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Synthesis of different ring-size heterocycles from the same propargyl alcohol derivative by ligand effect on Pd(0)

Yuji Kozawa and Miwako Mori*

Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

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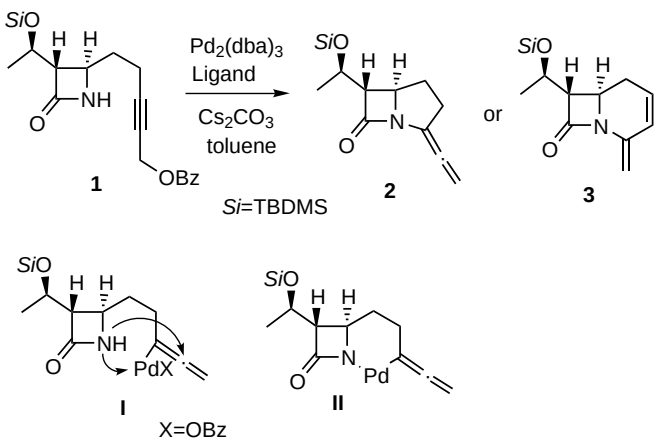
Abstract—The type of ligand on an allenylpalladium complex, which was prepared from propargyl alcohol derivative and Pd(0), plays an important role in determination of the ring size of the cyclized compound. An intermediary palladium complex bearing a monodentate ligand gave a cyclized compound via palladacycle, while that bearing a bidentate ligand gave one-carbon elongated cyclized compound via a η^3-propargylpalladium complex.

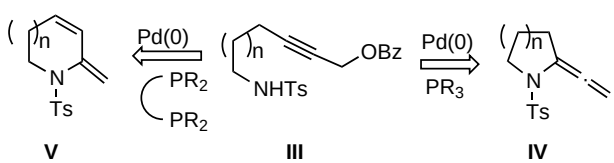
The reactivities of allenylpalladium complexes,[1] which are obtained by oxidative addition of propargyl alcohol derivatives to Pd(0), are very attractive in synthetic organic chemistry. We have already shown that carbapenam and carbacepham derivatives could be synthesized from the same propargyl benzoate derivative.[2] The only difference between these reaction conditions is the differences in ligands on a palladium catalyst. Namely, the reaction of propargyl benzoate derivative **1** with $Pd_2dba_3{\cdot}CHCl_3$ and P(*o*-tol)$_3$ in toluene gave carbapenam **2** in high yield, while DPPF and Pd(0) gave carbacepham **3** in high yield. In this reaction, allenylpalladium complex **I** is formed by oxidative addition of **1** to Pd(0), and then palladacycle **II** would be produced. From **II**, carbapenam **2** is formed.[3] On the other hand, carbacepham **3** would be produced by bond formation of amide nitrogen and the central carbon of allenyl moiety in **I** (Scheme 1).[4]

Although the above results are quite interesting, they may be a special case because the five- or six-membered ring formed in this reaction is connected with four-membered β-lactam. Thus, it was examined whether the different ring size heterocycles **IV** and **V** can be synthesized from the same simple propargyl alcohol derivative **III** using Pd(0) and mono- or bidentate ligand (Scheme 2).

When a toluene solution of propargyl benzoate **4a** bearing a tosylamide moiety in a tether, 5 mol% of $Pd_2dba_3{\cdot}CHCl_3$ and 20 mol% of P(*o*-tol)$_3$ as a monodentate ligand was warmed at 70°C for 3 h in the presence of Cs_2CO_3 (2 equiv.), pyrrolidine derivative **7a**, which is an olefin isomerization product of **IV** ($n=1$), was obtained in 85% yield. The use of 2.5 mol% of the palladium catalyst gave **7a** in 79% yield.



Scheme 1. Synthesis of carbapenam and carbacepham.



Scheme 2. Plan for two different ring formations by a mono- or bidentate ligand in palladium-catalyzed cyclization.

Keywords: allenylpalladium complex; η^3-propargylpalladium complex; heterocycles; π-allylpalladium complex; DPPF.

* Corresponding author.

