

Palladium-Catalyzed Rearrangement/ Arylation of 2-Allyloxypyridine Leading to the Synthesis of N-Substituted 2-Pyridones

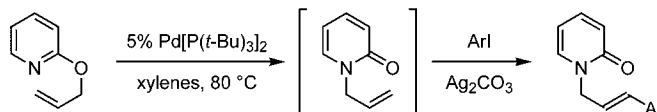
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ABSTRACT



The Pd-catalyzed one-pot rearrangement/arylation of 2-allyloxypyridine is described. The catalyst/base combination of Pd[P(*t*-Bu)₃]₂/Ag₂CO₃ was found to be optimal for this one-pot rearrangement/arylation. The initial rearrangement of 2-allyloxypyridine was found to be catalyzed by both Pd(0) and Pd(II) complexes with different mechanisms.

N-Substituted 2-pyridones, as exemplified by camptothecin¹ and cerpegin,² have emerged as a new class of compounds with interesting biological and pharmacological functions³ and, hence, an efficient entry into the N-substituted 2-pyri-

done structure has become an important task in organic synthesis.⁴ During the course of our investigation using 2-allyloxypyridine (**1**) as a substrate for the chelation-controlled Mizoroki–Heck reaction,⁵ we have discovered the Pd-catalyzed one-pot rearrangement/arylation of 2-allyloxypyridine (**1**) with aryl iodides as a novel synthetic method for N-substituted 2-pyridones.

In the course of the screening of catalyst and reaction conditions for Mizoroki–Heck reaction of **1**, we have encountered somewhat surprising results. Under the influence of Herrmann's palladacycle catalyst,⁶ **1** underwent the expected Mizoroki–Heck arylation with iodobenzene (Scheme 1). However, when we switched the arylating agent from iodobenzene to bromobenzene and base from NaOAc to Cy₂-NMe, quantitative conversion of **1** to N-allyl-2-pyridone (**2**) was observed (Scheme 1). Although somewhat apart from

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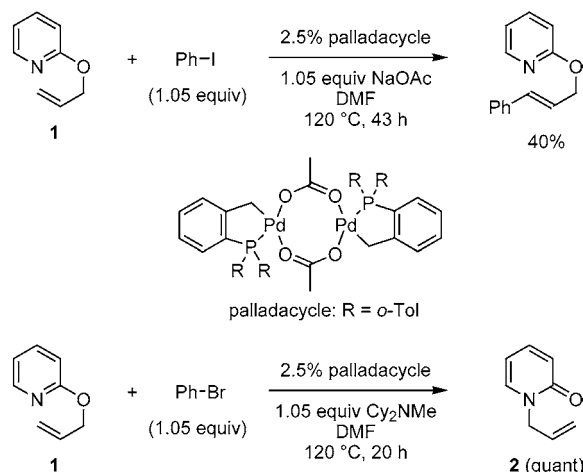
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Scheme 1



the initial thrust of project, we were particularly interested in this catalytic rearrangement because, if further functionalizations of the resultant *N*-allyl-2-pyridone using the same catalyst were feasible, it could offer an efficient entry into synthetically useful *N*-substituted 2-pyridone structure from readily available 2-allyloxy pyridine.

The Claisen [3,3] sigmatropic thermal rearrangement of 2-allyloxy pyridine (**1**) is known to occur around 255 °C to afford **2** (26%) and *C*-allylated product (29%).⁷ Stewart and Seibert found that H₂PtCl₆, Na₂PtCl₄, BF₃·OEt₂, and SnCl₄ could catalyze this rearrangement (140 °C).⁸ Pt(PPh₃)₄ catalyst was discovered by Balavoine and Guibe.⁹ The Pd(II)-catalyzed rearrangement of 2-allyloxy-4-trifluoromethylpyridines was found by Venkataratnam.¹⁰

Therefore, we initially examined the rearrangement of **1** to **2** with various Pd(II) and Pd(0) complexes (Table 1). The

Table 1. Rearrangement of **1** to **2** with Various Pd Complexes^a

entry	catalyst	time (h)	conversion (1 , %)
1	PdCl ₂ (PhCN) ₂	2	92
2	PdCl ₂	2	97
3	Pd(OAc) ₂	2	44
4	Pd(PPh ₃) ₄	2	98
5	Pd[P(<i>t</i> -Bu) ₃] ₂	2	98
6	Pd(PCy ₃) ₂	46	<20

