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Palladium(II)-catalyzed intermolecular oxidative C-3 alkenylations of imidazo[1,2-*a*]pyridines by substrate-contolled regioselective C–H functionalization†

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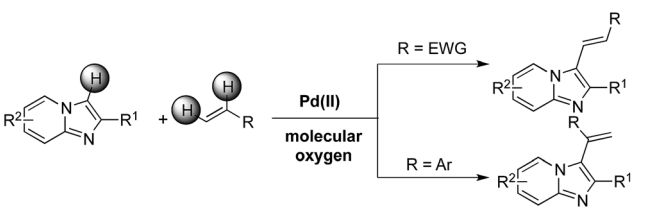
An efficient and highly regioselective palladium(II)-catalyzed oxidative C-3 alkenylation of imidazo[1,2-*a*]pyridines with acrylate, acrylonitrile, or vinylarenes has been developed by using oxygen as an oxidant. Substrates such as acrylate and acrylonitrile tended to form β-product, while vinylarenes tended to form the sole α-products.

The metal-catalyzed Heck reaction which received the Nobel Prize in 2010 has become one of the most widely used methods in chemical synthesis.[1] This approach offers the possibility for catalytic transformation of unactivated C–H bonds into diverse functionalities. Currently, direct oxidative alkenylation of heterocycles has already achieved widespread acceptance within the organic synthetic fields, because of its capacity to utilize simpler and cheaper precursors for the preparation of functionalized molecules. Consequently, the discovery of efficient methods for the assembly of carbon–carbon bonds has attracted attention in this field, which avoided synthesis of complex and expensive starting substrates. Since the pioneering Fujiwara and co-workers[2] have first described a wealth of palladium- and rhodium-catalyzed oxidative alkenylations. Many elegant direct oxidative alkenylations[3] have been achieved without the need for prior halogenation or metallization in this field. Despite of several methods have been reported during the last decades, there is still an intrinsic need for open new routes to synthesize of diverse heterocycles molecules.

Imidazo[1,2-*a*]pyridines are extremely important chemicals that exhibit a wide range of biological activities[4] and are used as antiviral,[5] antiulcer,[6] antibacterial,[7] antifungal,[8] antiprotozoal,[9] antiherpes,[10] anti-inflammatory.[11] Since the wide application of imidazo[1,2-*a*]pyridines in pharmaceutical research and drugs including Alpidem, Zolpidem, Necopidem, Olprinone, Divalpon and Zolimidine are available in the market, the development of efficient methods to synthesize imidazo[1,2-*a*]pyridines has continuously attracted the attentions of many chemists.[12] We have recently developed facile C–H transformation for the preparation of imidazo[1,2-*a*]pyridine[13] and other heterocyclic compounds. In this context, our attention is focused on the development alkenylations of imidazo[1,2-*a*]pyridine to prepare imidazo[1,2-*a*]pyridine derivatives (Scheme 1). Moreover, the reaction has proceeded by using molecular oxygen as terminal oxidant, which avoided the environmentally hazardous by-products obtained with other oxidants.[14]

The initial screening studies have been carried out using **1a** and **2a** as model substrate to identify and optimize many different combinations of potential catalysts, oxidants, additives, and solvents in order to improve the yields of the reaction. The results are summarized in Table 1. First, treatment of **1a** with **2a** in the presence of $PdCl_2$, $Cu(OAc)_2$ and AcOH at 120 °C in dioxane, a trace of the desired directly alkenylation product **3a** was observed (entry 1). Other Pd-catalyst was also tested (entries 2–5), including $Pd(O_2CCF_3)_2$, $Pd(CH_3CN)Cl_2$, $Pd(dba)_2$, $Pd(OAc)_2$. Interestingly, the use of $Pd(OAc)_2$ afforded the corresponding products **3a** in 9% GC yield, while other palladium sources gave poor yields. On changing the oxidants we observed a significant improvement by using Ag_2CO_3 as oxidant in the reaction and the product **3a** was obtained in 32% GC yield (entry 6). Other silver salts, such as AgOAc or AgOTf, were also employed and the desired product was obtained in 21%, 20% yields respectively (Table 1, entries 7 and 8). Other oxidants, such as BQ, DDQ, *t*BuOOBz, O_2 and air were also tested (entries



Scheme 1 Alkenylations of imidazo[1,2-*a*]pyridines.

