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M^{II}/M^{III}-Catalyzed *ortho*-Fluoroalkylation of 2-Phenylpyridine

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A one-step catalytic method for the *ortho*-fluoroalkylation of 2-phenylpyridine has been developed that employs the less-commonly used higher oxidation states of nickel or palladium by electro-oxidation of stable M^{II} precursors.

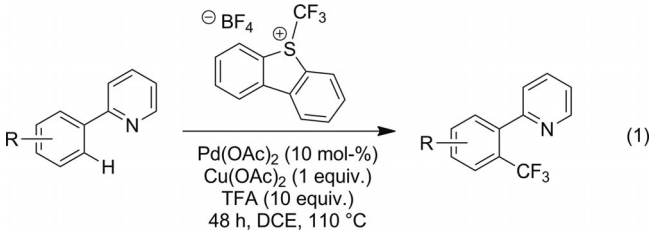
Introduction

Palladium-catalyzed transformations are routinely found as key steps in modern day synthetic chemistry. The functional group tolerance of palladium makes its use in the preparation of complex natural products, advanced materials, and high-value specialty chemicals possible. Many of these palladium transformations involve shuttles between the Pd^0 and Pd^{II} oxidation states. However, Pd^{IV}[1] and even Pd^{III}[2] have emerged as incredibly useful platforms in synthetic chemistry. The ability to access the Pd^{IV} oxidation state has been used to oxidatively induce reductive eliminations of atoms like fluorine [Equation (2)],[3] which have historically been difficult to couple. High-valent palladium chemistry is also incredibly useful for *catalytic* oxidative functionalizations, where directed C–H bond activation can lead to a variety of important synthetic products.[1,4]

One of the major problems in Pd^{II}/Pd^{IV} chemistry, however, is that the co-oxidants used are either expensive to purchase (silver and other metal salts are often used) or to separate from the product mixture (high molecular weight organic oxidants). Moreover, every time new ligands, substrates, or reaction conditions are used, screenings must often be performed to identify the optimal oxidant. One of our aims is to continue development of cheaper and more controllable electrochemical alternatives to these oxidation reactions. The advantages of electrochemical process would be a much cheaper and recyclable redox co-catalyst (the electrode vs. silver or organic oxidants), and a redox-co-catalyst where you can simply dial-in the potential.

We also wish to gain insight into how to develop more examples of catalytic C–H functionalization at nickel, as such examples are rare relative to palladium.[5] With the current state of the economy, geopolitics, and our environmental consciousness, the desire to develop inexpensive catalysts based on readily available first-row metals is stronger than ever. First-row late metals are particularly attractive for synthetic purposes, as their functional group tolerance makes them attractive candidates for C–C and C–X (X = F, NR_2, OR, SR, etc.) bond-forming processes. If one can complement (and hopefully supersede) the existing synthetic chemistry of palladium with nickel, then costs associated with chemical research, development, and processing will be significantly impacted.

One area of direct C–H functionalization that needs improvement is the area of perfluoroalkylation. Yu and coworkers were the first to report an exciting example where palladium was used to catalyze the direct trifluoromethylation of 2-phenylpyridine derivatives (Scheme 1).[6] While the functionalization was impressive, the reaction employs the expensive (trifluoromethyl)dibenzothiophenium salt and requires one full equivalent of a Cu^{II} salt and 10 equivalents of trifluoroacetic acid. $Cu(OAc)_2$ and CF_3COOH additives serve as a source of AcOH that is needed to oxidize the originally produced cyclopalladated dimer to the key mononuclear CF_3Pd^{IV} intermediate and may also improve the yield by scavenging reactive Pd species generated in the C–CF_3 coupling step.



Scheme 1. *ortho*-Trifluormethylation of substituted 2-phenylpyridine.