^a All reactions were performed at 80 °C in xylenes using **1** and Pd complex (5 mol %).

reactions were carried out at 80 °C in xylenes. As for Pd(II) complexes, PdCl₂(PhCN)₂ and PdCl₂ were found to be excellent catalysts while Pd(OAc)₂ was not. As for Pd(0)

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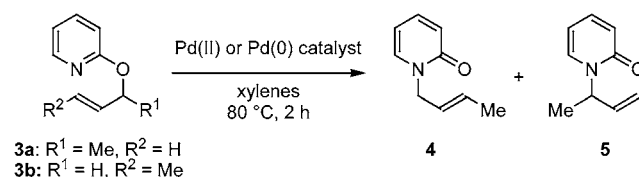
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complexes, Pd(PPh₃)₄ and Pd[P(*t*-Bu)₃]₂ were found to be excellent catalysts (98% conversion after 2 h) while Pd(PCy₃)₂ was found to be by far a less efficient catalyst. Though Pd(II)- and Pd(0)-catalyzed rearrangements were already reported for similar allyl imidates,^{11,12} this is the first demonstration that both Pd(II) and Pd(0) complexes could catalyze the rearrangement of 2-allyloxy pyridine (**1**) to *N*-allyl-2-pyridone (**2**).

We felt that the rearrangement catalyzed by Pd(II) and Pd(0) complexes must be different in mechanism despite the same outcome when using **1**. Thus, to shed light on the mechanism, 2-(1-methylallyloxy)pyridine (**3a**) and 2-crotyloxy pyridine (**3b**) were prepared and subsequently subjected to Pd(II)- and Pd(0)-catalyzed rearrangement (Table 2).

Table 2. Pd-Catalyzed Rearrangement of **3a** and **3b**^a

entry	3	catalyst	4/5
1	3a	PdCl ₂	100/0 ^b
2	3b	PdCl ₂	0/100
3	3a	Pd(PPh ₃) ₄	33/67 ^c
4	3b	Pd(PPh ₃) ₄	32/68 ^d

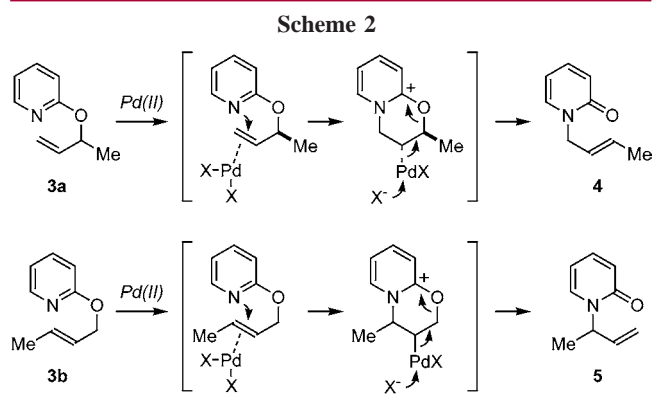
^a All reactions were performed at 80 °C in xylenes using **3** and Pd complex (5 mol %). ^b **4** was formed as a mixture of *E/Z* isomers (96/4). ^c **4** was formed as a mixture of *E/Z* isomers (79/21). ^d **4** was formed as a mixture of *E/Z* isomers (81/19).

Under the influence of PdCl₂ catalyst, **3a** and **3b** were smoothly and selectively converted to **4** and **5**, respectively (>99% regioselectivity). On the other hand, Pd(PPh₃)₄-catalyzed the rearrangement of **3a** and **3b** with lower regioselectivity. The ratio of regioisomers (**4** and **5**) was found to be almost equal (33/67 and 32/68). These results suggested that the catalytic rearrangement of 2-allyloxy pyridines resembles that of allyl imidates.^{11,12}

Clearly different scenarios can be envisaged for this rearrangement catalyzed by Pd(II) or Pd(0) complexes, respectively. In the Pd(II) catalysis, the rearrangement of **3** proceeded in a complete regioselective manner. This suggests that the mechanism of Pd(II)-catalyzed rearrangement may resemble the uncatalyzed thermal rearrangement. In the Pd(II)-catalyzed rearrangement, an electrophilic Pd(II) complex

