JOC Article

Novel Synthesis of Carbapenam by Intramolecular Attack of Lactam Nitrogen toward η^1-Allenyl and η^3-Propargylpalladium Complex

Yuji Kozawa and Miwako Mori*

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

mori@pharm.hokudai.ac.jp

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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 a 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 carbon of a η^3-propargylpalladium complex, which was formed from propargyl phosphate and Pd(0).

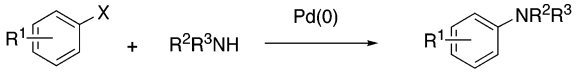
Introduction

Many works have been carried out to develop carbapenem antibiotics having chemical and biological properties for clinical use since the discovery by Merck's group of thienamycin, the first naturally occurring carbapenem antibiotic.[1] The establishment of a new method for forming a carbapenem skeleton is very important to develop new types of carbapenem antibiotics that have strong antibiotic activity.[2] Generally, a five-membered ring is formed from four-membered 2-azetidinone having proper residual groups at the 1- and/or 4-position for the construction of a carbapenam skeleton. However, it is not so easy to construct a carbapenam or carbapenem skeleton because carbapenam or carbapenem having a 4−5 fused ring system has a highly strained structure compared with the structures of other β-lactam antibiotics such as penam and penem, and there have been few reports on a simple method for constructing a carbapenam skeleton.

Organometallic reagents have been extensively studied over the past few decades by many organic chemists, and they now play very important roles in synthetic organic chemistry.

There are several notable reports on the construction of carbapenam skeletons with organometallic reagents.[3] As originally reported by Merck's group, intramolecular reaction of a rhodium−carbene complex with the N−H bond of β-lactam has often been used for the synthesis of a wide range of carbapenem derivatives.[4] Trost reported the synthesis of carbapenam derivatives using palladium-catalyzed cyclization.[5] Genet reported the synthesis of carbapenem derivatives by intramolecular nucleophilic attack of active methylene to a π-allylpalladium complex, and he recently also reported the synthesis of carbapenam derivatives using a metathesis reaction.[6] Recently, we have investigated potential methods for synthesizing a carbapenam and carbapenem skeleton by reductive elimination from a six-membered metalacycle.[7]

SCHEME 1. Palladium-Catalyzed C−N Bond-Forming Reaction between Aryl Halides and Amines



Palladium-catalyzed C−N bond-forming reactions between aryl halides and amines have been extensively investigated over the past few years by Buchwald, Hartwig, and others (Scheme 1).[8] This reaction has been

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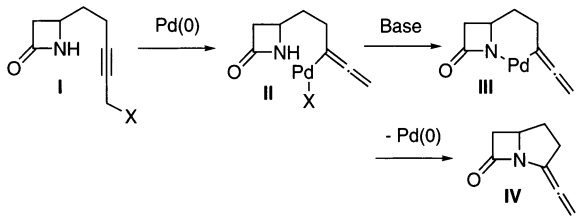
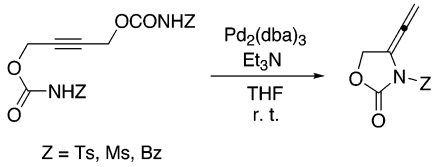
SCHEME 2. Palladium-Catalyzed C−N Bond-Forming Reaction between a Propargyl Group and β-Lactam Nitrogen



SCHEME 3. Palladium-Catalyzed Amide Cyclization of Biscarbamates



extended to intramolecular reactions of aryl halides and amides, carbamates, and sulfonamides, and these procedures have been utilized in many areas of organic synthesis.[9]

Our new plan for the construction of a carbapenam skeleton involving the coupling of a propargyl group is shown in Scheme 2.[7b] If the reaction of β-lactam **I** having a propargyl alcohol moiety and Pd(0) affords σ-allenylpalladium complex **II**,[10] the lactam nitrogen in **II** would react with the σ-allenylpalladium complex to give palladacycle **III**. Reductive elimination from **III** would give carbapenam **IV** having the ethenylidene group at the 3-position.

