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Aerobic Pd-Catalyzed sp^3 C−H Olefination: A Route to Both N-Heterocyclic Scaffolds and Alkenes

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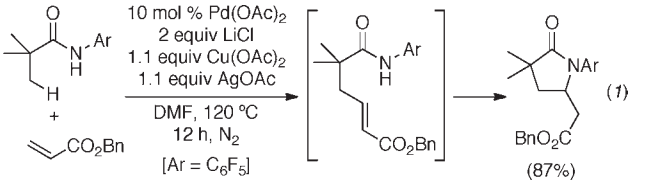
Supporting Information

ABSTRACT: This communication describes a new method for the Pd/polyoxometalate-catalyzed aerobic olefination of unactivated sp^3 C−H bonds. Nitrogen heterocycles serve as directing groups, and air is used as the terminal oxidant. The products undergo reversible intramolecular Michael addition, which protects the monoalkenylated product from overfunctionalization. Hydrogenation of the Michael adducts provides access to bicyclic nitrogen-containing scaffolds that are prevalent in alkaloid natural products. Additionally, the cationic Michael adducts undergo facile elimination to release α,β-unsaturated olefins, which can be further elaborated via C−C and C−heteroatom bond-forming reactions.

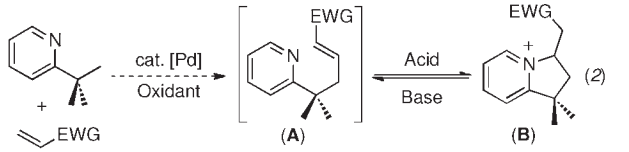
Transition-metal-catalyzed C−H olefination reactions have been the subject of tremendous research activity over the past 20 years.[1] These transformations provide atom economical methods for replacing simple carbon−hydrogen bonds with readily derivatizable alkene functional groups. A variety of different metals (for example, Pd, Cu, Ni, Co, Rh, and Ru) catalyze the olefination of arenes,[2] and these transformations have been applied to the synthesis and functionalization of biologically active target molecules.[3] Pd-based catalysts have been particularly well studied and effectively promote the reaction of alkenes with diverse arene and heteroarene substrates.[4]

While the olefination of sp^2 C−H bonds is a reliable and widely used synthetic method, analogous transformations at unactivated sp^3 C−H sites remain extremely rare.[5,6] Expanding this chemistry to unactivated alkyl groups is challenging for several reasons. First, metal-mediated cleavage of sp^3 C−H bonds is typically slow[7] and is expected to be even slower in the presence of an alkene, which can compete for coordination sites at the metal center. Second, the key C−C bond-forming event requires carbometalation of a Pd-alkyl intermediate. Such reactions (particularly intermolecular variants) are difficult, because they are frequently plagued by competing β-hydride elimination.[8,9] Finally, the nucleophilic directing groups required to promote sp^3 C−H activation can undergo intramolecular Michael addition to the olefinated products, thereby removing the versatile olefin functional group that was installed in the first step. Due to these challenges, there is currently only one report of the C−H olefination of unactivated sp^3 C−H bonds.[5] As shown in eq 1, this study by Yu and co-workers described the Pd-catalyzed reaction of pentafluorophenyl-substituted amides with benzyl acrylate (eq 1).[5] Although this was a landmark report, the transformation has a limited substrate scope, requires stoichiometric Cu^{II} and Ag^{I} salts as oxidants, and yields cyclic products derived from irreversible Michael addition of the amide to the alkene.



As part of a program aimed at developing Pd-catalyzed methods for the functionalization of unactivated C−H bonds,[10] we report herein a new nitrogen heterocycle-directed sp^3 C−H olefination reaction. This transformation utilizes air as the terminal oxidant and proceeds efficiently with a series of different 2-alkylpyridines and α,β-unsaturated alkenes. The olefin-containing products can be elaborated using a variety of synthetic methods. In addition, this reaction provides a conceptually novel entry to 6,5-nitrogen heterocycles, which constitute the cores of numerous alkaloid natural products.

