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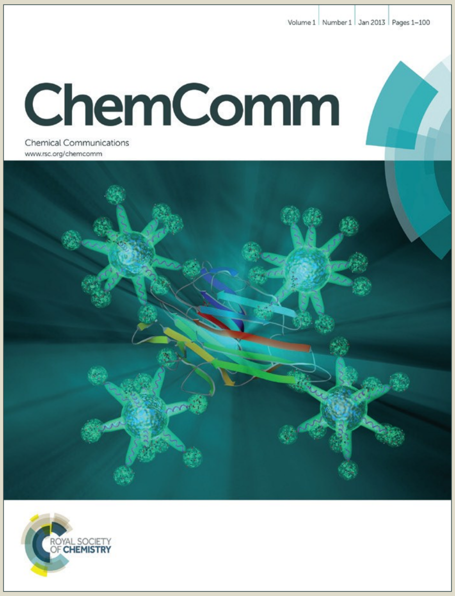

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ARTICLE TYPE

Palladium-Catalyzed Heck-Type Reaction of Oximes with Allylic Alcohols: Synthesis of Pyridines and Azafluorenones

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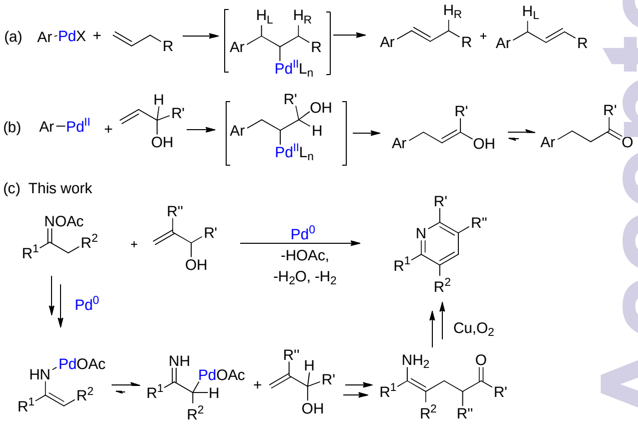
We describe herein a palladium-catalyzed Heck-type reaction of *O*-acetyl ketoximes and allylic alcohols to pyridines. This protocol allows robust synthesis of pyridines and azafluorenones in good to excellent yields with tolerance of various functional groups under mild conditions. The reaction is supposed to go through an oxidative addition of oximes to palladium(0) complexes generating alkylideneamino-palladium(II) species, which is utilized as a key intermediate to capture the nonbiased alkenes for carbon–carbon bond formation.

The N-heterocycles are some of the most important building blocks in organic chemistry.[1] Among that, pyridines are one of the most significant building blocks, which not only exist extensively in pharmaceuticals, agrochemicals, and functional materials, but also serve as useful synthetic intermediates in modern organic synthesis.[2] Considering the large spectrum of fascinating applications, the synthesis of pyridine derivatives has long been an area of intense interest, and a number of different methods have been devised for their preparation.[3] However, challenges still remains in the scope of group tolerance and equivalent usage of catalysts. Therefore, the development of methodologies for a more direct and efficient access to different substituted and specifically functionalized frameworks is always a great challenge in modern synthetic organic chemistry.