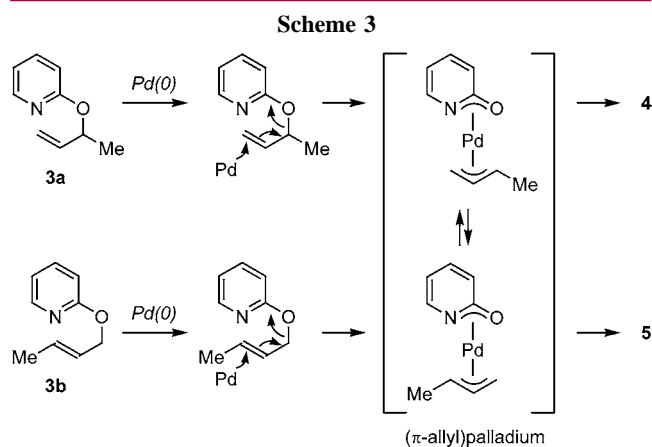
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(12) Pd(0)-catalyzed rearrangement of allyl imidates: ref 11c,d.



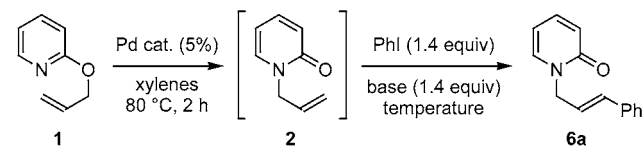
should coordinate to C=C bond and activate it toward nucleophilic attack (Scheme 2). Thereafter, the intramolecular nucleophilic attack of the lone pair of nitrogen to C=C bond occurs and produces a palladium-bound carbenium ion intermediate which rearranges to the product. This accounts for the observed regioselectivity.

On the other hand, the Pd(0)-catalyzed rearrangement might proceed through the intermediary of (π -allyl)palladium complex as shown in Scheme 3. First, nucleophilic Pd(0)



might attack the C=C bond of **3** followed by leaving of pyridonyl group to produce (π -allyl)palladium(II) intermediate. This resembles the formation of (π -allyl)palladium complex through the reaction of Pd(0) complex with allylic compound with a leaving group (a formal oxidative addition of Pd(0) to **3**). The final C–N bond-forming process may be either C–N reductive elimination from Pd(II) complex or nucleophilic attack of pyridonyl anion to the allyl ligand on Pd. If the former is the case, the fact that the ratio of regioisomers (**4** and **5**) was found to be almost equal either starting from **3a** or **3b** could be explained by rapid π - σ - π rearrangement prior to final C–N reductive elimination. Nonetheless, by assuming (π -allyl)palladium intermediates, the lack of regioselectivity and the similar regioselectivity for the rearrangement of **3a** and **3b** could be explained.

Table 3. Reaction Conditions for Pd-Catalyzed One-Pot Rearrangement/Arylation of **1**



entry	catalyst	base	<i>T</i> (°C)	time (h)	yield (%)
1	PdCl ₂	Cs ₂ CO ₃	130	21	50
2	Pd(PPh ₃) ₄	Cs ₂ CO ₃	130	20	18
3	Pd[P(<i>t</i> -Bu) ₃] ₂	Cs ₂ CO ₃	130	14	58
4	Pd[P(<i>t</i> -Bu) ₃] ₂	Cy ₂ NMe	130	20	30
5	Pd[P(<i>t</i> -Bu) ₃] ₂	Ag ₂ CO ₃	130	4	58
6	Pd[P(<i>t</i> -Bu) ₃] ₂	Ag ₂ CO ₃	100	24	70

Having established that the rearrangement of **1** could be catalyzed by both Pd(II) and Pd(0) complexes, we next examined the Pd-catalyzed rearrangement/arylation of **1** with aryl iodide as a new synthetic route toward synthetically useful *N*-substituted 2-pyridones. The reaction conditions were examined using iodobenzene as an arylating agent (Table 3). First, **1** was subjected to the Pd-catalyzed rearrangement in xylenes at 80 °C under argon giving **2** in situ. Thereafter, iodobenzene (1.4 equiv) and a base (1.4 equiv) were added to the reaction mixture to afford substituted pyridone **6a** in one-pot. The initial survey of catalyst precursor revealed that Pd[P(*t*-Bu)₃]₂ is a superior catalyst precursor over PdCl₂ and Pd(PPh₃)₄ giving **6a** in 58% yield (entry 3).¹³ The double-bond isomerization of **2** to give *N*-propenyl-2-pyridone was found to be a major side reaction in this process. To suppress this undesirable pathway, several bases other than Cs₂CO₃ were examined. Although the use of reputed Cy₂NMe^{13,14} resulted in slower reaction with significant double-bond isomerization of **2**, the use of Ag₂CO₃ resulted in faster reaction. Finally, it was found that **6a** could be obtained in 70% yield when the reaction was carried out at 100 °C (entry 6).^{15,16,17} Double-bond isomerization of **2** was found to be minimal at this temperature. The use of an equimolar amount of iodobenzene provided **6a** in 59% yield, albeit with a much longer reaction time.