Because of our long-standing interest in electrochemical perfluoroalkylation reactions,[7] we wondered if electrochemical versions of direct C–H perfluoroalkylations could

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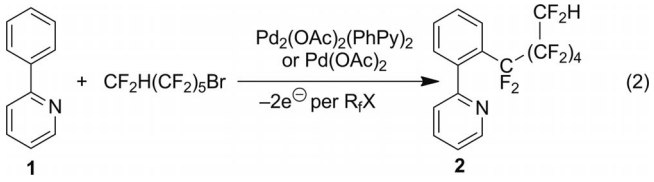
be developed, especially with the use of more inexpensive nickel catalysts. The results of our studies are presented below.

Results and Discussion

It was found that the joint electrochemical oxidation of 2-phenylpyridine (PhPy, **1**) and 6*H*-perfluorohexyl bromide in the presence of a $Pd_2(OAc)_2(PhPy)_2$ or $Pd(OAc)_2$ catalyst at a potential of 0.82 V vs. $Ag/AgNO_3$ leads to selective *ortho*-fluoroalkylation as described in Scheme 2. At these potentials, the palladium is clearly beyond the Pd^{II} oxidation state (Figures 1 and 2). Notably, the dimeric $Pd_2(OAc)_2(PhPy)_2$ complex was a more effective catalyst in this process (the yield of **2** was 30%) than palladium acetate (which gave yields of only 10%).



(2)

Scheme 2. Palladium-mediated electrooxidative *ortho*-fluoroalkylation of 2-phenylpyridine.

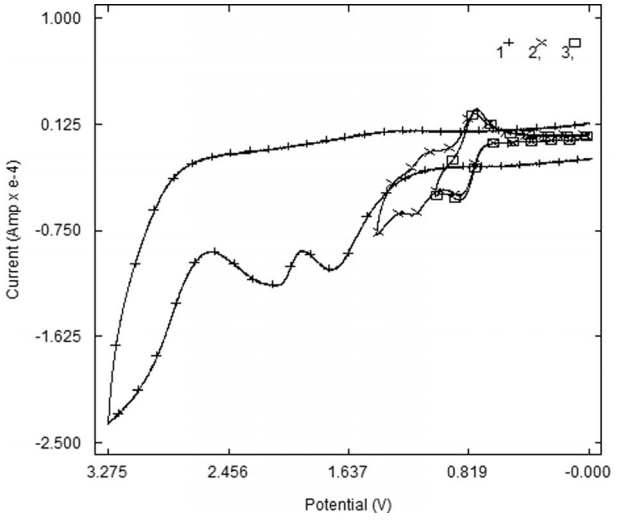


Figure 1. Cyclic voltammogram of 10^{-2} M $Pd(OAc)_2$ (curve 1) and a mixture of $Pd(OAc)_2$ and 10^{-2} M PhPy (1:1) (curves 2 and 3) in CH_2Cl_2 with the use of a glassy carbon electrode, 10^{-1} M $[NBu_4][PF_6]$ as supporting electrolyte, at a scan rate of 100 mV/s; reference electrode Ag/AgCl.

With promising results in hand, we also explored the reactivity of $[Ni(bpy)_3]^{2+}$ in the electrocatalytic perfluoroalkylation reactions (Scheme 3). 2-Phenylpyridine was mixed with 6*H*-perfluorohexyl bromide in the presence of $[Ni(bpy)_3]^{2+}$ at a potential of 1.3 V vs. $Ag/AgNO_3$ and *ortho*-6*H*-2-perfluorohexylpyridine (**2**) was obtained in higher yields than those observed with palladium at 62%. On the basis of the cyclic voltammogram of $[Ni(bpy)_3]^{2+}$ (Figure 3), the process was carried out at a potential needed for the Ni^{II}/Ni^{III} shuttle.

