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Ligand-Promoted C-3 Selective C−H Olefination of Pyridines with Pd Catalysts

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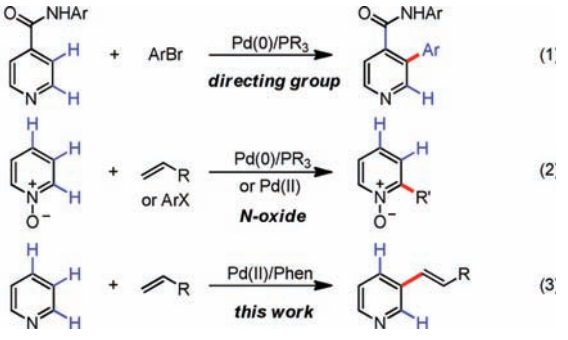
Supporting Information

ABSTRACT: Pd-catalyzed C-3 selective olefination of pyridines is developed for the first time using 1,10-phenanthroline as the ligand. This finding provides a novel disconnection for the synthesis of pyridine-containing alkaloids and drug molecules as well as a new approach for developing Pd-catalyzed C−H functionalizations of pyridines.

Pyridine rings are among the most important heterocyclic structural motifs and are found in a large number of natural products, pharmaceuticals, materials, and ligands.[1] Consequently, the development of short routes for the preparation of pyridine-containing compounds through pyridyl C−H functionalizations has received intensive attention.[2−11] The use of zirconium,[2] ruthenium,[3,4] rhodium,[5,6] and iridium[7] catalysts has yielded promising results with pyridine. Pioneering efforts by Hiyama and Nakao have recently led to important discoveries of novel Ni-catalyzed alkenylation of pyridyl C−H bonds.[8] Remarkably, two laboratories independently found that the coordination of a strong and bulky aluminum-based Lewis acid with the pyridyl N atom not only activated the pyridyl rings but also favored C(4)−H cleavage for the first time through steric hindrance.[9]

Among C−H functionalizations catalyzed by various metals, Pd-catalyzed C−H functionalizations directed by synthetically useful functional groups offer great versatility in terms of achieving a broad range of transformations.[12] Unfortunately, this approach has been largely unsuccessful with pyridyl C−H bonds.[13−16] Pd-catalyzed arylation of C(3)−H and C(4)−H bonds directed by an acidic amide has recently been reported, but with a limited substrate scope (eq 1).[14b] The use of pyridyl *N*-oxide and *N*-iminopyridinium ylide substrates has allowed for the development of a number of C−H functionalization reactions but is limited to the C-2 positions (eq 2).[15]



Despite such progress, palladium-catalyzed C-3 or C-4 selective C−H functionalizations of pyridine have not been achieved to date. Herein, we report the first Pd-catalyzed C-3 selective C−H olefination enabled by a bisdentate ligand that weakens the coordination of the Pd catalyst with the pyridyl N atom through the *trans*-effect (eq 3). This novel method provides access to 3-alkenyl pyridine derivatives that are closely related to a variety of biologically active natural products, such as sulcatin and acuminatopyrone, and drug molecules, including zimelidine (Figure 1).

At the onset of our studies, two major factors had to be considered. The reactivity of pyridyl C−H bonds is generally low due to the poor electron density of the pyridyl ring. In addition, strong coordination of the pyridine N atom with the Pd(II) center can prevent the catalyst from interacting with pyridine C(3)−H and C(4)−H bonds. Because this strong coordination is a major obstacle, we sought an operationally simple strategy to overcome this problem. Since pyridine could potentially coordinate with Pd(II) through either the N atom to form **I** or the electron-deficient pyridine ring to form **II**, we envisioned that a bisdentate pyridyl ligand could enhance the ligand exchange due to a strong *trans*-effect[17] of the pyridyl ligand (Scheme 1). Although pyridine prefers to coordinate with Pd(II) via the N atom, the presence of only a small amount of **II** could be sufficient to trigger the catalytic reaction. It was anticipated that solvent, ligands, and counteranions would significantly influence this equilibrium.