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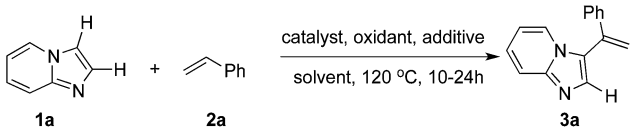
Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Oxidant	Additive	Solvent	t (h)	Yield[b] (%)
1	$PdCl_2$	$Cu(OAc)_2$	AcOH	Dioxane	24	trace
2	$Pd(O_2CCF_3)_2$	$Cu(OAc)_2$	AcOH	Dioxane	24	5
3	$Pd(CH_3CN)Cl_2$	$Cu(OAc)_2$	AcOH	Dioxane	24	trace
4	$Pd(dba)_2$	$Cu(OAc)_2$	AcOH	Dioxane	24	trace
5	$Pd(OAc)_2$	$Cu(OAc)_2$	AcOH	Dioxane	24	9
6	$Pd(OAc)_2$	AgOAc	AcOH	Dioxane	24	32
7	$Pd(OAc)_2$	Ag_2CO_3	AcOH	Dioxane	24	21
8	$Pd(OAc)_2$	AgOTf	AcOH	Dioxane	24	20
9	$Pd(OAc)_2$	BQ	AcOH	Dioxane	24	NR
10	$Pd(OAc)_2$	DDQ	AcOH	Dioxane	24	NR
11	$Pd(OAc)_2$	*t*BuOOBz	AcOH	Dioxane	24	NR
12	$Pd(OAc)_2$	O_2 (1 atm)	AcOH	Dioxane	24	27
13	$Pd(OAc)_2$	Air (1 atm)	AcOH	Dioxane	24	5<
14[c]	$Pd(OAc)_2$	O_2 (1 atm)/Ag_2CO_3	AcOH	Dioxane	24	69
15[c]	$Pd(OAc)_2$	O_2 (1 atm)/Ag_2CO_3	$PhCO_2H$	Dioxane	24	12
16[c]	$Pd(OAc)_2$	O_2 (1 atm)/Ag_2CO_3	AcOH/Ac_2O	Dioxane	24	81
17[c]	$Pd(OAc)_2$	O_2 (1 atm)/Ag_2CO_3	Py	Dioxane	24	40
18[c]	$Pd(OAc)_2$	O_2 (1 atm)/Ag_2CO_3	K_2CO_3	Dioxane	24	12
19[c]	$Pd(OAc)_2$	O_2 (1 atm)/Ag_2CO_3	AcOH/Ac_2O	Toluene	24	46
20[c]	$Pd(OAc)_2$	O_2 (1 atm)/Ag_2CO_3	AcOH/Ac_2O	DMA	24	60
21[c]	$Pd(OAc)_2$	O_2 (1 atm)/Ag_2CO_3	AcOH/Ac_2O	DMSO	24	13
22[c]	$Pd(OAc)_2$	O_2 (1 atm)/Ag_2CO_3	AcOH/Ac_2O	DMF	24	19
23[c]	$Pd(OAc)_2$	O_2 (1 atm)/Ag_2CO_3	AcOH/Ac_2O	Dioxane	30	77
24[c]	$Pd(OAc)_2$	O_2 (1 atm)/Ag_2CO_3	AcOH/Ac_2O	Dioxane	12	62

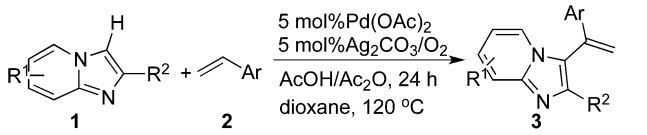
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (2.5 mmol), catalyst (5% mol), oxidant (1.2 mmol), additive (0.5 mmol), solvent (3.0 mL). [b] GC yields. [c] 5 mol% Ag_2CO_3, O_2 (500 mL).