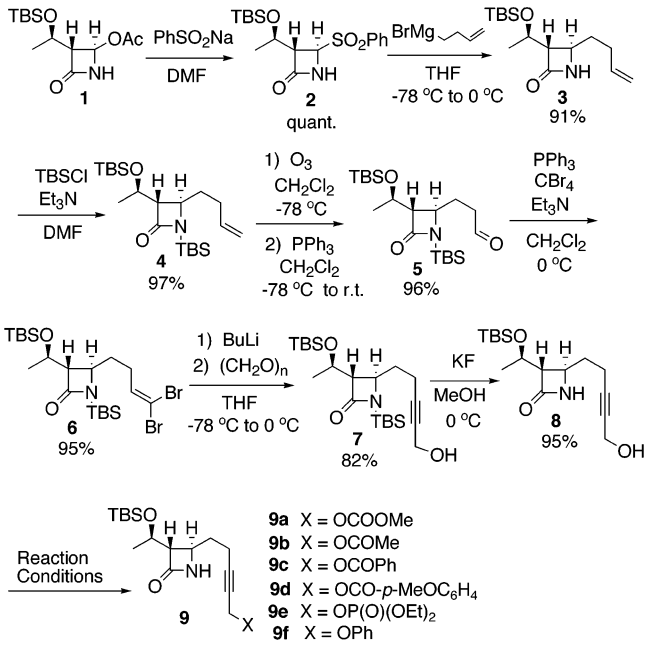
Little is known about the reaction between propargyl alcohol derivatives and amide in the presence of a palladium catalyst. Tamaru reported the synthesis of 4-ethenylidene-2-oxazolidinones in high yields by palladium-catalyzed aminocyclization of 2-butyn-1,4-diol biscarbamates (Scheme 3).[11]

We report the synthesis of a carbapenam skeleton using a palladium-catalyzed intramolecular C−N bond-forming reaction.

Results and Discussion

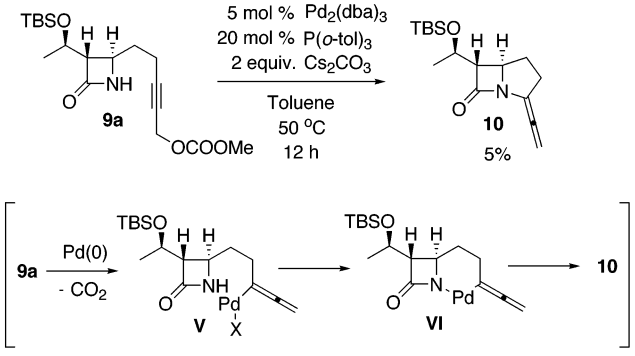
Construction of Carbapenam Having an Ethenylidene Group at the 3-Position via a σ-Allenylpalladium Complex. At first, we investigated the reaction of β-lactam having a methyl carbonate in a tether as a leaving group in palladium-catalyzed cyclization. Propargyl carbonate **9a** was synthesized from 4-acetoxy-2-azetidinone **1** (Scheme 4). 4-Acetoxy azetidinone **1** was converted into sulfone **2**, to which the substitution by Grignard reagent produced **3**. Protection of the amide nitrogen of **3** with a silyl group followed by

SCHEME 4. Synthesis of β-Lactams Having the Propargyl Moiety on the Side Chain[a]



[a] Reaction conditions: For **9a**, ClCOOMe, pyridine, CH_2Cl_2, 97%. For **9b**, Ac_2O, Pyridine, CH_2Cl_2, 97%. For **9c**, PhCOCl, pyridine, CH_2Cl_2, 91%. For **9d**, 4-$MeOC_6H_4COCl$, pyridine, CH_2Cl_2, 93%. For **9e**, $(EtO)_2P(O)Cl$, pyridine, DMAP, CH_2Cl_2, 85%. For **9f**, PhOH, PPh_3, DEAD, THF, 84%.

SCHEME 5. Reaction of 9a with a Palladium Catalyst



ozonolysis gave aldehyde **5**, which was reacted with triphenylphosphine and carbon tetrabromide to give dibromoalkene **6**. The resultant **6** was treated with BuLi and then paraformaldehyde to give propargyl alcohol **7**, which was converted into **8** by deprotection. The reaction of **8** with methyl chloroformate afforded **9a**.

Intramolecular coupling of **9a** in the presence of a palladium catalyst was examined. When a toluene solution of **9a** was heated in the presence of 5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$, 20 mol % of P(*o*-tol)$_3$, and 2 equiv of Cs_2CO_3 at 50 °C for 12 h, carbapenam **10** having an ethenylidene group at the 3-position was obtained, although the yield was only 5% (Scheme 5). The starting material **9a** was not recovered because of its unstability under the reaction conditions.

Presumably, the reaction of **9a** with Pd(0) gives σ-allenylpalladium complex **V** via decarboxylation, and it reacts with the lactam nitrogen in the presence of a base

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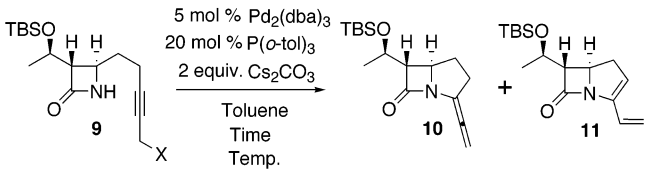
TABLE 1. Effects of Leaving Groups



run	X	compd no.	temp (°C)	time (h)	yield (%) 10	11
1	OCOMe	**9b**	70	4	6	
2	OCOPh	**9c**	70	5	44	2
3	OCOPh	**9c**	55	9	57[b]	
4	OCOPh	**9c**	40	48	32[b]	
5	OCO-*p*-MeOC$_6$H$_4$	**9d**	70	8	29	7
6	OP(O)(OEt)$_2$	**9e**	70	4	44	
7	OPh	**9f**	70	3[a]		

[a] The solution was warmed at 70 °C for 3 h and then at 90 °C for 2 h. [b] The starting material was recovered in 17% (run 3) or 45% yield (run 4).

to give palladacyclohexane **VI**. Reductive elimination from **VI** affords **10**.

