EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201403372

Palladium-Catalyzed α-Selective Alkenylation of Imidazo[1,2-*a*]pyridines through Aerobic Cross-Dehydrogenative Coupling Reaction

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Keywords: C–C coupling / Dehydrogenation / Alkenylation / Oxygen / Regioselectivity / Nitrogen heterocycles

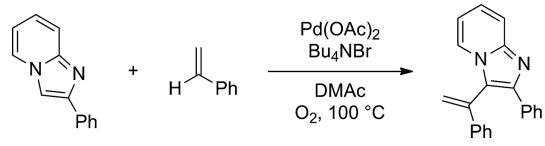
The palladium-catalyzed highly regioselective vinylation of imidazopyridines through a cross-dehydrogenative coupling reaction was developed. The reaction proceeds with the aid of molecular oxygen as the sole oxidant. A series of branched α-vinylated products were obtained with high efficiency.

Introduction

Imidazopyridines, in which the imidazole moiety is fused with a pyridine ring, is an important class of biologically active nitrogen-containing heterocycles.[1] Imidazopyridine derivatives show a wide range of biological activities, including antitumor, antiprotozoal, antiviral, antimicrobial, antiherpes, and fungicidal activities.[2] They are also used as β-amyloid formation inhibitors, GABA and benzodiazepine receptor agonists, and cardiotonic agents.[3] Many commercially available drugs such as zolpidem (used in the treatment of insomnia), alpidem (as an anxiolytic agent), olprinone (for the treatment of acute heart failure), zolimidine (used for the treatment of peptic ulcer), and necopidem and saripidem (both working as anxiolytic agents) are derived from this scaffold.[4] Owing to their diverse biological and pharmaceutical activities, there is continuous effort to develop newer strategies for the construction of functionalized imidazopyridines.[5]

Atom-efficient cross-dehydrogenative coupling (CDC) reactions are considered promising methods for new C–C bond formation. These methods avoid the prefunctionalization of starting materials (i.e., organohalides or organometallic species), which thus makes the synthetic routes straightforward and more efficient.[6] The cross-dehydrogenative coupling reaction of arenes and aromatic heterocycles with alkenes through C–H activation, particularly Pd-catalyzed oxidative cross-coupling, namely, the Fujiwara–Moritani reaction[7] or the so-called oxidative Heck-type reaction, has been proven to be the most reliable method in the field of chemical syntheses.[8] For the alkenylation process, positional selectivity attracts much attention owing to the formation of linear or branched olefins.[9] For decades, aerobic palladium(II)-catalyzed reactions involving C–H bond activation and functionalization have been studied extensively, and numerous palladium-catalyzed arene–olefin coupling reactions have been developed.[10] Although vinylation is a fundamental chemical transformation that is very useful for the synthesis of functionalized organic molecules, it is notable that direct alkenylation of imidazopyridines is very limited.[11] In fact, cross-dehydrogenative coupling for the functionalization of imidazopyridines is rare.[12] Thus, we became interested in the direct alkenylation of imidazopyridines through the cross-dehydrogenative coupling reaction.

In this context, our experiences in the syntheses of functionalized imidazo[1,2-*a*]pyridine derivatives[13] together with aerobic Pd catalysis[14] inspired us to explore the coupling between imidazo[1,2-*a*]pyridine and vinylarene. Herein, we report a highly regioselective aerobic Pd-catalyzed vinylation of imidazo[1,2-*a*]pyridines (Scheme 1). This ligand-free method affords only α-selective products and involves molecular oxygen as the sole green oxidant. Among various oxidants, molecular oxygen and air are recognized as the most effective ones[15] from the context of green and sustainable chemistry. Water is produced as the only by-product, and the use of oxygen shows a great demand from an industrial prospect.



Scheme 1. Pd-catalyzed vinylation of imidazo[1,2-*a*]pyridine; DMAc = *N*,*N*-dimethylacetamide.

Results and Discussion

Preliminary investigation of the reaction parameters was performed by using 2-phenylimidazo[1,2-*a*]pyridine (**1a**,

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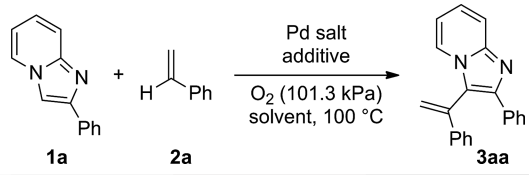
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201403372.