Our first efforts toward sp^3 C−H olefination focused on the reaction of 2-*tert*-butylpyridine (2-tbp) with electron-deficient alkenes (eq 2). Extensive previous work from our group[10a,b] and others[11] has shown that pyridine and quinoline derivatives are effective directing groups for the Pd-mediated cleavage of sp^3 C−H bonds. The resulting palladacyclic intermediates are generally slow to undergo β-hydride elimination (presumably due to the strong coordinating ability of pyridine), making them amenable to subsequent functionalization. In addition, we reasoned that a pyridine directing group could undergo *reversible* intramolecular Michael addition to the olefin product, thereby providing access to either olefin (**A**) or a cyclic pyridinium salt (**B**), depending on the reaction conditions (eq 2).



EWG = electron withdrawing group

Dioxygen is the most cost-effective and environmentally benign terminal oxidant for this transformation. As such, we first examined the reaction of 2-tbp with ethyl acrylate under conditions reported by Ishii for the Pd/polyoxometalate cocatalyzed aerobic

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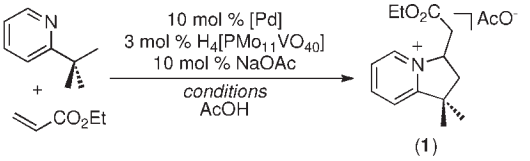
olefination of benzene derivatives.[12] Gratifyingly, the use of 10 mol % of $Pd(OAc)_2$ and 10 mol % of acetylacetone (acac) along with 3 mol % of $H_4[PMo_{11}VO_{40}]$ in AcOH at 90 °C under 1 atm of O_2 provided a 49% yield of product **1** (Table 1, entry 1). Increasing the temperature to 110 °C under 1 atm of O_2 significantly improved the yield to 81% (entry 2).

We were pleased to find that ambient air could be used in place of 1 atm of O_2 without any detrimental effect on the overall yield (Table 1, entry 3). Finally, removing the acac ligand (entry 4) and replacing $Pd(OAc)_2$ with the cationic catalyst $Pd(MeCN)_4(BF_4)_2$[13] (entry 5) both accelerated olefination and limited the formation of olefin-derived byproducts.[14] Interestingly, despite the presence of an excess (5 equiv) of alkene, this reaction exclusively afforded the monofunctionalized product **1**. This is in marked contrast to the C−H acetoxylation of 2-tbp with $PhI(OAc)_2$, which forms mixtures of mono-, di-, and triacetoxylated products.[10b] In the current system, the intramolecular Michael addition appears to play a key role in protecting the product from overfunctionalization.

As shown in Table 2, a variety of other 2-alkylpyridine derivatives participate in this sp^3 C−H olefination/cyclization reaction. We found that replacing NaOAc with 1.1 equiv of NaOTf allowed for the olefination of substrates lacking geminal dimethyl groups; for example, both 2-ethyl- and 2-*iso*-propylpyridine afforded high yields of the desired products (entries 1 and 2).

C−H activation/C−C coupling proceeded with >20:1 selectivity for 1° over 2° sp^3 C−H bonds (for example, see entry 3). However, a 2° C−H bond on the cyclopropane ring of 2-cyclopropyl-3-methylpyridine could be functionalized to form tricyclic product **5** in modest yield (entry 4). Both electron-withdrawing and electron-donating substituents were tolerated on the pyridine ring (entries 5−7), and a tethered ester functional group was also compatible with the reaction conditions (entry 9). Remarkably, even 2-methyl-6-*tert*-butylpyridine provided a moderate (36%) yield, despite the sterically crowded environment around the pyridine moiety (entry 8). Finally, quinoline was a useful directing group for sp^3 C−H olefination under these conditions (entry 10).

