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Construction of a carbapenam skeleton using palladium-catalyzed cyclization

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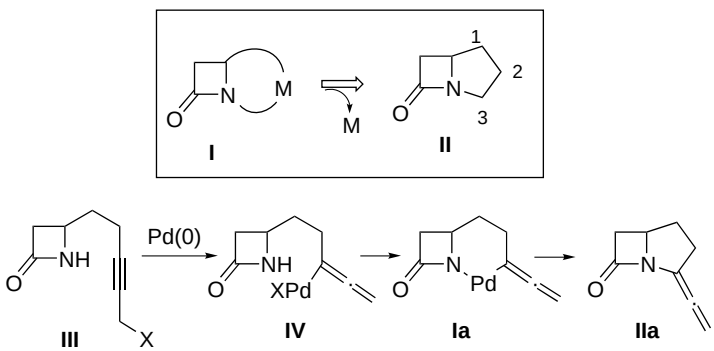
Abstract—When a THF solution of β-lactam having propargyl phosphate was warmed in the presence of 5 mol% of $Pd_2(dba)_3{\cdot}CHCl_3$, 20 mol% of bidentate ligand and sodium acetate (1.5 equiv.) at 40°C for 22 h, carbapenam was produced in high yield. In this reaction, the lactam nitrogen attacked the central *sp* carbon of a σ-allenylpalladium complex, which was formed from propargyl phosphate and Pd(0). © 2001 Elsevier Science Ltd. All rights reserved.

Carbapenem has an important antibiotic activity and the development of a novel method for synthesizing carbapenam is needed in order to find new β-lactam antibiotics. In general, for the construction of a carbapenam skeleton, a five-membered ring is formed from four-membered β-lactam. However, it is not so easy to construct carbapenam skeleton because of the highly strained structure. Organometallic reagents are very attractive tools for the construction of these skeletons.[1] Recently, we reported a novel method for synthesizing a carbapenam skeleton using ruthenium-catalyzed cyclization.[2] Our concept for the formation of carbapenam skeleton **II** using transition metals was to construct the five-membered rings by reductive elimination from six-membered metalacycle **I** fused by a four-membered β-lactam. Although the previous method for the construction of a carbapenam skeleton involved forming a C1–C2 bond,[2] the new method involves formation of a C3–N bond from palladacyclohexane **Ia**. For that purpose, we considered how to make palladacyclohexane having an N–Pd–C bond. It has been shown that the reaction of propargyl carbonate with Pd(0) affords a σ-allenylpalladium complex or a σ-propargylpalladium complex.[3] Recent works by Buchwald and Hartwig have indicated that the reaction of amine or amide with σ-arylpalladium halide affords amide, imide, or lactam in the presence of a base via the processes of an N–Pd–C bond formation and reductive elimination from it.[4] These results prompted us to try to construct carbapenam **IIa** from propargyl carbonate **III**. Our plan is shown in Scheme 1.



Scheme 1. Our plan for the synthesis of the carbapenam skeleton.

Keywords: β-lactam; carbapenam; cyclization; palladium catalysts; σ-allenylpalladium complex.

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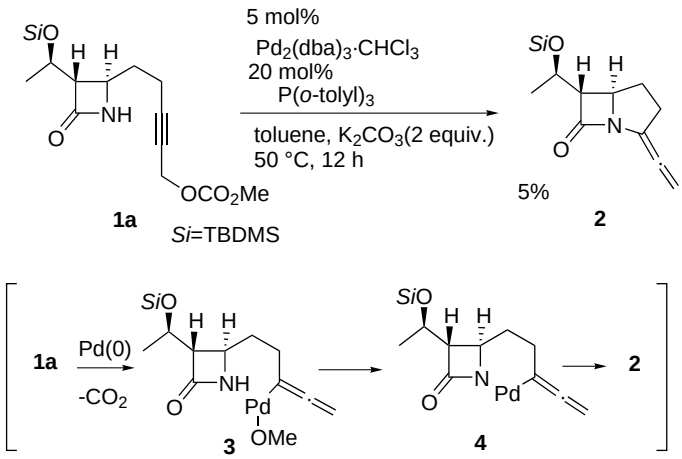
The reaction of propargyl carbonate and Pd(0) would afford a σ-allenylpalladium complex **IV**, and the reaction of lactam nitrogen with the σ-allenylpalladium complex would give palladacycle **Ia**, and then reductive elimination from **Ia** would produce **IIa**. When a toluene solution of methyl carbonate **1a** was warmed in the presence of 5 mol% of $Pd_2(dba)_3{\cdot}CHCl_3$, 20 mol% of P(*o*-tolyl)$_3$, and K_2CO_3 (2 equiv.) at 50°C for 12 h, a small amount of carbapenam **2** was obtained (Scheme 2).