Guided by this rationale, we used pyridine as the representative substrate to screen solvents, anions, and ligands. We found that the $Pd(OAc)_2$-catalyzed C-3 selective olefination of pyridine using ethyl acrylate as the limiting reagent occurred in DMF in the presence of air and a catalytic amount of Ag_2CO_3 to give the desired product in 21% yield (Table 1, entry 1). We reasoned that two molecules of pyridine acted as ligands as shown in Scheme 1. The excess pyridine relative to olefin in DMF is presumably required for the formation of **II** because the binding of Pd(II) with the π-ring is relatively weak. We, therefore, focused on the extensive screening of a variety of bisdentate pyridyl ligands to seek improved reactivity (entries 2−14).[18] A number of bisdentate pyridyl ligands were found to increase the yields of the olefination products, with 1,10-phenanthroline (Phen) and bathophenanthroline giving the highest yields (entries 9, 10, 12). Under these conditions, other solvents such as dioxane, acetonitrile, DMA, and DMSO gave less than 10% yields (see Supporting Information). Other palladium sources were also tested. The use of $Pd(TFA)_2$ afforded the olefinated product in 75% yield, while other catalysts such as $Pd(OTf)_2$ and

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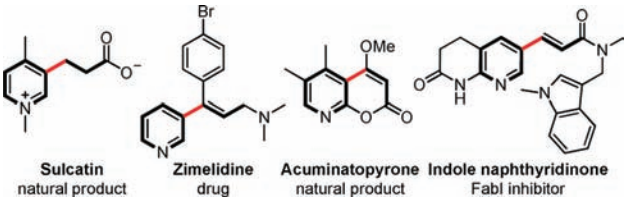


Figure 1. Bioactive 3-alkenyl or 3-alkyl pyridine derivatives.

Scheme 1. Assembly of Reactive Precursor via a *trans*-Effect

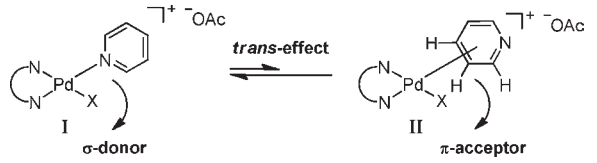
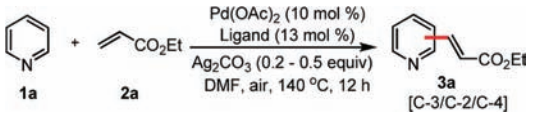
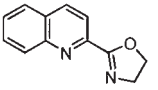
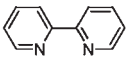
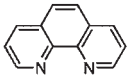
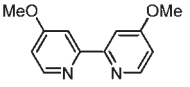
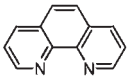
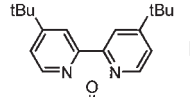
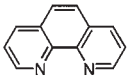
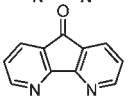
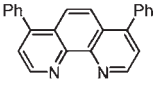
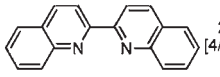
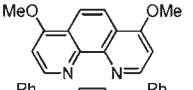
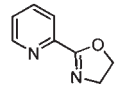
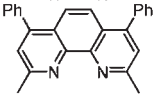


Table 1. Ligand Effects[a]

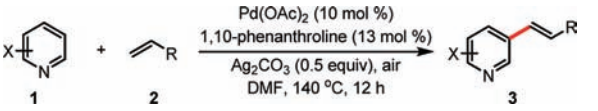


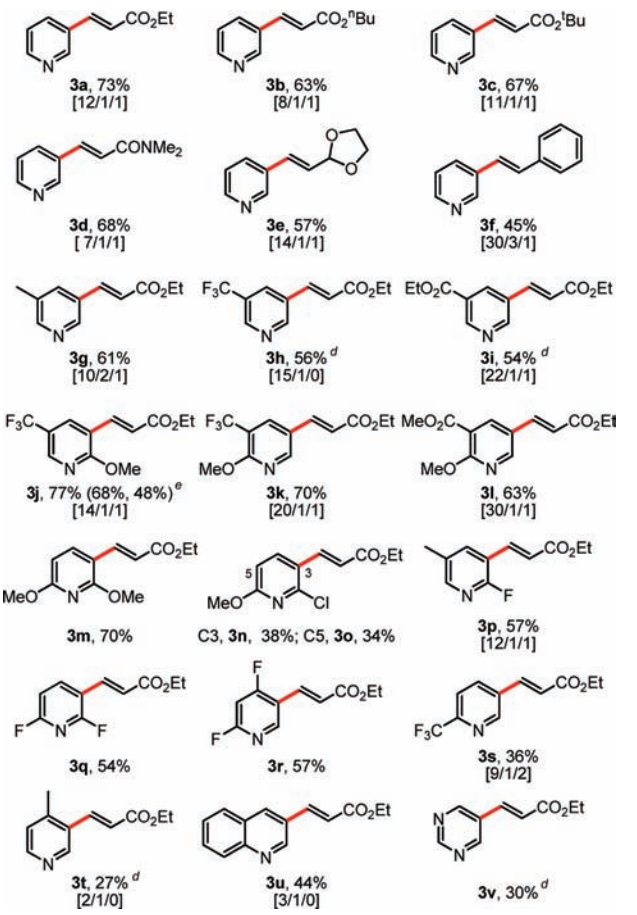
Entry	Ligand	Yield (%)[b]	Entry	Ligand	Yield (%)[b]
1	---	21 [5/1/1]	8		7 [5/1/1]
2		50 [14/1/2]	9		87 [12/1/1]
3		29 [5/1/1]	10		81[c] [12/1/1]
4		55 [11/1/1]	11		37[d] [10/1/1]
5		16 [3/1/1]	12		86 [12/1/1]
6		27 [4/1/1]	13		6 [1/1/1]
7		11 [6/4/1]	14		9 4/4/1]