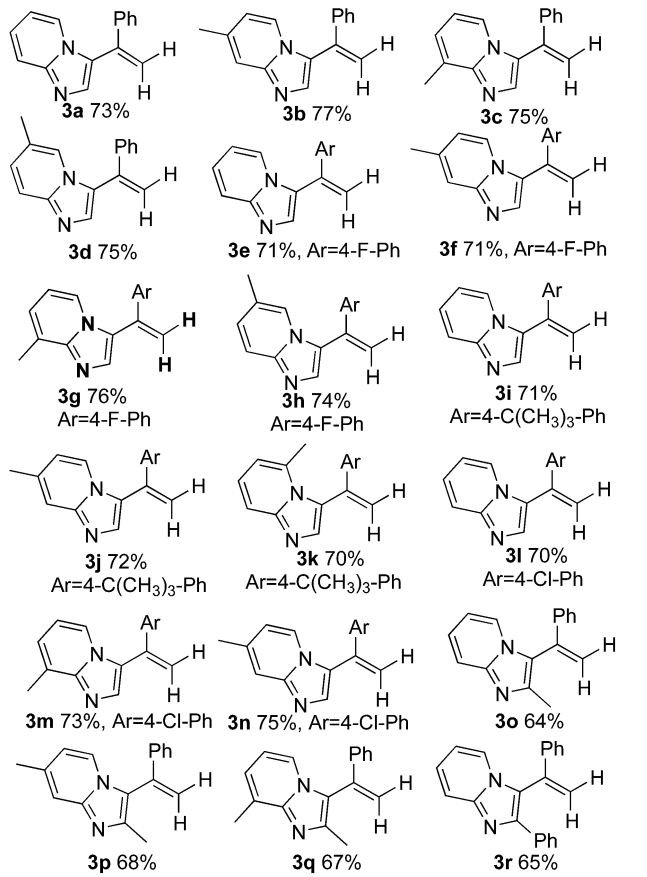
9–13). The results showed that O_2 was a choice for this transformation. To our delight, the good yield was obtained, when the reaction was carried out by using Ag_2CO_3 (5 mol%) and O_2 (with oxygen ballon) as co-oxidant (entry 14) in the presence of $Pd(OAc)_2$. These results encouraged us to adjust additives to improve the yield (entries 15–18). We were pleased to find that the yield of **3a** could be observed in 81% by using AcOH and Ac_2O as additives (entry 16). Effects of solvents and temperatures were also investigated in the following tests (entries 19–22). Among them, dioxane was demonstrated to be the best choice. Nonetheless, the yield could not be improved with the increasing reaction time to 30 h (entry 23). But decreasing the time to 12 h did affect the reaction efficiency and the low yields of **3a** were obtained (entry 24).

With the optimized conditions in hand, we next investigated the scope of this novel highly regioselective alkenylation of imidazo[1,2-*a*]pyridines with styrene for synthesis of α-products. And the results are described in Table 2. A variety of imidazo[1,2-*a*]pyridines with electrondonating methyl groups at the 2-, 6-, 7-, and 8-positions were smoothly alkenylated at the 3-position with styrene in good yields (Table 2). Thus, we turned our attention to examine the scope of vinylarenes. Various substituted styrene was reacted well with **1** and led to the desired α-products **4a–4r** in good yields. The presence of electron-withdrawing groups, such as F and Cl, were tolerated in the reaction and afforded the desired products smoothly.