Presumably, the reaction of **1a** with Pd(0) gives σ-propargylpalladium complex, which converts into σ-allenylpalladium complex **3** via decarboxylation, and it reacts with lactam nitrogen in **3** in the presence of a base to give palladacyclohexane **4**. Reductive elimination from **4** affords **2**.

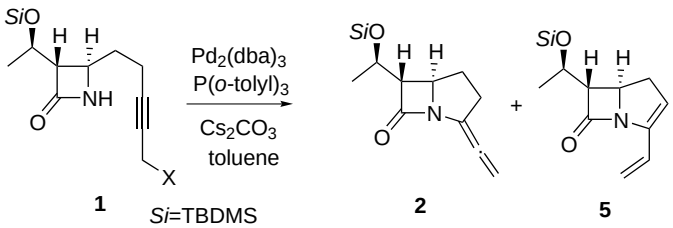
To increase the yield of the desired compound **2**, the reaction was carried out under various conditions, and the results are shown in Table 1. As a base, Cs_2CO_3 was used, and acetate **1b** afforded **2** in 6% yield (run 2). However, the reaction of benzoate **1c** with a palladium catalyst gave **2** in 44% yield (run 3). The electron-donating group on the aromatic ring of benzoate decreased the yield of **2** (run 4), and a lower reaction temperature increased the yield of **2** (run 8). Propargyl phosphate **1e** also gave moderate yield of **2** (runs 5 and 9).

Subsequently, the effects of the ligands were examined, and the results are shown in Table 2. Use of monodentate ligands such as P(*o*-tolyl)$_3$, P(2-furyl)$_3$ and P(cyclohexyl)$_3$ gave carbapenam **2** in moderate yields (runs 1–4). Surprisingly, the use of a bidentate ligand, such as



Scheme 2. Reaction of **1a** with palladium catalyst.

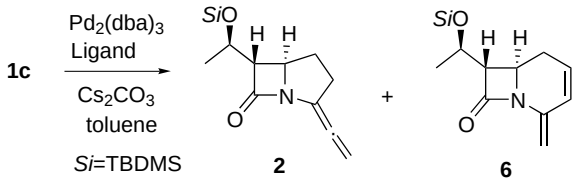
Table 1. Reaction of **1** with $Pd_2(dba)_3{\cdot}CHCl_3$ under various conditions[a]



Run	X		Temp. (°C)	Time (h)	Yield (%)	
					2	**5**
1	OCO_2Me	**1a**	50	12	6	–
2	OCOMe	**1b**	70	4	6	–
3	OCOPh	**1c**	70	5	44	2
4	OCO-*p*-$MeOC_6H_4$	**1d**	70	8	29	7
5	$OPO(OEt)_2$	**1e**	70	4	44	–
6	OPh	**1f**	70[b]	3	–	–
7	OCOPh	**1c**	40	48	32[c]	–
8	OCOPh	**1c**	55	9	57[c]	–
9	$OPO(OEt)_2$	**1e**	55	9	38	–

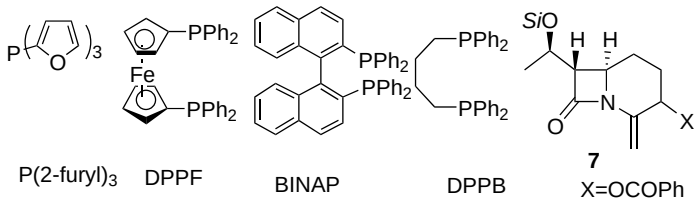
[a] All reactions were carried out using $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%), P(*o*-tolyl)$_3$ (20 mol%), and Cs_2CO_3 (2 equiv.) in toluene.
[b] After the solution was warmed at 70°C for 3 h and then at 90°C for 2 h.
[c] The starting material was recovered in 45% (run 7) or 14% yield (run 8), respectively.

Table 2. Effects of ligands[a]



Run	Ligand	Temp. (°C)	Time (h)	Yield (%)		
				2	**6**	**1c**
1	P(*o*-tolyl)$_3$	55	9	57	–	14
2	P(2-furyl)$_3$	70	8	19	–	35
3	P(cyclohexyl)$_3$	70	8	39	–	32
4	P(cyclohexyl)$_3$	55	21	33	–	40
5	DPPF	70	5	–	56[b]	–
6	(+)-BINAP	70	10	–	8	26
7	(−)-BINAP	70	8	–	24	10
8	DPPB	70	5	–	26	3
9	–	55	21	50	–	23