0.5 mmol) and styrene (**2a**, 2.5 mmol) as the model substrates. Initially, the reaction was performed by employing $Pd(OAc)_2$ (5 mol-%) in DMSO for 16 h under an atmosphere of O_2 (101.3 kPa). The olefinated product was obtained in 10% yield (Table 1, entry 1). After careful analysis it was found that the selective α-vinylation occurred only at the C-3 position of the imidazopyridine ring. Encouraged by this result, we added Bu_4NBr (2 equiv.) as an additive to the catalytic system, which we had used previously.[14] To our delight, α-vinylated product **3aa** was obtained in 45% yield (Table 1, entry 2). Next, we checked the effect of the different solvents such as DMF, DMAc (*N*,*N*-dimethylacetamide), NMP (*N*-methylpyrrolidone), and dioxane (Table 1, entries 3–6). Interestingly, DMAc was found to be superior to the other solvents, and it afforded the desired product in 75% yield (Table 1, entry 4). The amount of additive was also important. The yield of the product decreased if 1 equiv. of Bu_4NBr (TBAB) was used (Table 1, entry 7). No significant increase in yield was observed upon increasing the amount of TBAB (Table 1, entry 8). The use of Bu_4NI led to a decrease in the yield (Table 1, entry 9). The use of other Pd catalysts such as $PdCl_2$ and $Pd(PPh_3)_2Cl_2$ was also found to be ineffective (Table 1, entries 10 and 11). The effect of the catalyst loading was also studied. No improvement in the yield was observed upon increasing the amount of catalyst (Table 1, entry 12). The reaction produced only 52% of the desired product in ambient air without using molecular oxygen (Table 1, entry 13). A significant decrease in the yield was found upon lowering the temperature to 60 °C, even after 24 h (Table 1, entry 14).

Table 1. Optimization of the reaction parameters.[a]



