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Mild Aerobic Oxidative Palladium (II) Catalyzed C−H Bond Functionalization: Regioselective and Switchable C−H Alkenylation and Annulation of Pyrroles

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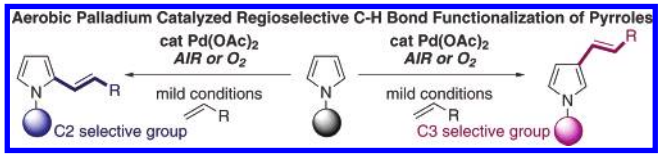
The development of direct C−H bond functionalization strategies for the facile generation of compounds with useful molecular architecture remains of high interest to academic and industrial chemists.[1] Such processes preclude the need for a prior functionalization step, making the overall chemical transformation highly efficient. We are particularly interested in the development of new methods for direct metal catalyzed oxidative C−H transformations of organic molecules under mild and operationally simple conditions. Catalytic reactions of this nature would be very useful for the elaboration of molecules that may be sensitive to the harsh conditions that can often be required for C−H functionalization processes. Recently, a number of groups,[2] including ourselves,[2e] have reported C−H bond transformations of indole. In contrast, the use of pyrrole in similar processes is rare,[3] and yet these heterocycles are ubiquitous in natural products[4] and medicinal agents[5] and are useful as intermediates in multistep synthesis.[6] Despite their potential in chemical synthesis, the instability of pyrroles toward acidic and oxidative environments has limited their utility in metal catalyzed C−H transformations. Herein, we report an efficient *aerobic palladium (II) oxidation system for C−H bond functionalization of sensitive molecules under ambient conditions*.

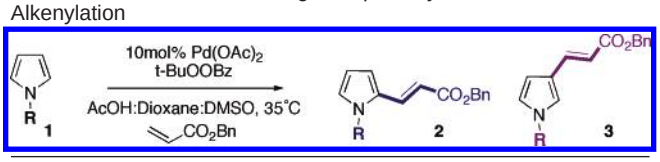


This method can be used to directly generate a range of functionalized and annulated pyrrole architectures and it is possible to *control the position* of C−H bond functionalization via simple steric and electronically tuned *N*-pyrrole protecting groups to form products with either C2 or C3 elaboration.

At the outset of our studies we were guided by our discovery that the solvent media could control positional selectivity during palladium catalyzed C−H bond functionalizations of indoles.[2e] Despite the success in the indole series the corresponding pyrrole systems suffered from unselective and polyalkenylation as well as significant polymerization. With this in mind we speculated that the reactivity of the pyrrole nucleus may enable a catalytic C−H bond functionalization at room temperature or under ambient conditions.

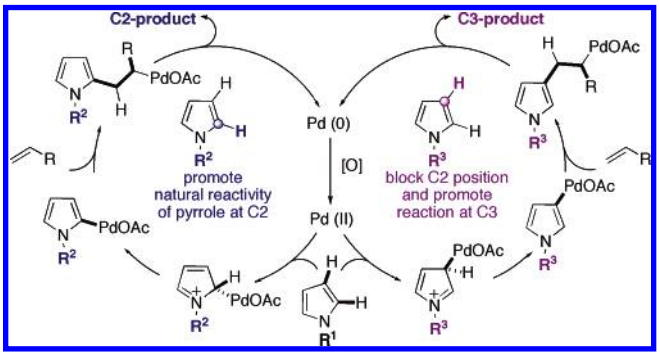
To test this hypothesis, we focused our attention on oxidative alkenylations of simple pyrroles. After initial optimization studies we identified that 10 mol % $Pd(OAc)_2$ in a dioxane−AcOH−DMSO solvent system and tBuOOBz as oxidant provided an effective system for pyrrole functionalization.[7] We found that *N*-Bn pyrrole reacted smoothly with benzyl acrylate at only 35 °C to form the alkenylated products. Although it was expected that the natural reactivity of pyrrole would direct reaction to the C2 position, we observed a 2:1 ratio of C2 to C3 isomers (Table 1, entry 1). A

Table 1. Effect of *N*-Protecting Group on Pyrrole C−H Alkenylation



entry	catalyst loading (%)	R	yield of C2	yield of C3	ratio 2:3
1	10	Bn	48	23	2.1:1
2	10	SEM	48	21	2.3:1
3	10	Ac	65	−	>95:5
4	10	Boc	73	−	>95:5
5	10	Ts	70	−	>95:5
6	10	TIPS	−	78	<5:95