Table 1. Optimization of Pd-Catalyzed Reaction between 2-*tert*-Butylpyridine and Ethyl Acrylate

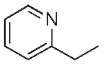
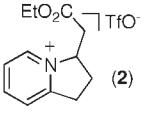
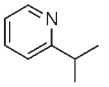
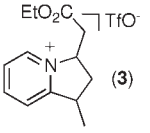
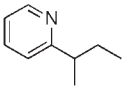
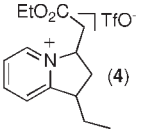
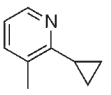
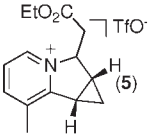
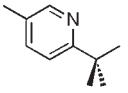
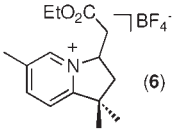
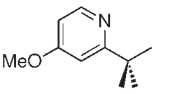
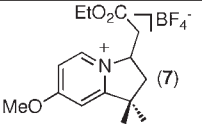
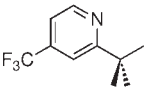
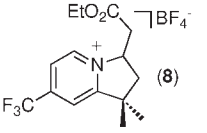
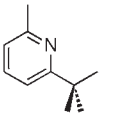
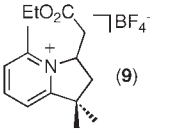
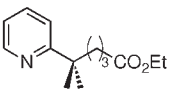
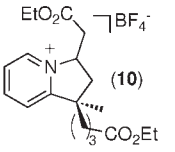
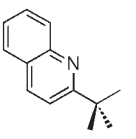
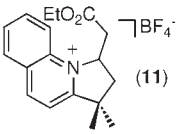


(**1**)

Entry	[Pd]	Conditions	Yield **1** (%)[a]
1	$Pd(OAc)_2$	90 °C, O_2, acac	49
2	$Pd(OAc)_2$	110 °C, O_2, acac	81
3	$Pd(OAc)_2$	110 °C, air, acac	83
4	$Pd(OAc)_2$	110 °C, air	89
5	$Pd(MeCN)_4(BF_4)_2$	110 °C, air	92

[a] Yield determined by ^1H NMR spectroscopic analysis.

Table 2. Pd-Catalyzed Olefination and Cyclization between Various Pyridines and Ethyl Acrylate

Entry	Substrate	Product	Yield
1[a]		 (**2**)	89%
2[a]		 (**3**)	81% (dr = 1.2 : 1)
3[a]		 (**4**)	55% (dr = 1.2 : 1)
4[a]		 (**5**)	43% (dr = 2.4 : 1)
5[b]		 (**6**)	70%
6[b]		 (**7**)	71%
7[b]		 (**8**)	75%
8[b]		 (**9**)	36%
9[b]		 (**10**)	49% (dr = 1 : 1)
10[b]		 (**11**)	39%

[a] Conditions: 1.1 equiv of NaOTf, 10 mol % of $Pd(MeCN)_4(BF_4)_2$, 3 mol % of $H_4[PMo_{11}VO_{40}]$, 5 equiv of ethyl acrylate, AcOH, air, 110 °C, 18 h. [b] Conditions: (i) 10 mol % of NaOAc, 10 mol % of $Pd(MeCN)_4(BF_4)_2$, 3 mol % of $H_4[PMo_{11}VO_{40}]$, 5 equiv of ethyl acrylate, AcOH, air, 110 °C, 18 h; (ii) saturated aq. $NaBF_4$.

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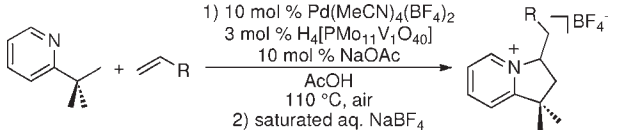
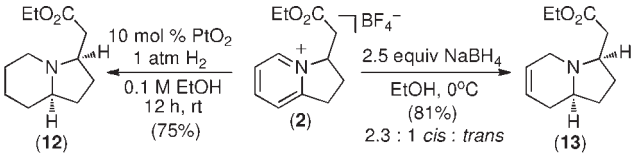
Table 3. Alkene Scope for C−H Bond Alkenylation



Entry	R	Yield (%)
1	CO_2Et	90[a]
2	CO_2Bu	80[a]
3	CO_2Bn	75[a]
4	CO_2H	69[b]
5	$CONMe_2$	55[b]
6	COEt	40[a]
7	Ph	<5[b]
8	Butyl	nr[c]

[a] Isolated yield. [b] Yield determined by ^1H NMR spectroscopic analysis. [c] nr = no reaction detected.