To increase the yield of the desired compound **10**, the reaction was carried out with substrates having various leaving groups. The results are shown in Table 1. Propargyl acetate **9b** afforded **10** in only 6% yield (run 1). However, surprisingly, the reaction of propargyl benzoate **9c** gave carbapenam **10** in 44% yield along with carbapenam **11**, produced by isomerization of allene to diene, in 2% yield (run 2). Presumably, in oxidative addition to Pd(0), the reactivity of benzoate **9c** is generally low but the stability of **9c** toward the base is higher than that of **9a**. A reduction in the reaction temperature resulted in an increase in the yield of **10** to 57% (run 3), but the reaction rate was much slower and the yield decreased when the reaction temperature was lowered far (run 4).

The electron-donating group on the aromatic ring of benzoate decreased the yield of **10** (run 5). Noticeably, propargyl phosphate **9e** also gave a good result as well as propargyl benzoate **9c** (run 6). Propargyl phenyl ether **9f** did not give carbapenam **10** (run 7).

Construction of Carbapenam Having a *β*-Methyl Group at the 1-Position. Next, we examined the construction of carbapenam having a *β*-methyl group at the 1-position. It is known that a carbapenam skeleton having a 1*β*-methyl group is both metabolically and chemically more stable than a nonsubstituented carbapenem skeleton, and attention has therefore been recently focused on its unique biological properties. A mixture of two diastereomers **13**[12] (ratio of 1 to 1) was ozonolyzed to aldehyde **14**, and this was followed by reaction with lithium acetylide to give propargyl alcohol **15**. Three isomers were separated by column chromatography on silica gel, and isomer **15-1*β*** having a *β*-methyl group was silylated to give **16**. Two silyl groups of **16** were deprotected, and the amide nitrogen was silylated again. The resultant **18** was treated with BuLi and then paraformaldehyde to give propargyl alcohol **19**, which was converted into **21** (Scheme 6).

The cyclization reaction of propargyl benzoate **21** having a *β*-methyl group at the 1-position was examined.

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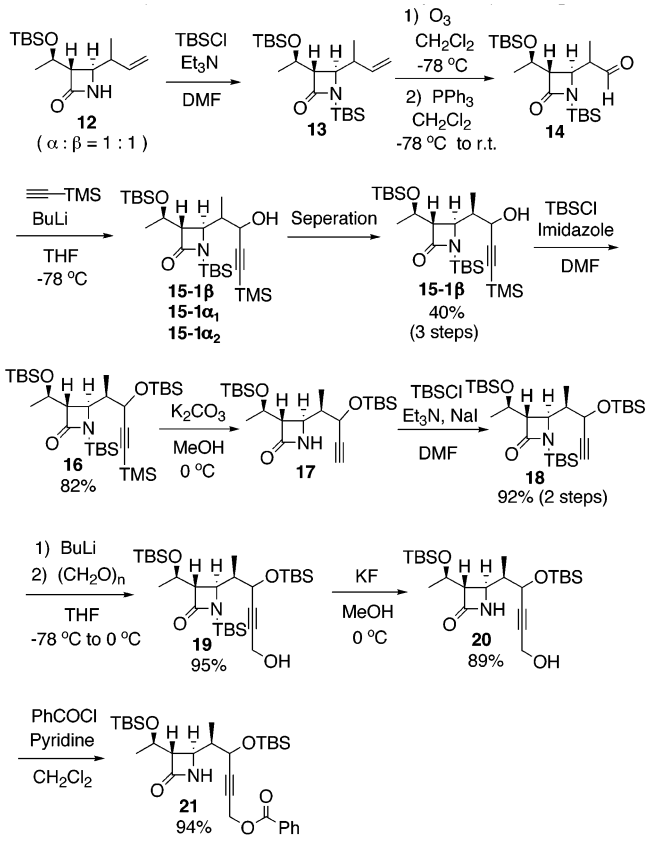
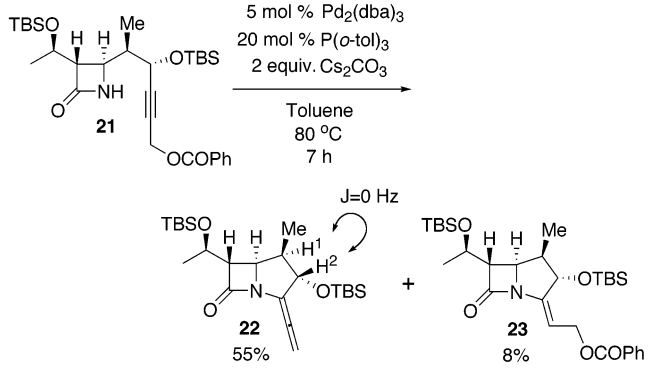
SCHEME 6. Synthesis of the Precursor for 1*β*-Methylcarbapenam



