Communication

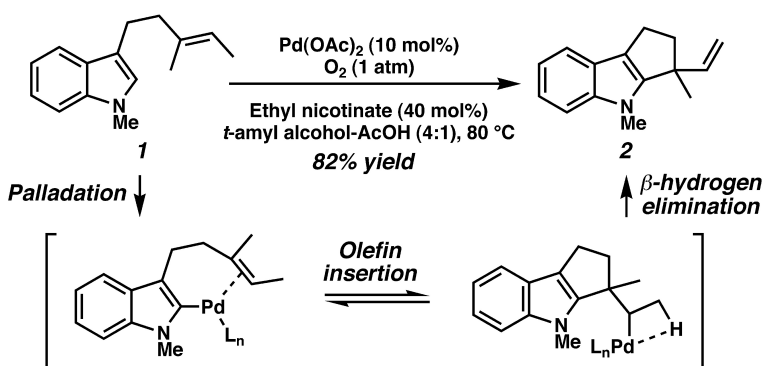# Catalytic C–H Bond Functionalization with Palladium(II): Aerobic Oxidative Annulations of Indoles

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Catalytic C−H Bond Functionalization with Palladium(II): Aerobic Oxidative Annulations of Indoles

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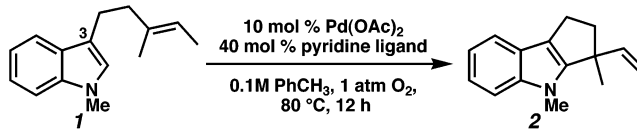
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The challenge of direct C−H bond functionalization continues to be an area of intense interest among academic and industrial chemists.[1] Catalytic transformations of this type involving the indole nucleus would be of particular value to the synthetic chemist. Palladium-mediated indole annulations have been used as the key step in several total syntheses; however, these reactions have exclusively required stoichiometric quantities of palladium.[2] Additionally, both Fujiwara and Itahara have studied related alkenylations and arylations of a variety of arenes including indoles.[3] Despite the obvious utility of these indole transformations, variants employing substoichiometric quantities of palladium have been highly limited.[4] An ideal oxidation catalyst system would employ an inexpensive, readily abundant terminal oxidant such as molecular oxygen. Although catalytic Pd(II) oxidations using O_2 as the sole stoichiometric oxidant are known, they are rare. In one example, Uemura found that pyridine-ligated palladium catalysts are active for alcohol oxidations under O_2.[5] Since that key discovery, the Pd−pyridine system has been utilized for several reactions, including oxidative ring-cleavage,[6a] oxidative amination,[6b] and Wacker-type cyclizations.[6c] Additionally, reports by our group and Sigman demonstrate that this system can be easily modified with chiral ligands to catalyze highly enantioselective processes.[6c,7] The Pd−pyridine system, however, has never been utilized in oxidative C−C bond-forming reactions. Intrigued by the potential of this oxidation system as an entry into indole annulation, we chose to investigate the aerobic cyclization of indole **1**. Herein, we report indole C−H bond functionalizations under mild, direct dioxygen-coupled catalysis. Moreover, this system has provided access to annulated indoles in high yields, previously unattainable via precedented palladium-catalyzed oxidation methods.

To our delight, treatment of indole **1** with catalytic Pd(OAc)$_2$ (10 mol %) and pyridine (40 mol %) under an atmosphere of oxygen in PhCH$_3$ resulted in oxidative cyclization to **2** (Table 1, entry 3). The conversion (23%), however, was noticeably low relative to that from the other oxidative processes reported under the Pd−pyridine system. We hypothesized that the active palladium species was not electronically suited to catalyze this transformation with high efficiency. Consequently, we surveyed a range of electronically differentiated pyridines with Pd(OAc)$_2$ (Table 1), and observed a correlation between the electronic nature of the ligand (i.e., pK_a)[8] and its ability to facilitate the cyclization.[9] Presumably, more electron-poor ligands resulted in a more electrophilic, and therefore more reactive, palladium catalyst. Ligands that were too electron-deficient, however, were unable to sufficiently ligate palladium,[10] likely hampering both reactivity and Pd(0) reoxidation. Ethyl nicotinate proved to be the maximally effective ligand for these indole annulations (Table 1, entry 5), proving that electronic modulation of the Pd−pyridine system can lead to altered and unique reactivity.[11]