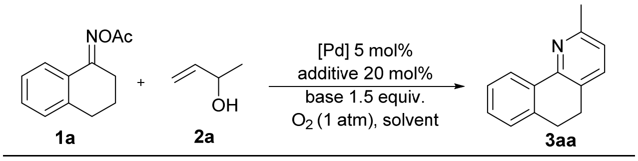
The development of catalytic C-C bond-forming reactions remains one of the main challenges in organic chemistry.[4] Among the transition metal-catalyzed reactions known to form C-C bonds, the palladium-catalyzed oxidative coupling by Mizoroki-Heck stands out as one of the most valuable synthetic tools.[5] Since its first report in 1970s, lots of efforts have been devoted to its utilization, and it is now fully recognized as one of the most significant methods for carbon–carbon bond formations.[6] Given that most of the oxidative Heck reaction was limited to active alkenes or styrenes due to the poor reactivity of unactivated olefins[7] and the dilemma of selective *β*-H elimination[8] (Scheme 1, a), therefore, transition metal-catalyzed olefination of nonbiased allylic alcohols, without the prior functionalization, is even more environmentally friendly and versatile (Scheme 1, b).[9] According to previous reports, oximes and their derivatives can be used as "internal oxidant" towards transition metal-catalyzed oxidative C-H functionalization and cleavage of the N-O bond by the participation of transition metals to form active alkylideneaminopalladium(II) species, which tautomerized to the key iminylpalladium(II) intermediates, making the following alkylpalladium-catalyzed oxidative Heck-type reaction possible (Scheme 1, c).[10,11] In this regard, based on our previous work on oximes[12] and allylic alcohols as alkyl ketone resourses[13], we design the possible [3 + 3] type cyclization with these two substrates and suppose the reaction to go through a palladium-catalyzed Heck-Type coupling of oximes with alkenes, with high efficiency under mild reaction conditions.



Scheme 1 Selective *β*-H elimination of Heck reaction

With the ability of palladium to reduce oxime N-O bonds, we chose 3,4-dihydronaphthalen-1(2*H*)-one *O*-acetyl oxime (**1a**) and but-3-en-2-ol (**2a**) as model substrates and screened different additives and other reaction conditions (Table 1). To our delight, the desired product **3aa** could be detected in 56% yield when the model reaction was conducted in CH_3CN with $CuBr_2$ as additive in the presence of $Pd(OAc)_2$ catalyst under dioxygen atmosphere at 80 °C for 24 h (entry 1). The screening of different additives including $Cu(OAc)_2$, KI, and $AgNO_3$, revealed that **3aa** could also be formed in lower yields (entries 2-4). And $Cu(OAc)_2$ was found to be the best additive and the yield of **3aa** could reach 87% (entry 2). However, with other additives, such as LiBr, NH_4Br, Bu_4NBr, and AgOAc, only trace amount of **3aa** was detected (entries 5-8). The model reaction was then tested using other palladium catalytic system, and $Pd(OAc)_2$ was found to be the most suitable catalyst system for the target reaction (entries 9-11). No reaction was observed in the absence of palladium catalyst (entry 12), while with the absence of $Cu(OAc)_2$, the reaction could give 10% yield of product **3aa** (entry 13). The yield was unsatisfactory with the decrease of the reaction temperature (entry 14), while raising the temperature to 100 °C improved the yield to 91% (entry 15). When the reaction was carried out in N_2 atmosphere, only trace amount of **3aa** was detected by GC-MS (entry 17).

Table 1 Screening for optimal reaction conditions[a]