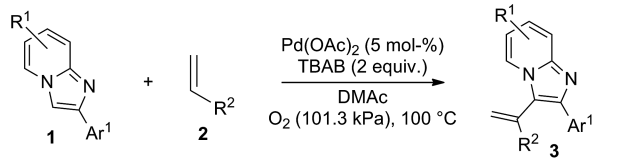
1a 2a 3aa

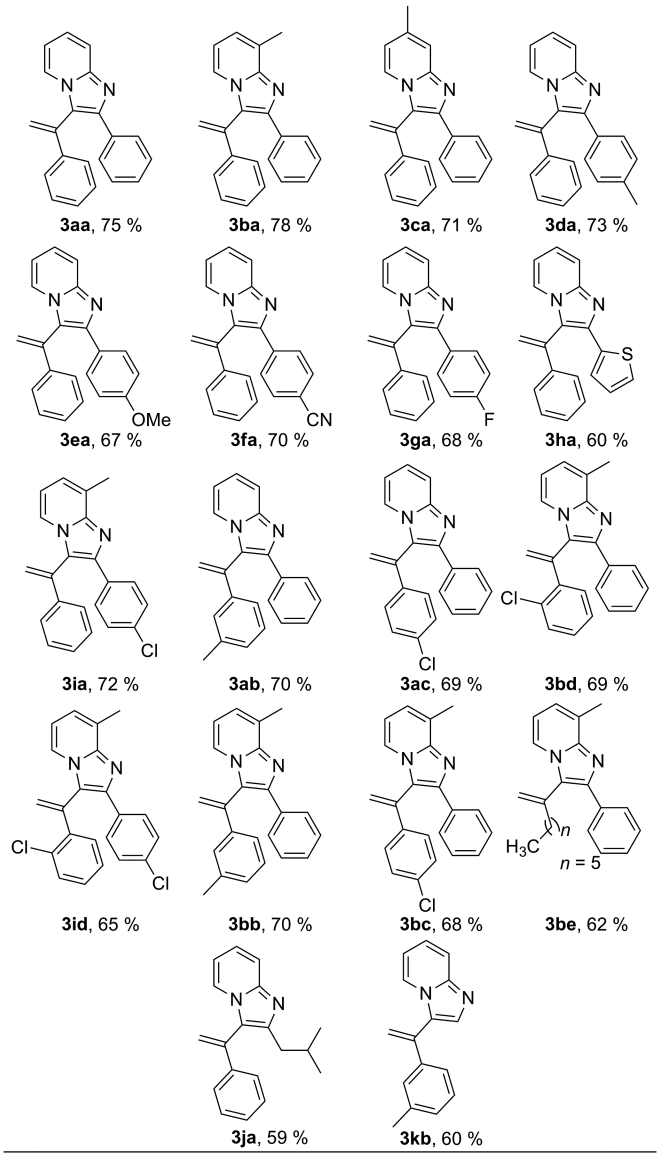
Entry	Catalyst	Additive (equiv.)	Solvent	Yield [%][b]
1	$Pd(OAc)_2$	–	DMSO	10
2	$Pd(OAc)_2$	Bu_4NBr (2)	DMSO	45
3	$Pd(OAc)_2$	Bu_4NBr (2)	DMF	50
4	$Pd(OAc)_2$	Bu_4NBr (2)	DMAc	75
5	$Pd(OAc)_2$	Bu_4NBr (2)	NMP	65
6	$Pd(OAc)_2$	Bu_4NBr (2)	dioxane	10
7	$Pd(OAc)_2$	Bu_4NBr (1)	DMAc	45
8	$Pd(OAc)_2$	Bu_4NBr (3)	DMAc	77
9	$Pd(OAc)_2$	Bu_4NI (2)	DMAc	40
10	$PdCl_2$	Bu_4NBr (2)	DMAc	15
11	$Pd(PPh_3)_2Cl_2$	Bu_4NBr (2)	DMAc	trace
12	$Pd(OAc)_2$	Bu_4NBr (2)	DMAc	78[c]
13	$Pd(OAc)_2$	Bu_4NBr (2)	DMAc	52[d]
14	$Pd(OAc)_2$	Bu_4NBr (2)	DMAc	35[e]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (2.5 mmol), Pd catalyst (5 mol-%), additive (2 equiv.), solvent (1.5 mL), 100 °C, 16 h. [b] Yield of isolated product. [c] $Pd(OAc)_2$ (10 mol-%). [d] In ambient air. [e] At 60 °C.

Having established the optimized reaction conditions (Table 1, entry 4), we studied the generality of this coupling reaction by using various imidazopyridines and vinylarenes (Table 2). Imidazopyridine moieties having a methyl substituent at C-6 and C-7 produced the corresponding 3-alkenylated products in high yields. Moreover, chloro and fluoro substituents at C-2 of the phenyl ring of the imidazopyridines reacted very well (see products **3ga** and **3ia**). Cyano-substituted imidazopyridine also reacted smoothly under the reaction conditions (see product **3fa**). Moreover, imid-

Table 2. Scope of the oxidative olefination of various imidazopyridines with vinylarenes.[a]

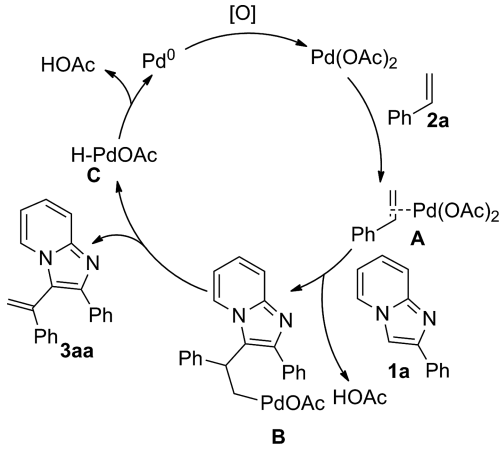




[a] Reaction conditions: **1** (0.5 mmol), **2** (2.5 mmol), $Pd(OAc)_2$ (5 mol-%), TBAB (2 equiv.), DMAc (1.5 mL), 100 °C, 16 h. [b] Yield of the isolated product.

azopyridine containing a thiophenyl substituent at C-2 afforded the desired product in 60% yield (see product **3ha**). Sterically hindered *ortho*-substituted vinylarenes furnished the desired products in good yields (see products **3bd** and **3id**). Chloro-substituted vinylarenes also underwent vinylation efficiently (see products **3ac** and **3bc**). Notably, 1-octene produced the corresponding vinylated imidazopyridine in good yield (see product **3be**). Furthermore, 2-isobutylimidazo[1,2-*a*]pyridine afforded the desired product in 59% yield (see products **3ja**), and 2,3-unsubstituted imidazopyridine selectively produced the C-3 vinylated product efficiently in good yield (see product **3kb**).