With this Pd catalyst in hand, we turned our attention to solvent effects (Table 2). An increase in reaction efficiency was observed

Table 1. The Effect of Pyridine Substitution on the Aerobic Indole Annulation

entry	pyridine ligand	pK_a (pyrH$^+$)	conversion (%)^a
1	4-MeO	6.47	3
2	4-t-Bu	5.99	1
3	unsubstituted	5.25	23
4	4-CO$_2$Et	3.45	52
5	3-CO$_2$Et	3.35	76
6	3-COCH$_3$	3.18	58
7	3-F	2.97	64
8	3-CN	1.39	55
9	3,5-di-Cl	0.90	22

^{a} Measured using GC by consumption of **1** relative to an internal standard (tridecane).

Table 2. Solvent Effects in the Reaction of **1** to **2**

entry	solvent	% conversion	% yield (GC)
1	toluene	88	33
2	chlorobenzene	85	40
3	butyl acetate	95	49
4	*tert*-amyl alcohol	94	53
5	pinacolone	95	58
6	AcOH	86	25
7.	pinacolone/AcOH (4:1)	91	76
8	*tert*-amyl alcohol/AcOH (4:1)	99	82^b

^{a} 10 mol % Pd(OAc)$_2$, 40 mol % ethyl nicotinate, 1 atm O_2, 80 °C, 24 h, 0.1 M substrate **1** in solvent. ^{b} Isolated yield.

as we moved from nonpolar aromatic solvents toward more polar solvents, suggesting the potential stabilization of charged intermediates in the catalytic cycle. Although the reactions proceeded to high conversions in high-boiling polar solvents such as *tert*-amyl alcohol and pinacolone, the disparity between the consumption of **1** and the yield of **2** was still troubling.[12] We reasoned that upon prolonged exposure to O_2, the indole products were oxidatively decomposing.[13,14] Interestingly, this problem could be minimized by the addition of AcOH as cosolvent. Since oxidative decomposition of indoles is known to proceed through oxygen addition at C(3), it is possible that under our conditions, AcOH acts as a competitive inhibitor via protonation at the C(3) position in these products.[15] With this optimized system, good to excellent yields of cyclized product were obtained (entry 8).

As shown in Table 3, a range of substituted indoles participate in this oxidative cyclization reaction. In addition to the C(3) to C(2) cyclizations (entries 1−10), annulation can proceed from the C(2) to C(3) positions (entries 11 and 12) as well as from N(1) to C(2) (entry 13). Furthermore, ring sizes of 5 and 6 (entry 10) are available from the oxidative cyclization.

Particularly interesting was the rate difference observed in the cyclization of substrates possessing stereocenters in the tether

**Table 3.** Pd-Catalyzed Oxidative Indole Cyclization[a]

entry	substrate[b]	product		time	% yield[c]
1.			R = Me	24 h	82
2.			R = Et	18 h	74
3.			R = CH₂OBn	24 h	60
4.			R = 6-Cl	32 h	62
5.			R = 5-OBn	20 h	73
6.				30 h	79[d]
7.				48 h	69
8.				18 h	76 (6:1 dr)
9.				53 h	64 (1:1 dr)
10.				39 h	66[e]
11.				6 h	73[f]
12.				5 h	68[f]
13.				18 h	74

[a] 10 mol % Pd(OAc)₂, 40 mol % ethyl nicotinate, 1 atm O₂, 80 °C, 0.1 M substrate in *tert*-amyl alcohol:AcOH (4:1). [b] Typically used as a mixture of olefin isomers, see Supporting Information. [c] Isolated yields. [d] Product isolated as a 58:42 mixture of *E* and *Z* isomers. [e] 0.1 M in pinacolone. [f] 0.1 M in *tert*-amyl alcohol.