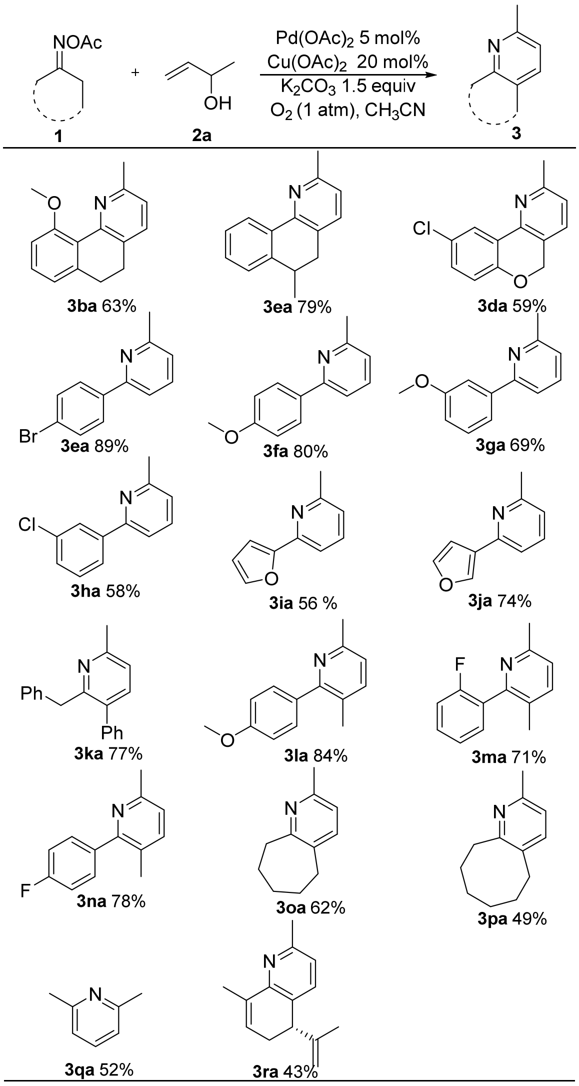


entry[a]	catalyst	additive	base	solvent	yield[b] (%)
1	$Pd(OAc)_2$	$CuBr_2$	K_2CO_3	CH_3CN	56
2	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	CH_3CN	87 (87)
3	$Pd(OAc)_2$	KI	K_2CO_3	CH_3CN	10
4	$Pd(OAc)_2$	$AgNO_3$	K_2CO_3	CH_3CN	25
5	$Pd(OAc)_2$	LiBr	K_2CO_3	CH_3CN	trace
6	$Pd(OAc)_2$	NH_4Br	K_2CO_3	CH_3CN	trace
7	$Pd(OAc)_2$	Bu_4NBr	K_2CO_3	CH_3CN	trace
8	$Pd(OAc)_2$	AgOAc	K_2CO_3	CH_3CN	trace
9	$PdCl_2$	$Cu(OAc)_2$	K_2CO_3	CH_3CN	57
10	$Pd(OTf)_2$	$Cu(OAc)_2$	K_2CO_3	CH_3CN	63
11	$Pd_2(dba)_3$	$Cu(OAc)_2$	K_2CO_3	CH_3CN	trace
12	---	$Cu(OAc)_2$	K_2CO_3	CH_3CN	n.d.
13	$Pd(OAc)_2$	--	K_2CO_3	CH_3CN	10
14[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	CH_3CN	35
15[d]	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	CH_3CN	91
16[e]	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	CH_3CN	78
17[f]	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	CH_3CN	trace

[a] Reaction conditions: Unless otherwise noted, the reaction was carried out with **1a** (0.2 mmol), **2a** (0.4 mmol), Pd catalyst (5 mol %), additive (20 mol %) and base (1.5 equiv) in solvent (1 mL) at 80 °C for 24 h. [b] Yield determined by GC-MS with dodecane as internal standard, and isolated yield in the parentheses. [c] The reaction was carried out at 60 °C. [d] The reaction was carried out at 100 °C. [e] The reaction was carried out in the open air. [f] The reaction was carried out in N_2 atmosphere.

With the optimal reaction conditions in hand, we subsequently explored the reaction scope. The oxime substrates derived from other aryl ketones such as tetralones, propiophenones and 2-phenylacetophenones could afford the products **3aa-3na** in good to excellent yields, respectively. Besides, oximes derived from aliphatic ketones afforded the pyridine derivatives **3oa-3ra** in moderate to good yields. To be specific, chroman-4-one oxime could afford **3da** in 59% yield. The formation of **3da** and **3ea** were inert under these conditions, indicating that the palladium catalyst preferentially reacts with the N-O bond of the oxime acetate over the carbon-halogen bonds. Other aryl functionalized amides could also undergo the pathway well. The 2-furan-substituted and 3-furan-substituted oximes could be tolerated in this transformation, generating **3ia** and **3ja** in 56% and 74% yields, respectively. It is noteworthy that alkyl-substituted oximes were also suitable substrates in this reaction with good yields (**3oa** to **3ra**). For example, propone oximes that contained short alkyl chains gave the products 2,6-dimethylpyrudine in moderate yield (**3qa**). Notably, L(-)-carvone derived oximes could transfer to **3ra** in 43% yield.