Scheme 1. Stereoelectronic Control Concept: Proposed Mechanism



coordinating *N*-SEM pyrrole derivative also failed to improve the selectivity (entry 2). We speculated that introduction of an electron-withdrawing *N*-protecting group would reduce the reactivity of the pyrrole and yield a more selective process. Accordingly, *N*-Ac, *N*-Ts, and *N*-Boc pyrrole afforded only the C2 product in good yield (entries 3−5) under mild conditions. In contrast, reaction with *N*-TIPS pyrrole gave only the C3 product (entry 6).[8] The switch in selectivity is attributed to the sterically demanding nature of the TIPS group that shields the C2 position from reaction with the palladium catalyst, forcing the reactive pyrrole to palladate at C3. To our knowledge this stereoelectronic strategy represents a new method for *controllable catalytic activation and functionalization of pyrroles under mild conditions* (see Scheme 1).

The catalyst loading can also be lowered to 5 mol %, and *N*-Boc pyrrole **2** was isolated in 70% yield after 36 h. The loading can be reduced to 1 mol % catalyst; however, the complete conversion takes longer to achieve. The turnover number (TON) at 60% (96 h) conversion is 55, suggesting that the process displays a high efficiency for palladium (II) processes.

With the goal of developing a more efficient process we investigated the nature of the oxidant in this C−H alkenylation process. When tBuOOBz was replaced with oxygen as oxidant, both *N*-Boc and *N*-TIPS pyrroles gave **2** and **3** in 73 and 75%, respectively (Table 2, entry 1). The ability of molecular oxygen to effect the facile oxidation of Pd(0) is ascribed to the presence of DMSO in the solvent media.[7] Furthermore, this *process also works*

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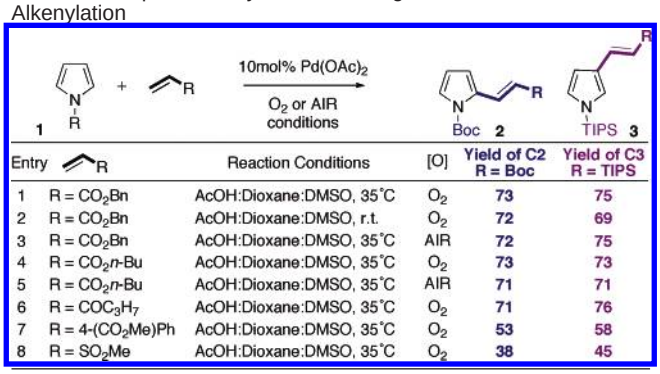
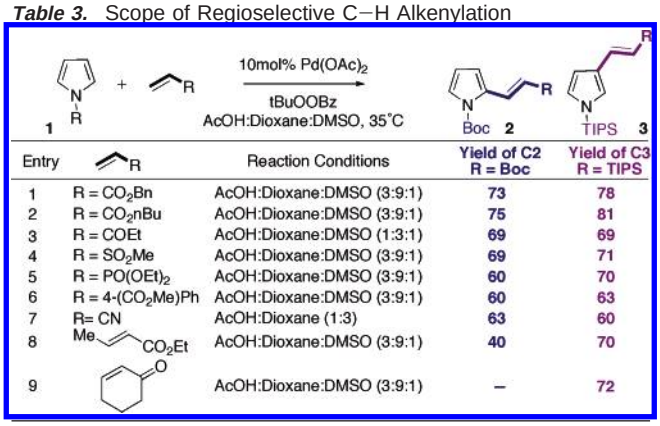
Table 2. Scope of Catalytic Aerobic Regioselective C−H Alkenylation



Entry	R	Reaction Conditions	[O]	Yield of C2 R = Boc	Yield of C3 R = TIPS
1	CO_2Bn	AcOH:Dioxane:DMSO, 35°C	O_2	73	75
2	CO_2Bn	AcOH:Dioxane:DMSO, r.t.	O_2	72	69
3	CO_2Bn	AcOH:Dioxane:DMSO, 35°C	AIR	72	75
4	CO_2n-Bu	AcOH:Dioxane:DMSO, 35°C	O_2	73	73
5	CO_2n-Bu	AcOH:Dioxane:DMSO, 35°C	AIR	71	71
6	COC_3H_7	AcOH:Dioxane:DMSO, 35°C	O_2	71	76
7	4-(CO_2Me)Ph	AcOH:Dioxane:DMSO, 35°C	O_2	53	58
8	SO_2Me	AcOH:Dioxane:DMSO, 35°C	O_2	38	45