(entries 8 and 9), coupled to the sense of diastereoinduction observed in entry 8 and the lack of selectivity for entry 9. These results pointed toward a mechanism wherein initial palladation at C(2)[2a] is followed by olefin insertion and β-hydrogen elimination (C−H bond functionalization). Palladation would be slowed by the branched 3α site (e.g., entry 9), and the insertion facial bias would be guided by the principles of acyclic stereocontrol (e.g., A(1,3) interactions in entry 8). An alternative mechanism would involve Pd-mediated olefin activation and subsequent attack by the indole nucleus. To distinguish between these two possibilities, substrate **3** was exposed to our standard annulation conditions and, as anticipated, afforded tetracycle **4** as a single diastereomer (Scheme 1).[16] The observed stereochemistry of diastereomer **4** supports a mechanism involving initial palladation, if the requirements for syn migratory insertion and syn β-hydrogen elimination are operative. This mechanism is in full agreement with those previously proposed for related reactions.[2,3b]

In conclusion, we have developed a remarkably mild oxidative C−C bond-forming reaction that relies on formal C−H bond

Scheme 1
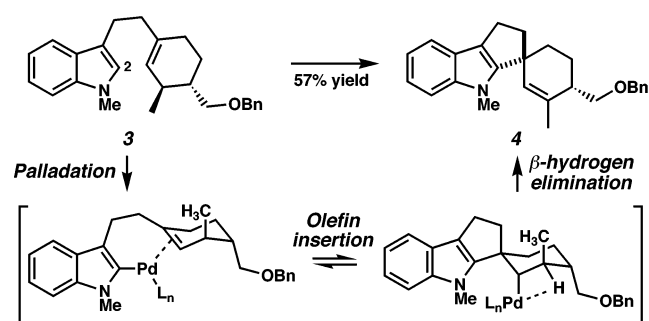
activation and uses molecular oxygen as the sole stoichiometric oxidant. To our knowledge, this represents the first example where the electronics of the Pd−pyridine catalytic system have been rationally evaluated, resulting in the discovery of the unique observed reactivity. Furthermore, this is the first report of oxidative indole annulations carried out using catalytic palladium. It is also remarkable that these oxidative cyclizations can proceed in good yield despite background oxidative decomposition pathways, testament to the facile nature with which molecular oxygen can serve as the direct oxidant for Pd(0). The discovery of specific electronic and medium effects in this system should be applicable to numerous other aromatic and olefinic systems, as well as asymmetric catalysis. Studies in these areas are currently ongoing.

Supporting Information Available: Experimental details and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) See Supporting Information for a full list of pK_a references.
(9) Although the use of pK_a values to determine ligand nature may be an oversimplification, it has served as a useful gauge in our study.
(10) Pd-black was observed in Table 1, entries 7−9.
(11) (a) The Pd source was also found to be critical. Pd(OAc)₂ was much more effective than PdCl₂ or Pd(TFA)₂ for these annulation reactions. (b) Attempts to convert **1**→**2** using a variety of other Pd(II) oxidative protocols have met with minimum success, see Supporting Information.
(12) (a) GC conversion was measured by consumption of **1** relative to an internal standard (tridecane). (b) GC yield was measured by the amount of **2** relative to an internal standard (tridecane).
(13) There are numerous reports dealing with the oxidation of indole by O₂. For a list of key references, see Supporting Information.
(14) For control experiments, see Supporting Information.
(15) AcOH is often used as a solvent for aryl palladations.[3] Thus, other possible effects cannot be ruled out, such as favorable interactions with catalytic intermediates. Studies elucidating the exact effect are underway.
(16) Relative configuration determined by NOE analysis, see Supporting Information.

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