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

Kenichiro Itami,* Daisuke Yamazaki, and Jun-ichi Yoshida*

Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Yoshida-Honmachi, Kyoto 606-8501, Japan

itami@sbchem.kyoto-u.ac.jp; yoshida@sbchem.kyoto-u.ac.jp

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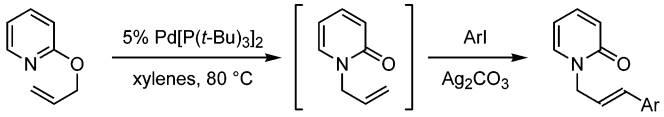
ABSTRACT



The Pd-catalyzed one-pot rearrangement/arylation of 2-allyloxypyridine is described. The catalyst/base combination of $Pd[P(t\text{-}Bu)_3]_2/Ag_2CO_3$ 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 camptothecin[1] and cerpegin,[2] have emerged as a new class of compounds with interesting biological and pharmacological functions[3] and, hence, an efficient entry into the N-substituted 2-pyridone 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 Cy_2NMe, quantitative conversion of **1** to *N*-allyl-2-pyridone (**2**) was observed (Scheme 1). Although somewhat apart from

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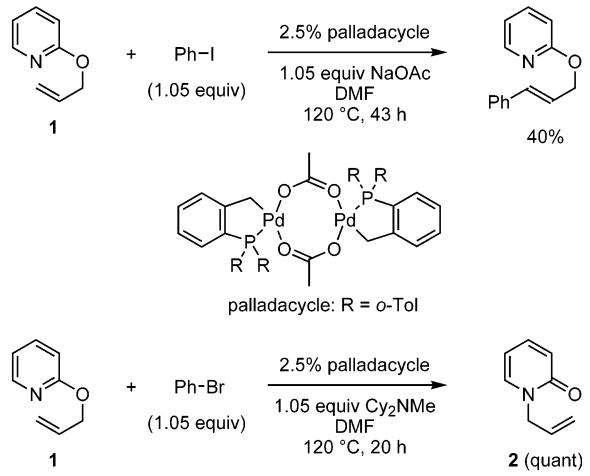
Scheme 1



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-allyloxypyridine.

The Claisen [3,3] sigmatropic thermal rearrangement of 2-allyloxypyridine(**1**) is known to occur around 255 °C to afford **2** (26%) and *C*-allylated product (29%).[7] Stewart and Seibert found that H_2PtCl_6, Na_2PtCl_4, BF_3·OEt_2, and $SnCl_4$ could catalyze this rearrangement (140 °C).[8] $Pt(PPh_3)_4$ 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]

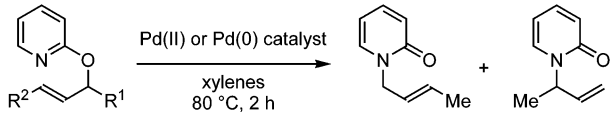
entry	catalyst	time (h)	conversion (**1**, %)
1	$PdCl_2(PhCN)_2$	2	92
2	$PdCl_2$	2	97
3	$Pd(OAc)_2$	2	44
4	$Pd(PPh_3)_4$	2	98
5	$Pd[P(t\text{-}Bu)_3]_2$	2	98
6	$Pd(PCy_3)_2$	46	<20

[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, $PdCl_2(PhCN)_2$ and $PdCl_2$ were found to be excellent catalysts while $Pd(OAc)_2$ was not. As for Pd(0) complexes, $Pd(PPh_3)_4$ and $Pd[P(t\text{-}Bu)_3]_2$ were found to be excellent catalysts (98% conversion after 2 h) while $Pd(PCy_3)_2$ 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-allyloxypyridine (**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-crotyloxypyridine (**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]



3a: R^1 = Me, R^2 = H
3b: R^1 = H, R^2 = Me

4 **5**

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 $PdCl_2$ catalyst, **3a** and **3b** were smoothly and selectively converted to **4** and **5**, respectively (>99% regiospecificity). On the other hand, $Pd(PPh_3)_4$-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-allyloxypyridines 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 regiospecific 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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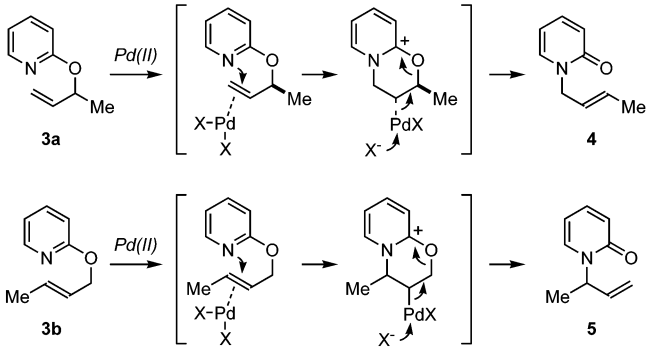
(11) Pd(II)-catalyzed rearrangement of allyl imidates: (a) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218. (b) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579. (c) Ikariya, T.; Ishikawa, Y.; Hirai, K.; Yoshikawa, S. *Chem. Lett.* **1982**, 1815. (d) Schenck, T. G.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2058. (e) Metz, P.; Mues, C.; Schoop, A. *Tetrahedron* **1992**, *48*, 1071. (f) Gonda, J.; Helland, A. C.; Ernst, B.; Belluš, D. *Synthesis* **1993**, 729. (g) Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449. (h) Uozumi, Y.; Kato, K.; Hayashi, T. *Tetrahedron*: *Asymmetry* **1998**, *9*, 1065.
(12) Pd(0)-catalyzed rearrangement of allyl imidates: ref 11c,d.