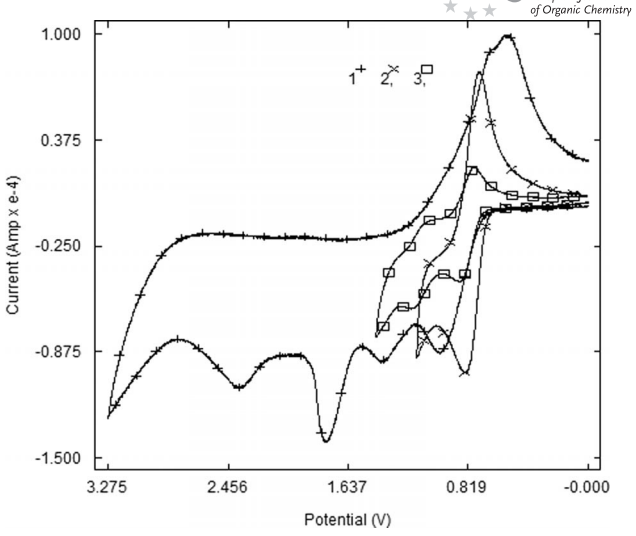
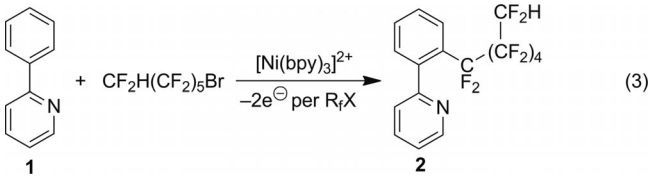


Figure 2. Cyclic voltammogram of 10^{-2} M $Pd_2(PhPy)_2(OAc)_2$ (curves 1 and 2) and a mixture of $Pd(OAc)_2$ and 10^{-2} M PhPy(1:1) (curve 3) in CH_2Cl_2 with the use of a glassy carbon electrode, 10^{-1} M $[NBu_4][PF_6]$ as supporting electrolyte, at a scan rate of 100 mV/s; reference electrode Ag/AgCl.



(3)

Scheme 3. Nickel-mediated electro-oxidative *ortho*-fluoroalkylation of 2-phenylpyridine.

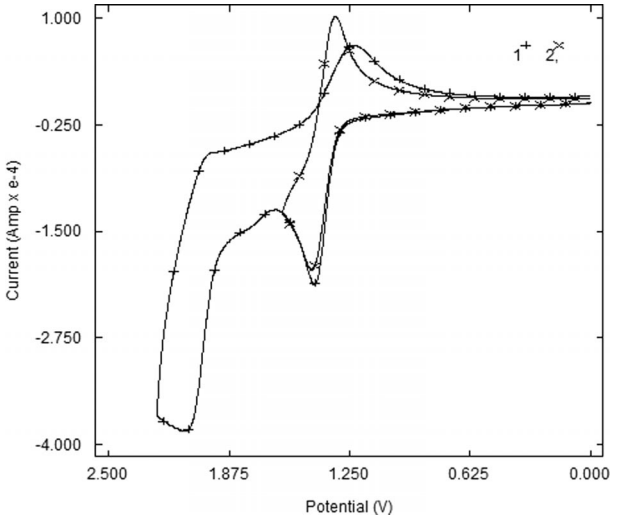
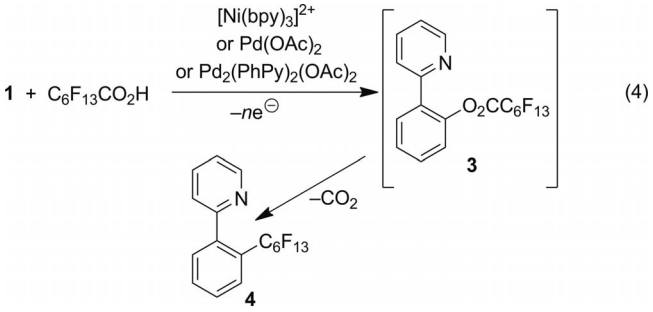


Figure 3. Cyclic voltammogram of 10^{-2} M $[Ni(BF_4)_2(bpy)_3]$ in MeCN with the use of a glassy carbon electrode, 10^{-1} M $[NBu_4][PF_6]$ as supporting electrolyte, at a scan rate of 100 mV/s; reference electrode Ag/AgCl.