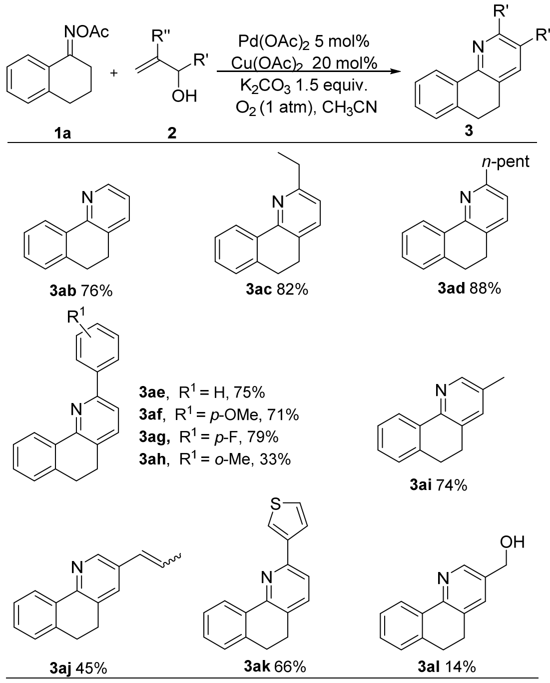
Table 2 Pd-catalyzed synthesis of substituted pyridines from different oximes[a]



[a] Reaction conditions: Unless otherwise noted, the reaction was carried out with **1** (0.5 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (20 mol %) and K_2CO_3 (1.5 equiv) in CH_3CN (1 mL) at 80 °C for 16-24 h.

We next focused our attention on the scope and generality of the olefin substrates in the oxidative coupling with oxime **1a**. This transformation displayed high functional group tolerance and proved to be a quite general method. Both aliphatic and aromatic allylic alcohols could undergo the protocol with good to excellent yields (Table 3). Alkyl-substituted allyl alcohols were found to be suitable substrates for this transformation and transferred to the desired products in good yields (**3aa** to **3ad** Even the bulky aromatic allylic alcohols with methyl, methoxy and fluoro on aryl rings all gave good to excellent yields of the corresponding pyridines (**3af-3ah**). To be specifically, **3ah** could be obtained in 35% yield, which implied the steric hindrance had no much effect on this transformation. And the substrate with aryl substitution of 1-(thiophen-3-yl)prop-2-en-1-ol underwent the Heck reaction smoothly and gave the corresponding product **3ak** in 66% yield. As for the application of hexa-1,5-dien-3-ol in this reaction, hydrogen immigration product **3aj** was obtained in 45% yield, which may further support the role of palladium in the *β*-H elimination. Besides, with the application of 2-methylenepropane-1,3-diol as the coupling reagent, the yield of the desired product **3al** sharply decreased to 14% and 50% yield of **3ai** was obtained.[14]

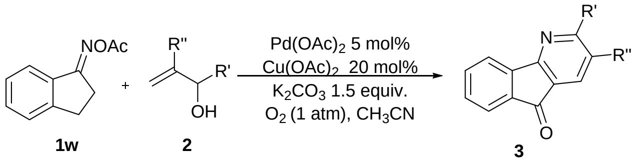
Table 3 Pd-catalyzed synthesis of substituted pyridines from different allylic alcohols[a]

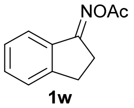
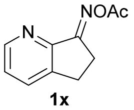


[a] Reaction conditions: Unless otherwise noted, the reaction was carried out with **1a** (0.5 mmol), **2** (1.0 mmol), Pd(OAc)$_2$ (5 mol %), Cu(OAc)$_2$ (20 mol %) and K$_2$CO$_3$ (1.5 equiv) in CH$_3$CN (1 mL) at 80 °C for 16-24 h.