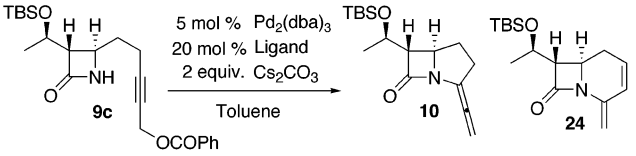
SCHEME 7. Reaction of 21 with a Palladium Catalyst



When a toluene solution of **21**, $Pd_2dba_3{\cdot}CHCl_3$, P(*o*-tol)$_3$, and Cs_2CO_3 was heated at 55 °C for 22 h, carbapenam **22** was obtained in only 29% yield along with the starting material **21** in 60% yield. When the reaction temperature was raised to 80 °C, the yield of carbapenam **22** increased to 55% along with **23** in 8% yield (Scheme 7). The mechanism of the formation of **23** is not clear. The reason for the good yield even at a higher temperature was thought to be the superior stability of carbapenam or the substrate having a 1*β*-methyl group. From the coupling constant between the proton at the 1-position and the proton at the 2-position of **22**, it is clear that the stereochemistry of the methyl group at the 1-position and the silyloxy group at the 2-position is trans.[13]

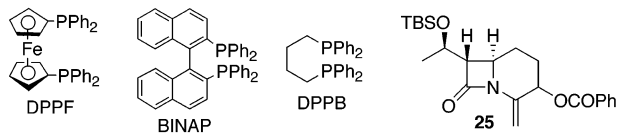
Effects of Ligands. Subsequently, the effects of ligands were examined. The results are shown in Table

TABLE 2. Effects of Ligands on the Reaction of 9c with a Palladium Catalyst



Run	Ligand	Temp. (°C)	Time (h)	Yield (%) 10	Yield (%) 24
1	P(*o*-tol)$_3$	55	9	57	-
2	P(2-furyl)$_3$	70	8	19	-
3	P(cyclohexyl)$_3$	70	8	39	-
4	DPPF	70	5	-	56 [a]
5	(+)-BINAP	70	10	-	8
6	(-)-BINAP	70	8	-	24
7	DPPB	70	5	-	26
8	-	55	21	50	-

a) **25** was obtained in 9% yield along with **24** in 56% yield.

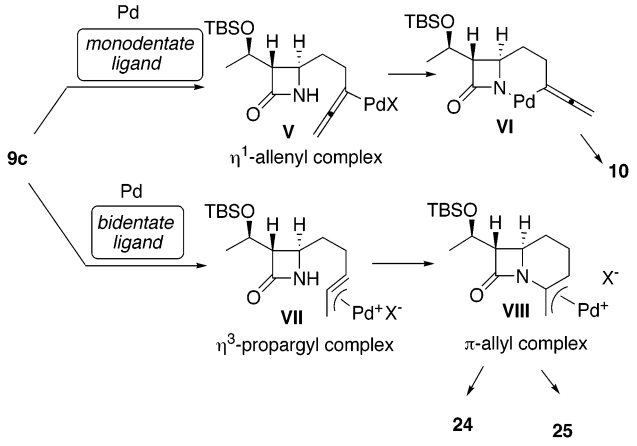


2. No ligand gave a better yield than that obtained by the use of P(*o*-tol)$_3$. However, interestingly, the use of monodentate ligands such as P(2-furyl)$_3$ and P(cyclohexyl)$_3$ gave carbapenam **10** in moderate yields (runs 2 and 3), but the use of bidentate ligands such as DPPF, BINAP, and DPPB gave carbacepham **24** instead of carbapanam **10** (runs 4−7).