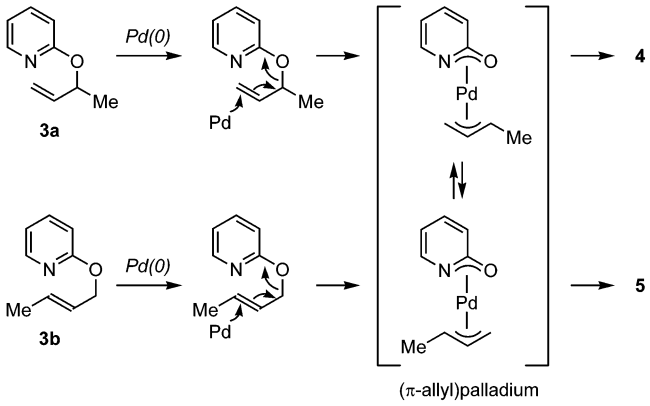
Scheme 2



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 regiospecificity.

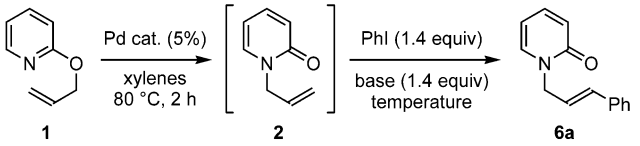
On the other hand, the Pd(0)-catalyzed rearrangement might proceed through the intermediary of (π-allyl)palladium complex as shown in Scheme 3. First, nucleophilic Pd(0)

Scheme 3



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 $\pi-\sigma-\pi$ rearrangement prior to final C−N reductive elimination. Nonetheless, by assuming (π-allyl)palladium intermediates, the lack of regiospecificity 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	T (°C)	time (h)	yield (%)
1	$PdCl_2$	Cs_2CO_3	130	21	50
2	$Pd(PPh_3)_4$	Cs_2CO_3	130	20	18
3	$Pd[P(t\text{-}Bu)_3]_2$	Cs_2CO_3	130	14	58
4	$Pd[P(t\text{-}Bu)_3]_2$	Cy_2NMe	130	20	30
5	$Pd[P(t\text{-}Bu)_3]_2$	Ag_2CO_3	130	4	58
6	$Pd[P(t\text{-}Bu)_3]_2$	Ag_2CO_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 $Pd[P(t\text{-}Bu)_3]_2$ is a superior catalyst precursor over $PdCl_2$ and $Pd(PPh_3)_4$ 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 Cs_2CO_3 were examined. Although the use of reputed Cy_2NMe[13,14] resulted in slower reaction with significant double-bond isomerization of **2**, the use of Ag_2CO_3 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 $Pd[P(t\text{-}Bu)_3]_2/Ag_2CO_3$ catalytic system, in situ generated **2** was arylated

(13) $Pd/P(t\text{-}Bu)_3$ catalyst for Mizoroki−Heck reaction: Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.

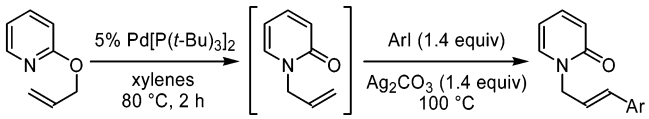
(14) Gürtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107.

(15) When bromobenzene was used as an arylating agent in place of iodobenzene under the influence of the $Pd[P(t\text{-}Bu)_3]_2/Ag_2CO_3$ 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.

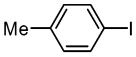
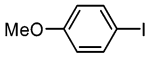
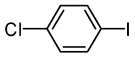
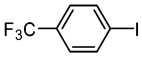
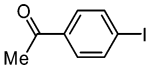
(16) Toluene can also be used as a solvent in place of xylenes.

(17) When isolated rearrangement product **2** was subjected to Pd-catalyzed arylation (5 mol % $Pd[P(t\text{-}Bu)_3]_2$, 1.4 equiv of PhI, 1.4 equiv of Ag_2CO_3, 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 unstability of **2**. Alternatively, the use of "fresh" $Pd[P(t\text{-}Bu)_3]_2$ may be detrimental in the arylation step. In the one-pot process, more active "$Pd[P(t\text{-}Bu)_3]$"[13] may be generated in situ during the rearrangement reaction.

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



1 2 6

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 $Pd[P(t\text{-}Bu)_3]_2/Ag_2CO_3$ 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 $Pd[P(t\text{-}Bu)_3]_2$ (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), Ag_2CO_3 (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.