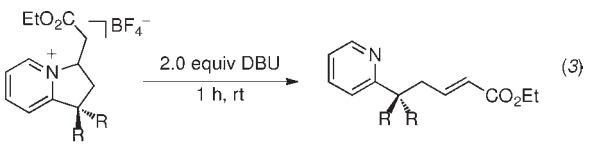
Scheme 1. Reduction Reactions of 2



The reaction of 2-tbp was also examined with a series of other olefinic substrates. As shown in Table 3, α,β-unsaturated esters, amides, and ketones were effective alkene coupling partners. Remarkably, the free carboxylic acid moiety of acrylic acid was also well tolerated (entry 4). In contrast, more electron-rich olefins like styrene and 1-hexene exhibited low reactivity under the current conditions (entries 7 and 8). This is also a common limitation of Pd-catalyzed arene C−H alkenylation reactions.[4]

The cationic bicyclic products in Tables 1−3 are useful synthetic intermediates. For example, the PtO_2-catalyzed reduction of **2** with H_2 formed piperidine **12** in 75% yield as a 28:1 mixture of *cis* and *trans* isomers (Scheme 1).[15] In addition, partial reduction of **2** with $NaBH_4$ in EtOH afforded 1,2,3,6-tetrahydropyridine **13** in 81% yield as a 2.3:1 mixture of readily separable *cis* and *trans* isomers (Scheme 1).[16] This chemistry provides an expedient route to 6,5-nitrogen heterocycles, which are a common structural motif in naturally occurring alkaloids.

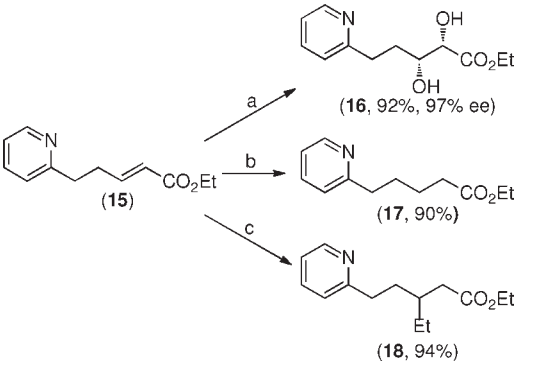
The pyridinium products of sp^3 C−H olefination/cyclization can also be converted to the corresponding alkenes by treatment with base. For example, the reaction of **2** with 2 equiv of DBU in CH_2Cl_2 for 1 h afforded olefin **15** in 95% yield (eq 3).



(**1**): R = Me
(**2**): R = H
(**14**): R = Me 82%
(**15**): R = H 95%

The ability to readily generate the olefin-containing products allowed us to explore the further functionalization of these molecules. In particular, we sought to demonstrate that the pyridine moiety was compatible with various transition-metal-mediated olefin functionalization reactions. As shown in Scheme 2, **15** underwent smooth and high yielding asymmetric dihydroxylation[17] (to form **16** in 97% ee), Pd/C-catalyzed hydrogenation[18] (to form **17**), and Cu-catalyzed conjugate addition of EtMgBr[19] (to form **18**).

Scheme 2. Functionalization of C−H Olefinated Product 15[a]



[a] Conditions: (a) AD-mix β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C, 92%, 97% ee. (b) H_2, Pd/C, EtOH, rt, 90%. (c) CuBr, LiCl, EtMgBr, TMSCl, THF, 0 °C, 94%.

In conclusion, this communication describes a new Pd-catalyzed reaction for the pyridine-directed aerobic olefination of unactivated sp^3 C−H sites. This transformation provides a convenient route to 6,5-N-fused bicyclic cores as well as readily functionalizable alkene products. Ongoing work is focused on expanding the scope of this transformation with respect to both the directing group and alkene substrate, and these results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Experimental and isolation procedures, and characterization data for all new compounds. This material is free of charge via the Internet at http://pubs.acs.org.

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(14) Product **1** was also formed when $H_4[PMo_{11}VO_{40}]$/air was replaced with other oxidants (*e.g.*, $Cu(OAc)_2$ or benzoquinone); however, significantly lower yields were obtained with these oxidants. See Table S3 for details.

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