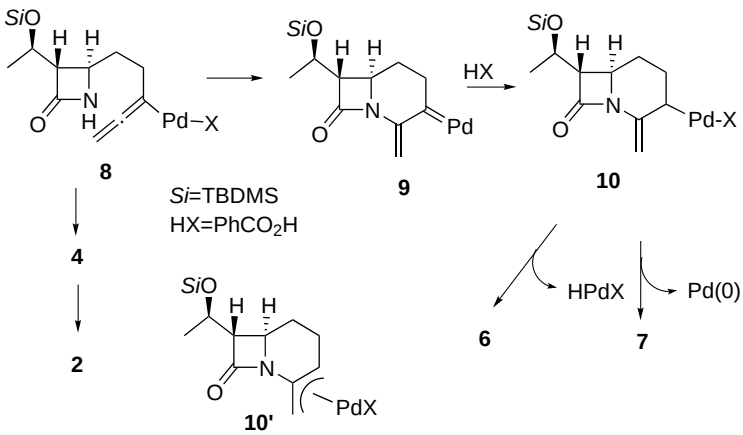
[a] All reactions were carried out using $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%), ligand (20 mol%) and Cs_2CO_3 (2 equiv.) in toluene.
[b] **7** was obtained in 9% yield along with **6** in 56% yield.



DPPF, BINAP and DPPB, produced carbacepham **6** instead of carbapenam **2** (runs 5–8). In the absence of a ligand, the desired carbapenam **2** was produced in good yield (run 9).

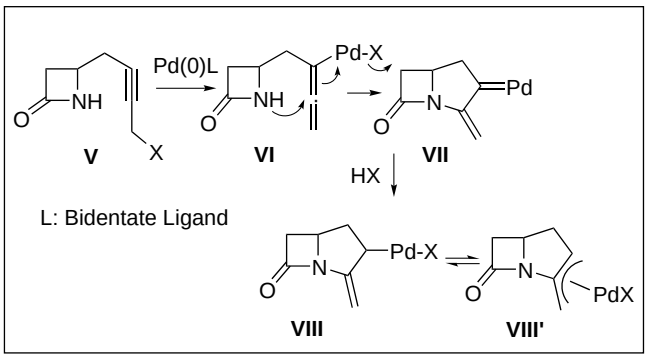
The possible reaction course was shown in Scheme 3. The lactam nitrogen of σ-allenylpalladium complex **8** reacts with palladium metal to give palladacyclohexane **4**, which converts into carbapenam **2**. On the other hand, the lactam nitrogen of **8** attacks the central *sp* carbon of the allenyl group to give palladium carbene complex **9**.[3,5] Reaction of **9** with HX gives σ-allylpalladium complex **10**, which is in a state of equilibrium with π-allylpalladium complex **10′**. Reductive elimination from **10** affords **7** and β-hydride elimination from **10** gives **6**. It means that when the palladium complex has bidentate ligand, the lactam nitrogen reacts with the central *sp* carbon of the σ-allenylpalladium complex, not the palladium metal.

Although the reasons why a monodentate ligand accelerates the formation of palladacycle **4** and a bidentate ligand accelerates the formation of palladium carbene complex **9** are not clear, the results are very interesting.



Scheme 3. Possible reaction mechanism for the formation of **6** and **7**.

On the basis of these results, if one carbon of the side chain of β-lactam is shortened, σ-allenylpalladium complex **VI** would be formed. In this reaction, if bidentate ligand is used, the lactam nitrogen of σ-allenylpalladium complex **VI** attacks the central *sp* carbon of the allenyl group to form palladium carbene complex **VII**, which would react with HX to give σ-palladium complex **VIII** or π-allylpalladium complex **VIII′**. From **VIII** or **VIII′**, carbapenam would be produced (Scheme 4).



Scheme 4. Plan for the synthesis of the carbapenam skeleton.

When a toluene solution of propargyl benzoate **11a** was warmed in the presence of 5 mol% of $Pd_2(dba)_3{\cdot}CHCl_3$, 20 mol% of DPPF and Cs_2CO_3 (2 equiv.) at 50°C for 12 h, desired carbapenams **12** and **13a** were obtained in 9 and 2% yields, respectively (Table 3, run 1). Although the yield was not good, the lactam nitrogen attacked the central *sp* carbon of σ-allenylpalladium complex **VI** to form palladium carbene complex **VII**, which gave carbapenam. The reaction was carried out under various conditions, and the results are shown in Table 3. When the reaction was carried out using sodium benzoate as a base, the yield of carbapenams increased (run 2).