Furthermore, with 1-indanone oximes as substrate, different azafluorenones could be obtained in this system.[15] For example, the reaction of 2,3-dihydro-1*H*-inden-1-one *O*-acetyl oxime (**1w**) afforded the corresponding 4-azafluorenones in good yield. Pleasingly, when 5,6-dihydro-7*H*-cyclopenta[*b*]pyridin-7-one *O*-acetyl oxime (**1x**) was applied, 39% yield of 4,5-diazafluorenone was obtained.[16]

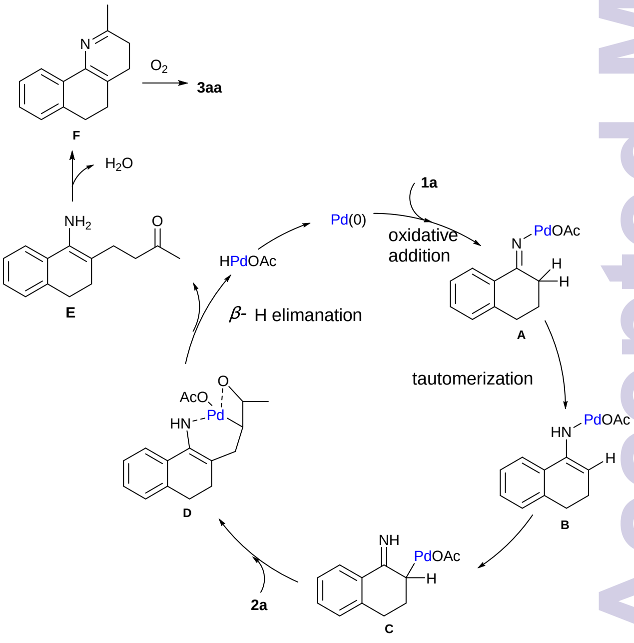
Table 4 Synthesis of azafluorenones[a]



entry	R', R''	oximes	yield (%)
1	R' = Me, R'' = H	 **1w**	45
2	R' = H, R'' = H,		67
3	R' = H, R'' = Me		47
4	R' = H, R'' = H	 **1x**	39

[a] Reaction conditions: Unless otherwise noted, the reaction was carried out with **1** (0.5 mmol), **2** (1.0 mmol), Pd(OAc)$_2$ (5 mol %), Cu(OAc)$_2$ (20 mol %) and K$_2$CO$_3$ (1.5 equiv) in CH$_3$CN (1 mL) at 80 °C for 16-24 h.

Based on the experimental results[17] and previous reports, a plausible mechanism is proposed in Scheme 2. Firstly, the oxidative addition of the oxime N-O bond to Pd(0) species easily transformed to palladium enamide intermediate **A**. Subsequent tautomerization affords the enamine-derived amido-Pd(II) species **B**.[11] Further isomerization of this species results in the conversion of this N-bound enamido-Pd(II) **B** species to its C-bound isomer **C**.[18] Followed by Mizoroki-Heck reaction of allylic alcohol **2** inserting into the carbon-palladium bond of alkylpalladium species **C** forms intermediate species **D**.[19] Then, intermediate **D** undergoes *β*-H elimination to give intermediate **E** and regenerates the active palladium catalyst.[14] The intramolecular condensation of the amine and ketone moieties of intermediate **E** forms **F**. Finally, the dehydrative oxidation gives the pyridine product **3aa**.[20] Alternative mechanism is shown in the Supporting Information.



Scheme 2 Possible mechanism

In summary, we have successfully developed a palladium-catalyzed strategy to construct pyridines from *O*-acetyl oximes and nonbiased alkenes. This protocol provides a possible pathway for the insertion of alkenes to oximes. With the operational simplicity, efficiency and functional group compatibility, this protocol will expand the scope of pyridine derivatives. Furthermore, the present method also enables the direct construction of a diverse array of azafluorenone cores, which may find applications in natural product synthesis and medicinal chemistry.

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† Electronic Supplementary Information (ESI) available: Experimental section, characterization of all compounds, copies of ^{1}H and ^{13}C NMR spectra for selected compounds. See DOI: 10.1039/b000000x/

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