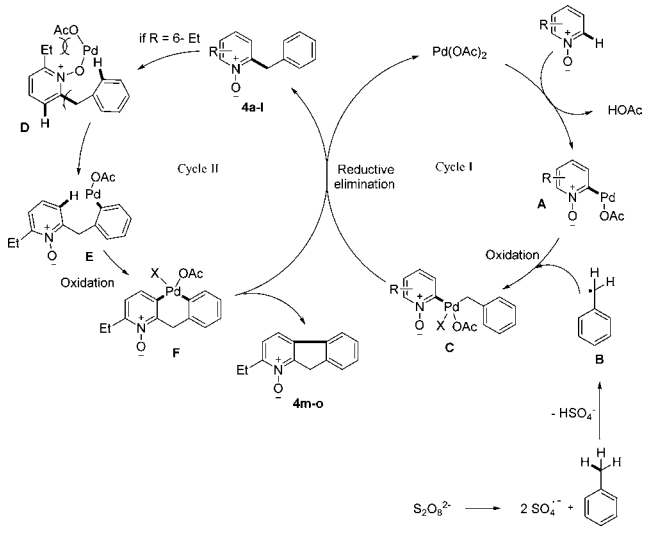
effect of the methyl group may be effective in the concerted metalation−deprotonation step.

Gratifyingly, when 2-ethylpyridine *N*-oxide was used as a substrate, the reaction led to the formation of the azafluorene *N*-oxide derivative through four tandem C−H bond activations with sequential bond making (Scheme 3, **4m−o**).

To prove the role of the $K_2S_2O_8$ as a radical agent, a control reaction was performed. When **3a** was treated with TEMPO (2,2,6,6-tetramethylpiperidin-*N*-oxyl) as a radical inhibitor, no desired product **4a** was detected upon addition of TEMPO.[18]

On the basis of the above results and previous reports, a plausible mechanism for the reaction is proposed in Scheme 4. Initially, an electrophilic palladation occurs preferentially at the C2-position of the pyridine *N*-oxide and leads to the formation of intermediate **A**.[19] Radical intermediate **B** is generated in situ by hydrogen-atom abstraction from the toluene facilitated by

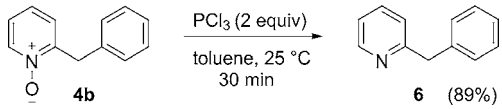
Scheme 4. Plausible Mechanism for Palladium-Catalyzed Benzylation of Pyridine *N*-Oxide



the sulfate radical anion that is produced from the heated $K_2S_2O_8$.[20] Next, coordination of the palladium complex **A** with radical **B** gives intermediate **C** which reductively eliminates to 2-benzylpyridine *N*-oxides (**4a−l**) and Pd(II) (cycle I). 2-Substituted pyridine *N*-oxides with bulky groups may be involved in another catalytic cycle after benzylation (cycle II in Scheme 4) to produce azafluorene *N*-oxides through dual C−H bond activations. As the results of Scheme 3 show, for construction of the azafluorene core structure the presence of an ethyl group on position 2 of the pyridine *N*-oxide is necessary (**4m−o**). It seems that C−H bond activation of the aryl ring (**D** to **E** in Scheme 4) is facilitated by the buttressing effect of the ethyl group on the pyridine *N*-oxide ring, which finally leads to the formation of the azafluorene *N*-oxide by heteroarylation through the fourth successful C−H bond activation and subsequent reductive elimination.

2-Benzylpyridine *N*-oxides can easily be deoxygenated to pyridines by reaction with PCl_3, making the present route an attractive approach to 2-benzylpyridine and azafluorene derivatives (Scheme 5).[21]

Scheme 5. Deoxygenation of Pyridine *N*-Oxide by PCl_3



In summary, we have demonstrated the first palladium-catalyzed direct benzylation of pyridine *N*-oxides for the synthesis of 2-benzylpyridine *N*-oxides and azafluorene *N*-oxides using $K_2S_2O_8$ as the oxidant and toluene derivatives as ideal benzyl sources via multiple C−H bond activations. The dehydrogenative cross-coupling reaction of the sp^3 C−H bond in toluenes with the sp^2 C−H bond in pyridine *N*-oxides proceeds smoothly, providing the corresponding products in good yields. The reaction provides a new, simple, and mild method for generating the useful 2-benzylpyridine *N*-oxides and azafluorene *N*-oxides of interest for future pharmaceutical and chemical applications.

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■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kianmehr@khayam.ut.ac.ir.

Notes

The authors declare no competing financial interest.

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