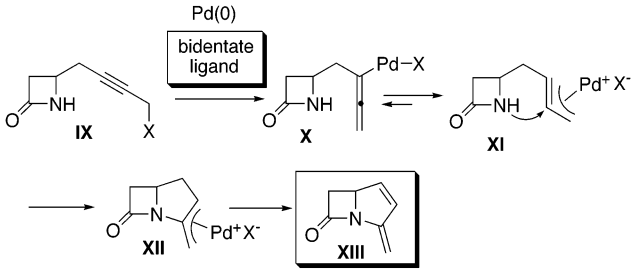
Notably, when DPPF was used as a ligand, carbacephams **24** and **25** were obtained in 56% and 9% yields, respectively (run 4). These results suggested that a five-membered carbapenam should be obtained by using a monodentate ligand, while a six-membered carbacepham should be obtained by using a bidentate ligand from the same substrate. It is known that a σ-allenylpalladium complex is in a state of equilibrium with a η^3-propargylpalladium complex and that the latter is formed in a more stable manner in the presence of a bidentate ligand than in the presence of a monodentate ligand.[14] It has also been reported that the central carbon of the η^3-propargylpalladium complex is attacked by a nucleophile to give a π-allylpalladium complex, which is further attacked by a second nucleophile.[15]

The possible reaction courses for the formation of carbapenam and carbacepham are shown in Scheme 8. When a monodentate ligand is used, the lactam nitrogen of σ-allenylpalladium complex **V** reacts with palladium metal to give palladacyclohexane **VI**, which is converted into carbapenam **10**. On the other hand, when a bidentate ligand is used, the lactam nitrogen attacks the central carbon of the η^3-propargylpalladium complex **VII**, which is formed in a more stable manner, to give π-allylpalladium complex **VIII**. β-Hydride elimination from **VIII** gives **24**, and the reaction of **VIII** with the benzoate anion gives **25**.

SCHEME 8. Possible Reaction Course



SCHEME 9. Alternative Plan for the Synthesis of Carbapenem



Construction of Carbapenam via a η^3-Propargylpalladium Complex. Encouraged by the interesting finding that six-membered carbacephams **24** and **25** were formed from **9c** in the presence of a bidentate ligand, DPPF, in good yields, we tried to construct a carbapenam skeleton by an alternative plan (Scheme 9). If β-lactam **IX**, in which one carbon of the side chain is shortened, is used in palladium-catalyzed cyclization in the presence of a bidentate ligand, allenylpalladium complex **X**, which would be in a state of equilibrium with η^3-propargylpalladium complex **XI**, would be formed. The lactam nitrogen attacks the central carbon of η^3-propargylpalladium complex **XI** to form π-allylpalladium complex **XII**. From **XII**, carbapenam **XIII** would be formed.

To examine this reaction, β-lactams **32a** and **32b**, of which one carbon was shortened compared with that of **9**, were synthesized from 4-allyl-2-azetidinone **26**[12] (Scheme 10). Protection of the amide nitrogen of **26** with a silyl group followed by ozonolysis gave aldehyde **28**, which was reacted with triphenylphosphine and carbon

(13) The coupling constant *J* between 1- and 2-positions of **41-2α** having the 2α-benzoyloxy group is 0 Hz. On the other hand, the coupling constant *J* between the 1- and 2-positions of **41-2*β*** having the 2β-benzoyloxy group is 5.9 Hz. The fact that the coupling constant *J* between the 1- and 2-position of **22** was 0 Hz indicates that the silyloxy group was placed at the α-position.

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SCHEME 10. Synthesis of Precursors

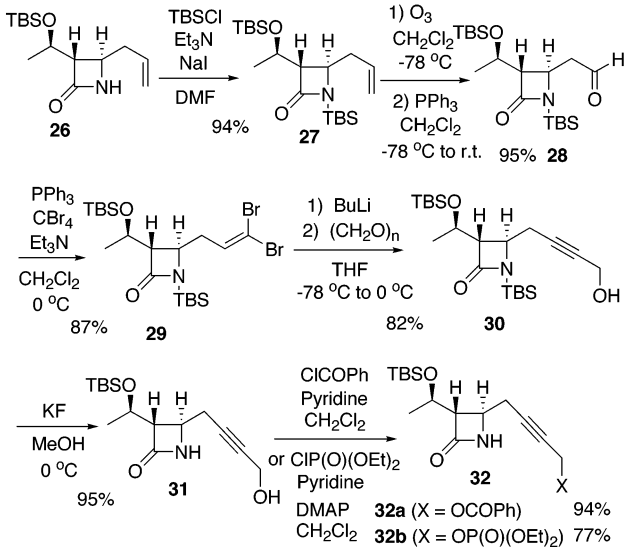
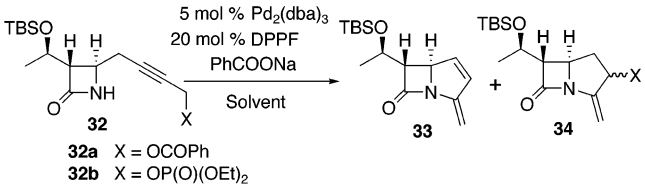
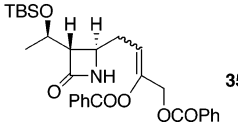


TABLE 3. Synthesis of Carbapenem Under Various Reaction Conditions



Run	X	Solvent	PhCOONa (equiv.)	Temp. (°C)	Time (h)	Yield (%) 33	34[b]	32a	35
1	OCOPh	Toluene	2 [a]	50	12	9	2	-	-
2	OCOPh	Toluene	2	70	8.5	4	31	33	-
3	OCOPh	THF	4	55	17	23	32	16	-
4	OP(O)(OEt)$_2$	THF	4	55	5	27	35	-	26
5	OP(O)(OEt)$_2$	THF	1.5	55	5	22	44	13	15

a) Cs_2CO_3 was used instead of PhCOONa. b) The ratio of **34-2**β to **34-2**α was about 1 : 1.