Table 3. Scope of Regioselective C−H Alkenylation



Entry	R	Reaction Conditions	Yield of C2 R = Boc	Yield of C3 R = TIPS
1	CO_2Bn	AcOH:Dioxane:DMSO (3:9:1)	73	78
2	CO_2nBu	AcOH:Dioxane:DMSO (3:9:1)	75	81
3	COEt	AcOH:Dioxane:DMSO (1:3:1)	69	69
4	SO_2Me	AcOH:Dioxane:DMSO (3:9:1)	69	71
5	$PO(OEt)_2$	AcOH:Dioxane:DMSO (3:9:1)	60	70
6	4-(CO_2Me)Ph	AcOH:Dioxane:DMSO (3:9:1)	60	63
7	CN	AcOH:Dioxane (1:3)	63	60
8	Me, CO_2Et	AcOH:Dioxane:DMSO (3:9:1)	40	70
9	O	AcOH:Dioxane:DMSO (3:9:1)	–	72

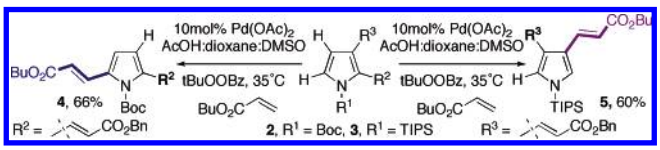
at room temperature, highlighting the ambient nature of this C−H bond functionalization process (entry 2). Remarkably, conducting the reaction in a flask that is left open to the atmosphere forms **2** or **3** respectively in 72 and 75% yield after 96 h with 10 mol % catalyst (entry 3). The use of air as oxidant without any further additives significantly increases the efficiency of this process.

The utility of our oxidative pyrrole C−H alkenylation was evaluated using the *N*-Boc and *N*-TIPS derivatives with a range of alkenes. Table 2 shows alkene coupling partners that can be exploited in this new process with good yields obtained in most cases using either O_2 or air as the oxidizing system.

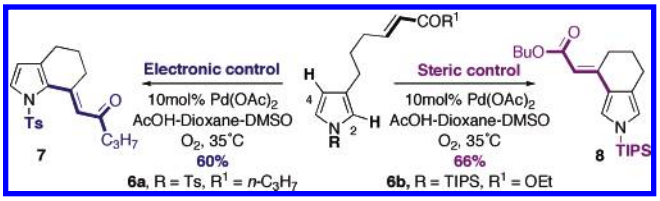
The aerobic conditions work well for reactive alkenes (entries 1−7), but the process is less effective when the reaction is slower (entries 7, 8) as the precipitation of the Pd(0) becomes a problem over the prolonged reaction time. To address this limitation we returned to the tBuOOBz oxidant that had been used during optimization. With this catalytic system we were pleased to find that a range of alkenes could be successfully used in the regioselective coupling (Table 3).

Trisubstituted alkene products were also formed from TIPS pyrrole in good yields with more substituted alkenes using this process (entries 8, 9).[9] In all cases *N*-Boc pyrrole underwent C−H alkenylation at C2, whereas *N*-TIPS directed reaction to C3.

The substituted pyrrole products can be differentially elaborated through catalytic regioselective functionalization. Accordingly, pyrroles **2** and **3** undergo selective C−H bond alkenylation forming only **4** and **5**, respectively, in good yield.



Intramolecular pyrrole C−H alkenylation can also be effected with complete control of the sense of cyclization. When Ts pyrrole **6a** is treated with $Pd(OAc)_2$ under the aerobic conditions, the C−H annulation is observed at C2 position as predicted by our model, leading to pyrrole **7**. However, by switching to *N*-TIPS derivative **6b** the annulation reaction formed the cycle at the C4 position, affording the alternative pyrrole molecular architecture, **8**. The annulation process works well and provides a facile method for the generation of complex polycyclic ring systems. Importantly, reaction occurs exclusively at the position predicted by our model.



In summary, we have developed a new mild aerobic palladium (II) catalyst system for C−H bond functionalization. This catalyst system enables a direct and regioselective pyrrole C−H bond alkenylation and annulation process where reaction at either the C2 or C3 position can be effected. We are currently investigating the application of this mild aerobic catalyst system in other palladium (II) transformations as well as exploring the utility of pyrrole C−H bond transformation as a versatile platform for complex molecule synthesis.

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

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(9) We speculate that a clash between the Boc group and the tri-substituted alkene is responsible for the poor reaction in the C2 alkenylation of entries 8−9.

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