Under the influence of this newly developed Pd[P(*t*-Bu)₃]₂/Ag₂CO₃ catalytic system, in situ generated **2** was arylated

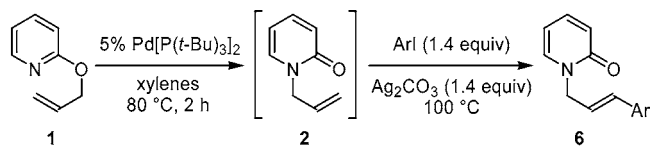
(13) Pd/P(*t*-Bu)₃ catalyst for Mizoroki–Heck reaction: Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.

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(15) When bromobenzene was used as an arylating agent in place of iodobenzene under the influence of the Pd[P(*t*-Bu)₃]₂/Ag₂CO₃ catalytic system, **6a** was obtained in 16% yield after 96 h at 100 °C. Phenyl triflate was a totally ineffective arylating agent in this reaction.

(16) Toluene can also be used as a solvent in place of xylenes.

(17) When isolated rearrangement product **2** was subjected to Pd-catalyzed arylation (5 mol % Pd[P(*t*-Bu)₃]₂, 1.4 equiv of PhI, 1.4 equiv of Ag₂CO₃, xylenes, 100 °C, 24 h), **6a** was obtained in 30% yield together with a considerable amount (23%) of *N*-propenyl-2-pyridone. The lower yield compared with that of the one-pot rearrangement/arylation process may be due to the instability of **2**. Alternatively, the use of “fresh” Pd[P(*t*-Bu)₃]₂ may be detrimental in the arylation step. In the one-pot process, more active “Pd[P(*t*-Bu)₃]₂”¹³ may be generated in situ during the rearrangement reaction.

Table 4. Pd-Catalyzed One-Pot Rearrangement/Arylation of **1**

entry	ArI	time (h)	6 (yield, %)
1		20	6a (70)
2		19	6b (73)
3		19	6c (72)
4		22	6d (95)
5		22	6e (64)
6		47	6f (64)
7		21	6g (69)

with various structurally and electronically diverse aryl iodides in good to excellent yields (Table 4).¹⁸ Because it

exerts high regioselectivity (>99% γ) and stereoselectivity (>99% *E*), this novel catalytic one-pot rearrangement/arylation of 2-allyloxypyridine should find many uses in organic synthesis.

In summary, we have established that the rearrangement of 2-allyloxypyridine (**1**) to *N*-allyl-2-pyridone (**2**) could be catalyzed by both Pd(II) and Pd(0) complexes with different mechanisms. Moreover, we have also established that the one-pot rearrangement/arylation of **1** with aryl iodide took place under the influence of Pd[P(*t*-Bu)₃]₂/Ag₂CO₃ catalytic system to afford synthetically useful *N*-substituted 2-pyridones **6** in good to excellent yields with virtually complete regio- and stereoselectivity.

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

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(18) Typical procedure for one-pot rearrangement/arylation of **1** with aryl iodide (Table 4, entry 4): A solution of **1** (53.8 mg, 0.40 mmol) and Pd[P(*t*-Bu)₃]₂ (10.3 mg, 5 mol %) in dry xylenes (1.5 mL) was stirred at 80 °C for 2 h under argon to give **2** in situ. To this solution were added 4-iodoanisole (132.2 mg, 0.56 mmol), Ag₂CO₃ (154.3 mg, 0.56 mmol), and dry xylenes (0.5 mL). After the resultant mixture was stirred at 100 °C for 22 h, the catalyst and inorganic salts were removed by filtration through a short silica gel pad (EtOAc). The filtrate was evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc = 1/1) to afford **6d** (90.8 mg, 95%) as pale yellow oil.