As a solvent, THF gave a good result and the total yield of carbapenam was 55% (run 3). Phosphate can be used as a leaving group (runs 4–7), but the lower temperature decreased the yield of **12** (run 5). When the amount of the base decreased, the yields of **12** and **13a** increased to 66% (run 6). The use of sodium acetate as a base gave **12** and **13c** in 59% yield (run 7).[6]

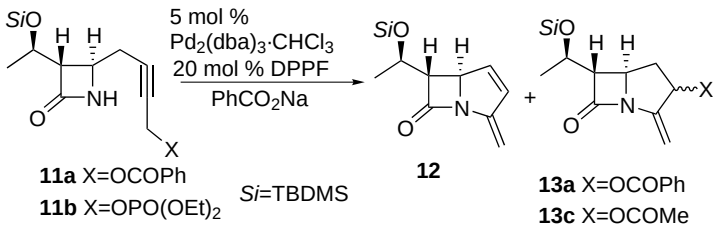
Finally, we tried to synthesize 1-β-methylcarbapenam. The starting material **14a** was synthesized from **17**, whose stereochemistry has been already determined.[7]

When phosphate **14a** was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ and DPPF in THF at 40°C for 22 h, the desired 1-β-methylcarbapenams **15a** and **16** were obtained in 78 and 8% yields, respectively (Scheme 5). The result of an NOE experiment indicates that the stereochemistry of the methyl and acetoxy groups on the five-membered ring is *cis*. This means that the nucleophile attacks from the backside of the π-allylpalladium complex **18**[8] and it attacks the carbon on the five-membered ring of π-allylpalladium complex.

It was quite interesting that 1-β-methylcarbapenam could be synthesized from β-lactam **14a** having a propargyl derivative on the side chain by palladium-catalyzed cyclization in high yield.

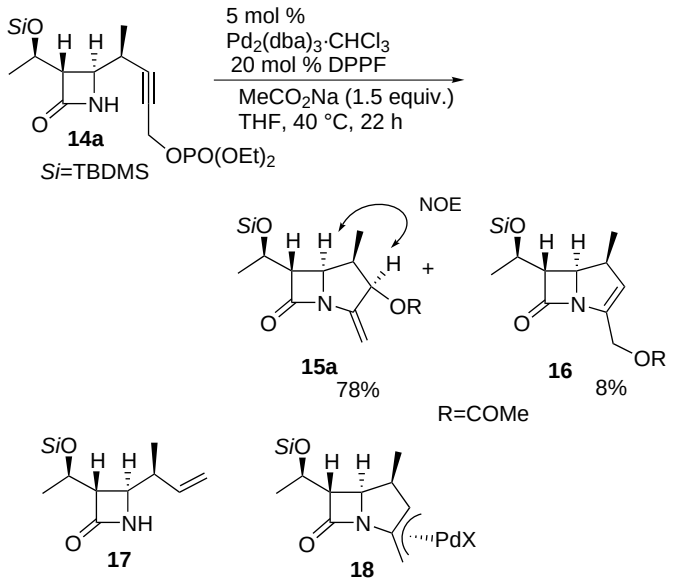
Further studies are in progress.

Table 3. Cyclization of **11** under various conditions



Run	X	$PhCO_2Na$ (equiv.)	Solvent	Temp. (°C)	Time (h)	Yield (%)		
						12	**13**	**11**
1	OCOPh[a]	2	Toluene	50	12	9	2	–
2	OCOPh	2	Toluene	70	8.5	4	31	33
3	OCOPh	4	THF	55	17	23	32	16
4	$OPO(OEt)_2$	4	THF	55	5	27	35	–
5	$OPO(OEt)_2$	4	THF	40	6	7	24	71[b]
6	$OPO(OEt)_2$	1.5	THF	55	5	22	44	13[b]
7	$OPO(OEt)_2$[d]	1.5	THF	55	5	26	33[e]	7[c]

[a] Cs_2CO_3 was used instead of $PhCO_2Na$.
[b] **11a**.
[c] **11c**.
[d] MeCOONa was used instead of $PhCO_2Na$.
[e] **13c** was obtained.



Scheme 5. Formation of the carbapenam skeleton from **14**.

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6. The ratio of α to β of the acetoxy or benzoyloxy group at the 2-position in **13a** or **13c** is 1:1.
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8. When **14a** (1β-Me) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%) and DPPF (20 mol%) in the presence of $PhCO_2Na$ (1.5 equiv.) in THF at 55°C for 5 h, **15b** (1β-Me, 2β-OCOPh) was obtained in 60% yield along with **15c** (1β-Me, 2α-OCOPh) in 11% yield. On the other hand, under similar conditions, **14b** (1α-Me) afforded **15d** (1α-Me, 2α-OCOPh) in 40% yield along with **15e** (1α-Me, 2β-OCOPh) in 10% yield.