35 (E : Z = 1 : 5)

tetrabromide to give dibromoalkene **29**. The resultant **29** was treated with BuLi and then paraformaldehyde to give propargyl alcohol **30**, which was converted into β-lactams **32a** and **32b** by the usual methods.

When a toluene solution of propargyl benzoate **32a** was heated in the presence of 5 mol % of $Pd_2dba_3{\cdot}CHCl_3$, 20 mol % of DPPF, and 2 equiv of Cs_2CO_3 at 50 °C for 12 h, the desired carbapenams **33** and **34** were obtained, although the yields were only 9% and 2%, respectively (Table 3, run 1). Compound **34** consists of two isomers in a ratio of 1 to 1, and the stereochemistry at the 2-position of **34** was determined by NOE experiments to be **34-**β and **34-**α (Figure 1).

Various reaction conditions were used to try to increase the yield of carbapenams **33** and **34**. It was found that

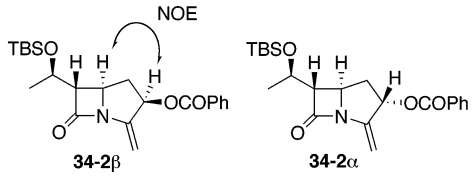
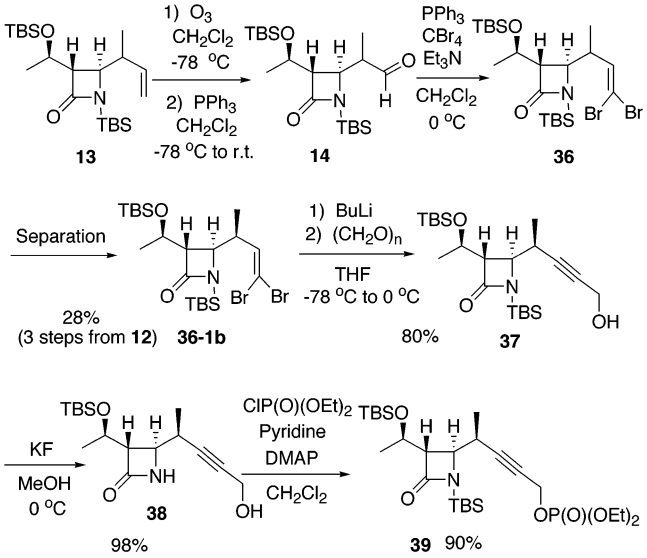


FIGURE 1.

SCHEME 11. Synthesis of Precursors for 1β-Methylcarbapenam



the use of sodium benzoate as a base resulted in a better yield, since sodium benzoate worked as not only a base but also a nucleophile, and the formation of carbapenam **34** from π-allylpalladium complex **XII** would progress easily (Table 3, run 2). The use of THF instead of toluene as a solvent gave a good result, the total yield of carbapenam being 55% (run 3).

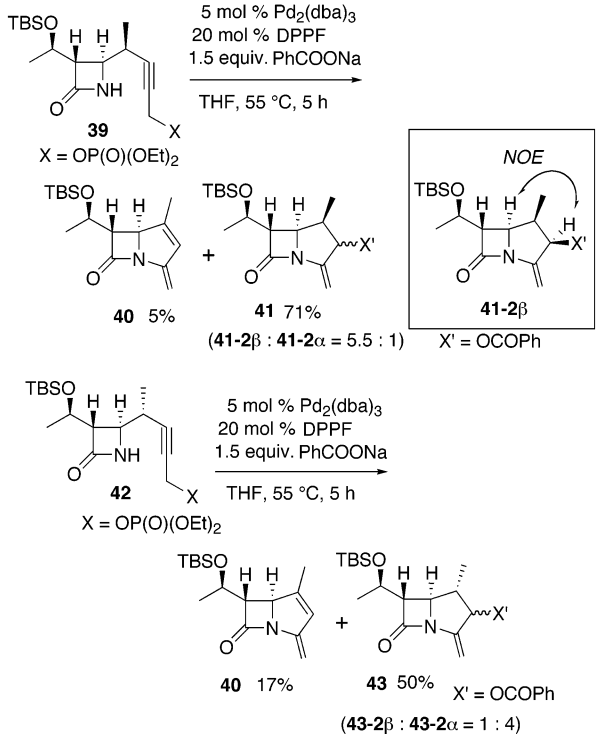
Next, the leaving group was changed from a benzoate group to a phosphate group (runs 4 and 5). When 4 equiv of sodium benzoate was used, the total yield of carbapenams was 62%, and the carbapenams were obtained along with undesired product **35** in 26% yield (run 4). The latter compound **35** would be obtained by attack of 2 mol of benzoate anions to η^3-propargyl complex **XI**. To avoid the production of **35**, when only 1.5 equiv of sodium benzoate was used, the total yield of carbapenams slightly increased (66%, run 5).