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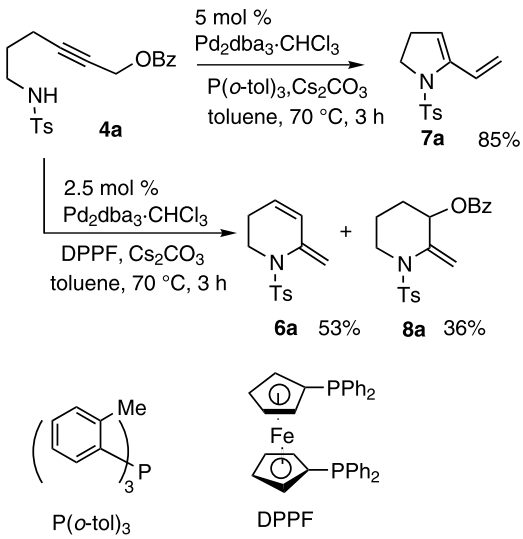
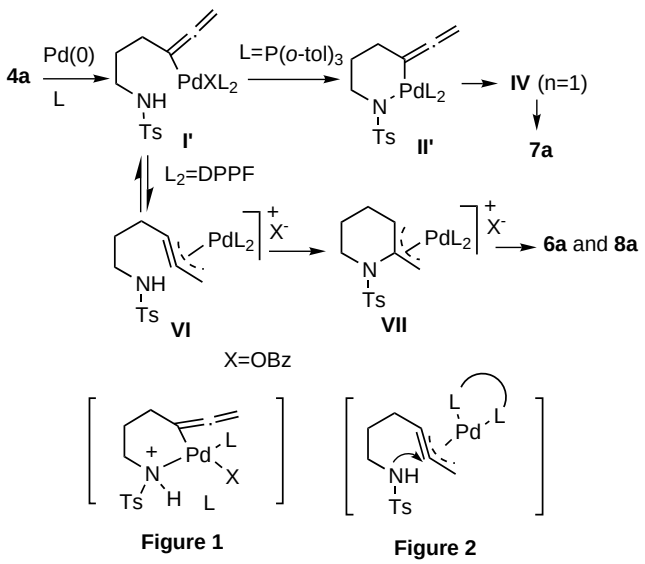
On the other hand, treatment of **4a** with 2.5 mol% of palladium catalyst and 10 mol% of DPPF as a bidentate ligand gave piperidine derivatives **6a** and **8a** in 53 and 36% yields, respectively (Scheme 3).

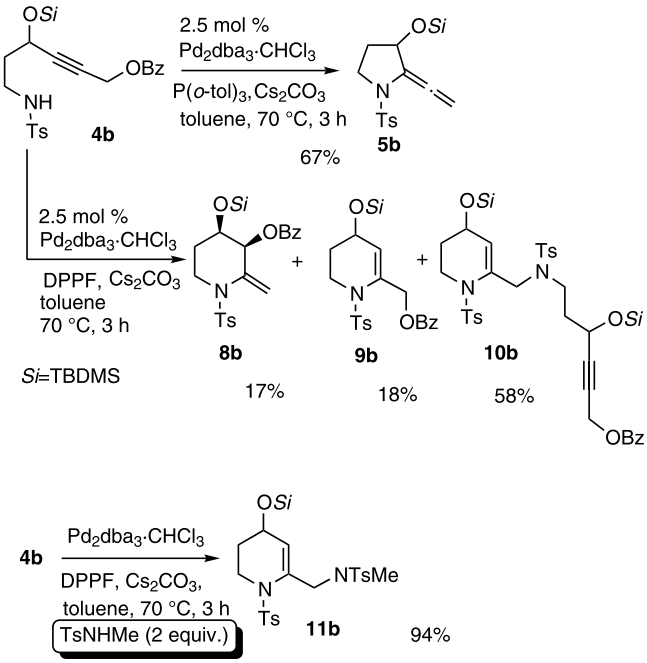
The possible reaction course is shown in Scheme 4. Oxidative addition of propargyl benzoate **4a** to Pd(0) gives allenylpalladium complex **I′**. Tosylamide nitrogen of **I′** attacks palladium metal to give palladacycle **II′** and reductive elimination from **II′** gives the five-membered ring compound **IV** ($n=1$), whose double bond is isomerized to give **7a**. When DPPF is used as a bidentate ligand for this reaction, tosylamide nitrogen attacks the central carbon of η^3-propargylpalladium complex **VI**, which is in a state of equilibrium with allenylpalladium complex **I′**,[5] to give π-allylpalladium complex **VII**. β-Hydrogen elimination from **VII** gives **6a** and the nucleophile attacks π-allylpalladium complex **VII** to give **8a**. It was thought that allenylpalladium complex **I′** bearing a monodentate ligand gave five-membered ring compounds because the monodentate ligand can dissociate from **I′** and tosylamide nitrogen can coordinate to palladium metal to give palladacycle **II′**, as shown in Figure 1 of Scheme 4. However, in the case of a bidentate ligand, nitrogen cannot coordinate to palladium metal because of the coordination of the bidentate ligand to palladium metal. It is known that the bidentate ligand is more favorable for the η^3-coordination of propargyl ligand than monodentate ligand,[5] and that a nucleophile attacks at the central carbon of