[a] Reaction conditions: **1a** (8.0 mmol), **2a** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), Ligand (13 mol %), and Ag_2CO_3 (0.25 mmol) in DMF (1 mL). [b] Yield and isomer ratio (C-3/C-2/C-4) were determined by ^1H NMR of crude reaction mixture. [c] Ag_2CO_3 was reduced to 0.1 mmol under 1 atm of O_2. [d] **1a** was reduced to 2.0 mmol.

$PdCl_2$ gave poor yields (~40%). Using the Phen ligand, the amount of Ag_2CO_3 could be reduced to 0.2 equiv without decreasing the yield significantly (entry 10). However, the yield was found to decrease from 87% to 37% when the amount of pyridine was reduced from 16 to 4 equiv (entry 11).

Table 2. Pd-Catalyzed Olefination of Pyridine Derivatives [a,b,c]





[a] Reaction conditions: **1a** (8.0 mmol), **2a** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), Ligand (13 mol %), and Ag_2CO_3 (0.25 mmol) in DMF (1 mL). [b] Isolated yield of C-3 product. [c] Ratio of C-3/C-2/C-4 was determined by ^1H NMR. [d] Bathophenanthroline (13 mol %), 24 h. [e] 3.0 and 1.5 mmol of pyridine substurate were used respectively.

In general, broadening the scope of substrates and reaction partners in C-3 or C-4 pyridyl C−H functionalizations has proven extremely challenging in previous studies.[2−9,13−16] We first examined the compatibility of the olefin coupling partners (Table 2). Terminal olefin coupling partners containing ester, amide, ketal, and aryl moieties were found to be suitable reactants (**3a**−**3f**) while internal olefins gave low yields (~15%). The scope of the pyridine substrates was also extensively surveyed. Pyridines containing both electron-donating and -withdrawing groups were olefinated selectively in synthetically useful yields (**3g**−**3i**). Substitution at the C-2 position by either methoxy, chloride, or fluoride was also tolerated (**3j**−**3r**). The relatively high reactivity of 2-methoxy-5-trifluoromethylpyridine allowed for the use of 6.0 or 3.0 equiv of the pyridine substrate to give product (**3j**) in 68% and 48% yields respectively. It is worth noting that methoxy, chloride, and fluoride on C-2 are versatile handles for further transformations.[19] The presence of a 2-CF_3

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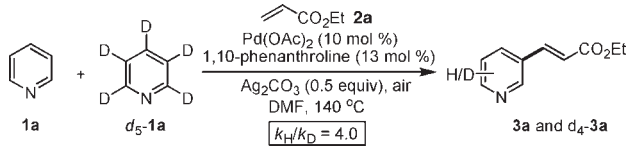
Scheme 2. Kinetic Isotope Effect



group resulted in a low yield (**3s**). *Para*-substitution also reduced the yield significantly due to steric hindrance (**3t**). Olefination of quinoline and pyrimidine also gave relatively low yields (**3u** and **3v**, respectively).

To gain insights into the origin of the reactivity and selectivity of this novel Pd-catalyzed C−H functionalization of pyridines, we performed a kinetic isotope effect study (Scheme 2). A significant isotope effect was observed (k_H/k_D = 4.0), which is consistent with a mechanism that involves a Pd-mediated C−H cleavage step rather than a Lewis acid mediated Friedel−Crafts reaction. Further kinetic studies are necessary to determine whether C−H cleavage is the rate-limiting step.

In summary, a novel protocol to effect Pd-catalyzed C(3)−H olefination of pyridines has been developed using air and catalytic Ag_2CO_3 as the oxidants. The assembly of the reactive complex is enabled by a strong *trans*-effect from the bispyridine ligands. The resulting C-3-olefinated pyridines are highly useful building blocks for the synthesis of bioactive alkaloid natural products and drug molecules. This initial success in achieving selective palladation of pyridyl C−H bonds should now permit exploitation of previously established catalytic systems for Pd-catalyzed C−H functionalization, providing a new avenue for developing C−C and C−heteroatom bond-forming reactions of pyridines.

■ 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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