Construction of Carbapenam Having a β-Methyl Group at the 1-Position. Subsequently, we tried to synthesize 1β-methylcarbapenam. For the synthesis of 1β-methylcarbapanam, substrate **39** was synthesized in a similar manner as that for the synthesis of non-substituented **32b** (Scheme 11).

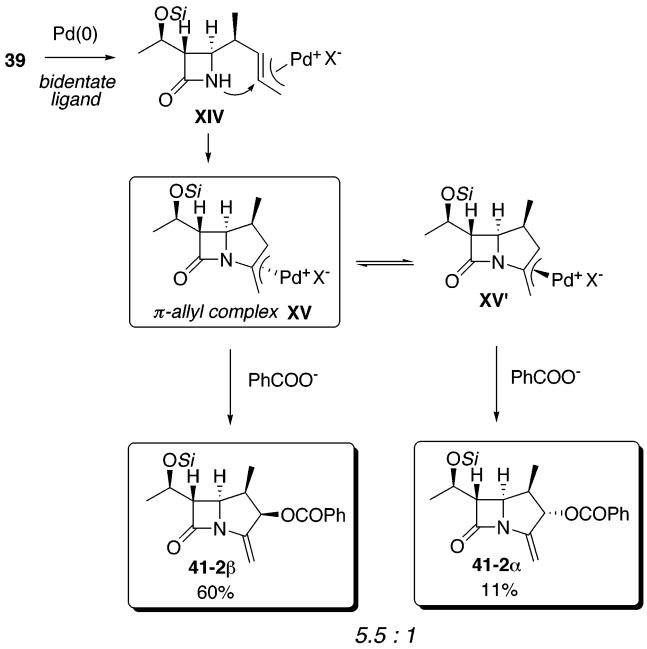
When phosphate **39** was treated under the best conditions for the synthesis of carbapenams **33** and **34**, the desired carbapenams **40** and **41** were obtained in 5% and 71% yields, respectively (Scheme 12). The latter compound **41** consists of two diastereomers at the 2-position and the ratio of β to α is 5.5 to 1. The stereochemistry was determined by an NOE experiment on **41-2β** to be **41-2β** and **41-2α**.

To examine the effect on the stereochemistry of the methyl group at the β-position on the formation of 1β-

SCHEME 12. Synthesis of 1*β*-Methyl- and 1α-Methylcarbapenams



SCHEME 13. Possible Reaction Course



methylcarbapenam, 1α-methylcarbapenam was synthesized. For that purpose, **42** was synthesized from **36-1α**. When phosphate **42** was treated under the same reaction conditions, the desired carbapenams **40** and **43** were obtained in 17% and 50% yields, respectively, and the ratio of **43-2*β*** to **43-2α** was 1 to 4.

The possible reaction course is shown in Scheme 13. Oxidative addition of propargyl phosphate **39** to Pd(0) in the presence of a bidentate ligand gives a σ-allenylpalladium complex, which is in a state of equilibrium with η^3-propargylpalladium complex **XIV**. The lactam nitrogen

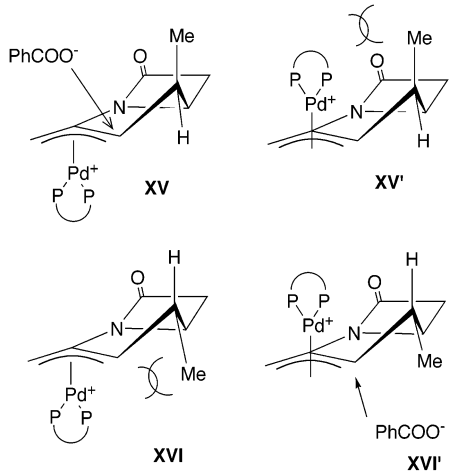


FIGURE 2.

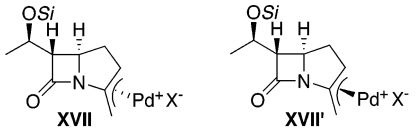


FIGURE 3.

attacks the central carbon of η^3-propargylpalladium complex **XIV** to give π-allylpalladium complex **XV** or **XV′**. The benzoate anion attacks from the backside of the palladium metal on π-allylpalladium complex **XV** and **XV′** to give **41-2*β*** and **41-2α**, respectively.