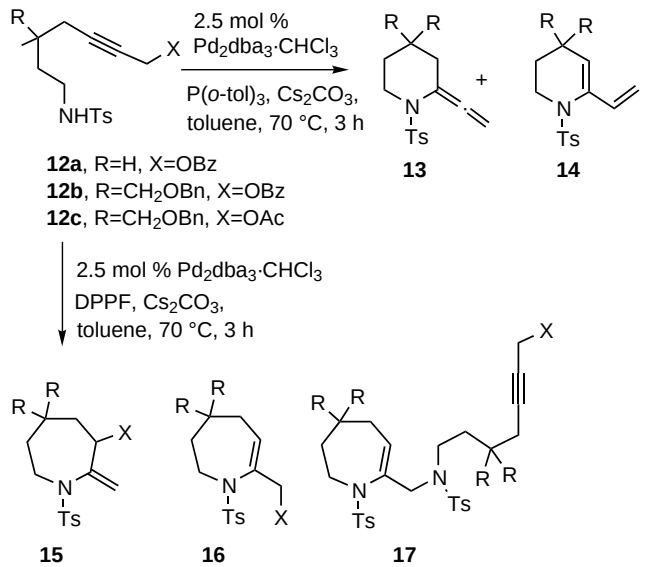
Scheme 3. Palladium-catalyzed cyclization of **4a** using P(*o*-tol)$_3$ or DPPF as a ligand.



Scheme 4. Possible reaction course.



Scheme 5. Synthesis of five- and six-membered heterocycles.



Scheme 6. Synthesis of six- and seven-membered heterocycles.

Table 1. Synthesis of six- and seven-membered heterocycles[a]

Run	R	X		Ligand	Yield (%)				
					13	**14**	**15**	**16**	**17**
1	H	OBz	**12a**	P(*o*-tol)$_3$	41	19	–	–	–
2	CH_2OBn	OBz	**12b**	P(*o*-tol)$_3$	–	70[b]	–	–	–
3	H	OBz	**12a**	DPPF	–	–	51	–	–
4	CH_2OBn	OBz	**12b**	DPPF	–	–	37	20	34
5	CH_2OBn	OAc	**12c**	DPPF	–	–	12	40	38

[a] All reactions were carried out using $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol%), P(*o*-tol)$_3$ (10 mol%) or DPPF (10 mol%) as a ligand, and Cs_2CO_3 (2 equiv.) in toluene at 70°C for 3 h.

[b] The ratio of **13b** to **14b** of the crude product was 1:1, but after column chromatography on silica gel **13b** was converted into **14b**.

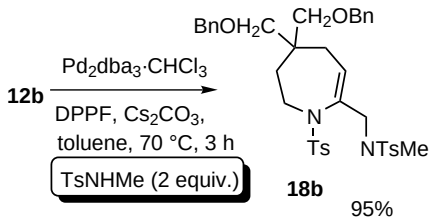
η^3-propargylpalladium complex.[5,6] Thus, nitrogen attacks the central carbon of **VI** to produce π-allylpalladium complex **VII**, as shown in Figure 2 of Scheme 4.