Perfluoroalkyl carboxylic acids were also tested for their ability to react with nickel and palladium, as perfluoroalkyl carboxylic acids are believed to be a very useful source of the perfluoroalkyl functional group.[8] Joint electrochemical

oxidation of 2-phenylpyridine/perfluoroheptanoic acid (1:1) in the presence of various catalysts led to direct perfluoroalkylation products through a decarboxylative pathway, as described in Scheme 4. Good yields {81% for $Pd_2(OAc)_2(PhPy)_2$ and 85% for $[Ni(bpy)_3]^{2+}$} were obtained demonstrating that the perfluoroalkyl carboxylic acids are in fact better substrates than the perfluoroalkyl bromide in direct functionalization reactions.

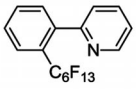
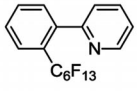
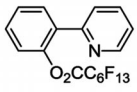
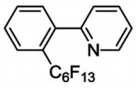
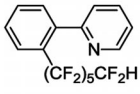
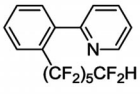
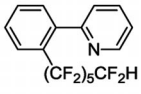


(4)

Scheme 4. Electrooxidative *ortho*-fluoroalkylation of 2-phenylpyridine with perfluoroheptanoic acid.

We speculate that intermediate **3** is generated on route to product formation. The presence of **3** in the reaction mixtures was confirmed by GC–MS. When $Pd(OAc)_2$ was used as a catalyst there were three products in the reaction mixture: the intermediate palladium complex {fragment peaks in the mass spectrum at 106 [Pd], 154 [$C_6H_4C_6H_4N$], 319 [$C_6H_4C_6H_4NPdOAc$], 378 [$C_6H_4C_6H_4NPd(OAc)_2$]}; *ortho*-carboxylated species **3** with m/z = 517 $[M]^+$, and oxidation product **4** with m/z = 473 $[M]^+$). An increase in electrolysis time leads to final product **4**. A summary of the results for the M^{II}/M^{III}-catalyzed *ortho*-fluoroalkylation of 2-phenylpyridine is shown in Table 1.

Table 1. Products of *ortho*-C–H substitution in Ph-Py with different catalysts.

Catalyst/ Precursor	$Pd_2(PhPy)_2(AcO)_2$	$Pd(OAc)_2$	$[Ni(bipy)_3]^{2+}$
$C_6F_{13}COOH$	 81%	 (up to 18%) + 	 85%
$CF_2H(CF_2)_5Br$	 30%	 10%	 62%

Conclusions

The electrocatalytic syntheses of fluoroalkylated 2-phenylpyridine proceeded under mild conditions at potentials that clearly generate high oxidation state nickel and palladium complexes. Only the electrocatalyst and the substrates are required for the reaction to occur. To broaden the scope of the proposed method we are planning to examine various substrates for C–H activation like substituted arenes that have been previously studied,[5,10] as well as more sophisticated structures. The mechanisms of these redox processes are currently under study in efforts to optimize the reactions even further.

Experimental Section

Preparative Electrolysis: An electrochemical cell was loaded with a mixture of 2-phenylpyridine (7 mmol), 6*H*-perfluorohexyl bromide or perfluoroheptanoic acid (14 mmol) and the catalyst (0.7 mmol) in acetonitrile (70 mL). Electrolysis was conducted in a divided cell at a platinum anode with the use of Et_4NBF_4 as the background electrolyte. The mixture was stirred with a magnetic stirrer and a constant stream of argon. 2*F* per R_fX (X = Br, COOH) electricity was passed through the electrolyte. At the end of electrolysis, the reaction mixture was placed in 250-mL flask, the solvent was removed on a rotary evaporator, and the residue was washed with water and extracted with benzene (3 × 50 mL). The organic layer was dried with $MgSO_4$, then the solvent was removed, and the residue was washed with diethyl ether and dried in a vacuum. The product was purified by silica gel column chromatography (ethyl acetate/hexane).

Supporting Information (see footnote on the first page of this article): General information, characterization data, and copies of the ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra of new compounds.

Acknowledgments

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