Subsequently, a variety of acrylates were examined. The desired α-product was not formed, while only β-products obtained under the optimized conditions. The results are described in Table 3. A variety of acrylates were examined. It was observed that alteration of an alkoxy part of acrylate did not change the reaction efficiency, and a similar level of product yields was obtained in the alkenylation of butyl, methyl, ethyl, and cyclohexyl acrylate. The scope of various types of imidazo-[1,2-*a*]pyridine substrates was also extensively surveyed. The imidazo[1,2-*a*]pyridine and its derivatives with electrondonating methyl groups at the 2-, 6-, 7-, and 8-positions were smoothly alkenylated at the 3-position with acrylate in good yields. The substrate ethyl imidazo[1,2-*a*]pyridine-2-carboxylate with electronwithdrawing CO_2Et group at 2-positions also performed very well and afforded the desired product **4j** in good yield. Notably, high regioselectivity was observed, when the reactions were carried out by using 2,3-dihydro-imidazo[1,2-*a*]-pyridines with acrylate. All the results indicated that this process is highly regioselective for C-3 alkenylation.

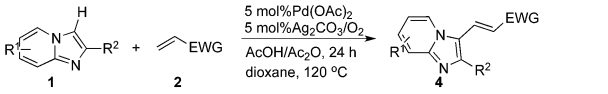
Table 2 Alkenylations of imidazo[1,2-*a*]pyridines with styrenes[a]

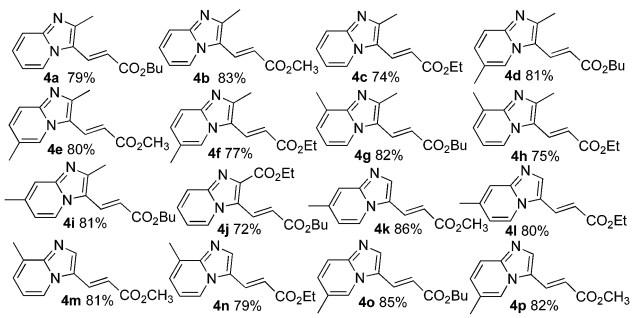




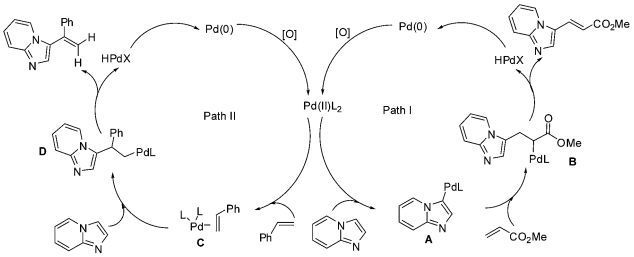
[a] Isolated yields.

Table 3 Alkenylations of imidazo[1,2-*a*]pyridines with acrylates[a]





[a] Isolated yields.



Scheme 2 Proposed mechanism.

On the basis of the previous report and our results at this stage, we have proposed two plausible pathways for the two oxidative coupling reactions in Scheme 2. Path I:[2,15] palladation at C-3 of imidazo[1,2-*a*]pyridine (electrophilic substitution) was thought to occur intermediate **A** with the aid of oxidant. Active intermediate **A** then inserts into the methyl acrylate to give intermediate **B**, which rapidly decomposes through β-elimination to generate the desired product and Pd catalyst (regular Heck-reaction product); Path II:[1b,3l,16] palladium(II) salts tend to react with styrene to give the intermediate **C**, which then can undergo an intermolecular nucleophilic attack of **1a** (usually at the more substituted vinylic carbon) to generate intermediate **D**. The corresponding product is formed *via* β-hydride elimination from intermediate **D** and releases the Pd catalyst.

In summary, we have developed an efficient method for the selective intermolecular alkenylation of substituted imidazo-[1,2-*a*]pyridines with diverse acrylate, acrylonitrile, and styrenes through a palladium-catalyzed C–H functionalization reaction. It represents a novel, regio- and stereoselective oxidative alkenylation process. This transformation using molecular oxygen to avoid excessive silver levels also results in a clean and rather waste-free process.

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