Furthermore, when compound **4b** was treated with $Pd_2dba_3{\cdot}CHCl_3$ and P(*o*-tol)$_3$ under the same reaction conditions, the desired five-membered ring compound **5b** was obtained in 67% yield, while treatment of **4b** with $Pd_2dba_3{\cdot}CHCl_3$ and DPPF in a similar manner gave the six-membered ring compounds **8b**,[7] **9b**, and **10b** in 17, 18 and 58% yields, respectively. These results indicate that the use of $Pd_2dba_3{\cdot}CHCl_3$ and a monodentate ligand gives a five-membered ring compound and a six-membered ring compound is obtained using Pd(0) and a bidentate ligand.

Formation of compound **10b** indicates that the starting tosylamide **4b** acts as a nucleophile to π-allylpalladium complex. Thus, when the reaction of **4b** was carried out using $Pd_2dba_3{\cdot}CHCl_3$ and DPPF in the presence of methyltosylamide (2 equiv.), we are very pleased to find that piperidine derivative **11b** was obtained in 94% yield as a sole product. The reason why methyltosylamide attacks the primary carbon on π-allylpalladium complex is thought to be due to the steric effect of the bulky tosylamide group (Scheme 5).

Experiments were also carried out to examine whether six- and seven-membered ring compounds can be synthesized from propargyl alcohol derivative.

When propargyl benzoate **12a** was treated with $Pd_2dba_3{\cdot}CHCl_3$ and P(*o*-tol)$_3$ in a similar manner, piperidine derivatives **13a** and **14a** were obtained in 41 and 19% yields, respectively (Scheme 6, Table 1, run 1). Furthermore, compound **12b** was treated with $Pd_2dba_3{\cdot}CHCl_3$ and P(*o*-tol)$_3$ in a similar manner. Although the ^{1}H NMR spectrum of the crude product indicates that the desired six-membered ring compounds **13b** and **14b** were formed in 70% yield in a ratio of 1:1, **13b** was changed into **14b** during column chromatography on silica gel (run 2). On the other hand, when compound **12a** was treated with $Pd_2dba_3{\cdot}CHCl_3$ and DPPF, azepane derivative **15a** was obtained in 51% yield (run 3). Moreover, compound **12b** was treated in a similar manner using $Pd_2dba_3{\cdot}CHCl_3$ and DPPF to give azepane derivatives **15b**, **16b** and **17b** in 37, 20 and 34% yields, respectively (run 4). Similar treatment of propargyl acetate **12c** with $Pd_2dba_3{\cdot}CHCl_3$ and DPPF afforded the azepane derivatives, **15c**, **16c**, and **17c** (run 5).



Scheme 7. Reaction of **12d** with $Pd_2dba_3{\cdot}CHCl_3$ and DPPF in the presence of TsNHMe.

When the reaction of **12b** with $Pd_2dba_3{\cdot}CHCl_3$ and DPPF in the presence of methyltosylamide (2 equiv.) was carried out, azepane derivative **18b** was produced in 95% yield as a sole product (Scheme 7).[8]

The results showed that the different ring-size heterocycles can be synthesized from the same propargyl alcohol derivatives using Pd(0) with mono- or bidentate ligand. The type of ligand on η^1-propargylpalladium complex, which is in a state of equilibrium with an allenylpalladium complex and η^3-propargylpalladium complex, plays an important role in determination of the ring size of the cyclized compound: that is, an allenylpalladium complex bearing a monodentate ligand gives cyclized compound via palladacycle, which is formed by attack of tosylamide nitrogen to palladium metal, while that bearing a bidentate ligand gives one-carbon elongated product by an attack of tosylamide nitrogen to a central carbon of the η^3-propargylpalladium complex.

Further studies are in progress.

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7. Based on the reaction mechanism,[2] the stereochemistry of 3- and 4-substituents on a piperidine ring would be *cis*. To confirm this, **8b** was ozonolyzed, and the J value ($J=2.4$ Hz) of C-3 and C-4 protons on piperidone indicates that the stereochemistry of the substituents on **8b** is *cis*.
8. Addition of sodium acetate (5 equiv.) to the solution of **12c** gave no change in the results and **15c**, **16c**, and **17c** were obtained in 7, 29, and 52% yields, respectively.