On the basis of literature reports,[16] a plausible reaction mechanism for the Pd-catalyzed aerobic oxidative C–H alkenylation of imidazopyridine is shown in Scheme 2. The reaction is initiated by activation of styrene (**2a**) by $Pd(OAc)_2$ to form intermediate **A**. Subsequent intermolecular nucleophilic attack by the 3-position of imidazopyridine moiety **1a** to intermediate **A** produces intermediate **B**. Consequently, β-hydride elimination from intermediate **B** produces corresponding branched α-product **3aa** and HPdOAc (**C**). The resultant palladium hydride (HPdOAc) then undergoes a reductive elimination/oxidation sequence to regenerate the active Pd^{II} catalyst by the aid of molecular oxygen. Possibly, the ammonium salt stabilizes the catalytically active Pd species that is formed during the course of reaction in the form of nanoclusters or nanoparticles.[17]



Scheme 2. Plausible reaction mechanism.

Conclusions

In summary, we developed a Pd^{II}-catalyzed convenient method for the vinylation of imidazo[1,2-*a*]pyridines. The reaction proceeds through a cross-dehydrogenative coupling path with the aid of molecular oxygen as the sole green oxidant. The excellent regioselectivity of this method furnished only α-vinylated product in high yields. We believe this strategy will broaden the scope of synthesizing functionalized imidazopyridine derivatives through cross-dehydrogenative coupling.

Experimental Section

Typical Procedure for the Synthesis of 2-Phenyl-3-(1-phenylvinyl)imidazo[1,2-*a*]pyridine (3aa): A sealed tube was charged with a mixture of 2-phenylimidazo[1,2-*a*]pyridine (**1a**; 0.5 mmol, 97 mg) and styrene (**2a**; 2.5 mmol, 0.290 μL). $Pd(OAc)_2$ (5 mol-%, 6 mg), TBAB (2 equiv., 322 mg), and DMAc (1.5 mL) were added under an atmosphere of O_2 (balloon, 101.3 kPa). The resulting mixture was stirred at 100 °C for 16 h. Upon cooling to room temperature, the mixture was extracted with ethyl acetate. The organic phase was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude residue, which was purified by column chromatography (silica gel, 60–120 mesh; petroleum ether/ethyl acetate = 9:1) to afford pure olefinated product **3aa** (111 mg, 75%) as a colorless oil.

Supporting Information (see footnote on the first page of this article): General experimental procedures, characterization data, and NMR (^1H and ^{13}C) spectra of all compounds.

Acknowledgments

A. H. acknowledges financial support from the Council of Scientific and Industrial Research (CSIR), New Delhi [grant number 02 (0168)/13/EMR-II]. The authors are thankful to the Department of Science and Technology (DST)-FIST and University Grants Commission (UGC)-SAP. M. G. thanks UGC and A. N. thanks CSIR for their fellowships.

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Received: October 30, 2014
Published Online: ■

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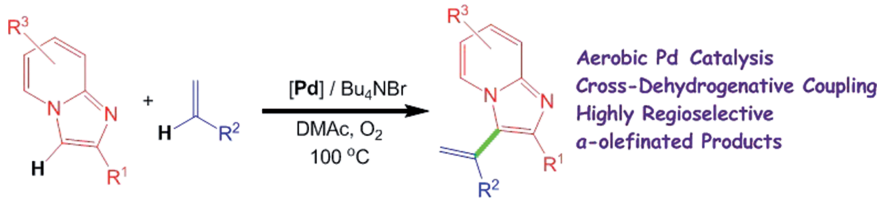
Cross-Dehydrogenative Coupling



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