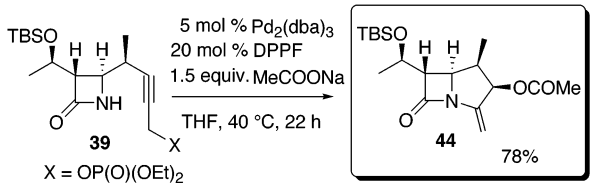
The reason for the difference between the ratio of **41-2*β*** to **41-2α** (5.5 to 1) and that of **34-2*β*** and **34-2α** (1 to 1) is thought to be the steric hindrance between the palladium metal on the π-allylpalladium complex and the 1β-methyl group. Formation of π-allylpalladium complex **XV** should be easier than that of **XV′** because of the steric hindrance of the β-methyl group on the five-membered ring of carbapenam. Since the nucleophile attacks from the backside of **XV** and **XV′**, the yield of **41-2*β*** is higher than that of **41-2α** (Figure 2).

However, in the case of the reaction of **32**, α- and β-π-allylpalladium complexes **XVII** and **XVII′** should be formed in the same ratios, and the nucleophile attacks from each opposite side to give **34-2*β*** and **34-2α** in a ratio of 1 to 1 (Figure 3).

On the other hand, in the case of **42**, the ratio of **43-2*β*** to **43-2α** is 1 to 4. Presumably, the structures of π-allylpalladium complexes would be **XVI** and **XVI′**. The benzoate anion would attack from the backside of the palladium metal. In these cases, formation of **43-2α** is easier than that of **43-2*β*** because of the steric hindrance between the α-methyl group and the palladium metal on **XVI**. Finally, we found that when sodium acetate was used instead of sodium benzoate as a base under the condition of a lower reaction temperature (40 °C), only 1β-methylcarbapenam **44** was obtained in 78% yield (Scheme 14).

In conclusion, we have developed a novel method for synthesizing carbapenam via a η^3-propargylpalladium complex. It is interesting that different ring-sized heterocycles, carbapenam and carbacepham, can be conveniently synthesized from the same β-lactam having a propargyl alcohol moiety, using Pd(0) with a monodentate

SCHEME 14. Synthesis of 1β-Methylcarbapenam



ligand or a bidentate ligand. In this reaction, the type of ligand plays an important role in determination of the ring size of the cyclized compound, and two types of 1β-methylcarbapenams, which are expected to have potentially unique biological properties, can be synthesized from β-lactams having a propargyl group on the side chain by palladium-catalyzed cyclization by two different methods.

Experimental Section

Typical Procedure for the Synthesis of Carbapenam: (1*R*,2*R*,5*R*,6*S*)-2-Acetoxy-6-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-1-methyl-3-methylidene-carbapenam (44). To a suspension of $Pd_2(dba)_3CHCl_3$ (5.7 mg, 0.00551 mmol), DPPF (12.2 mg, 0.0220 mmol), and MeCOONa (13.5 mg , 0.165 mmol) in THF (1 mL) was added a solution of **39** (49.2 mg, 0.110 mmol) in THF (2 mL) at 0 °C followed by degassing, then the mixture was stirred at room temperature for 5 min, then at 40 °C for 22 h. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/Et_2O 5/1) to afford **44** (30.3 mg, 0.0857 mmol, 78%) as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.80 (d, J = 7.3 Hz, 3 H), 0.87 (s, 9 H), 1.22 (d, J = 6.5 Hz, 3 H), 2.16 (s, 3 H), 2.80 (qdd, J = 7.3, 5.9, 5.9 Hz, 1 H), 3.15 (dd, J = 5.9, 2.7 Hz, 1 H), 3.87 (dd, J = 5.9, 2.7 Hz, 1 H), 4.22 (qd, J = 6.5, 5.9 Hz, 1 H), 4.47 (dd, J = 2.2, 2.2 Hz, 1 H), 4.96 (dd, J = 2.2, 2.2 Hz, 1 H), 5.69 (ddd, J = 5.9, 2.2, 2.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.91 (CH_3), −4.18 (CH_3), 8.55 (CH_3), 17.97 (C), 20.80 (CH_3), 22.60 (CH_3), 25.71 (CH_3), 36.37 (CH), 53.93 (CH), 60.77 (CH), 65.62 (CH), 77.26 (CH), 92.14 (CH_2), 140.90 (C), 169.84 (C), 170.19 (C). IR (neat) 2955, 2930, 2885, 2857, 1777, 1751, 1658 cm^{-1}. LRMS (EI, *m*/*z*) 338 (M − Me)$^+$, 296 (M − ^{t}Bu)$^+$. HRMS (EI) calcd for $C_{14}H_{22}NO_4Si$ 296.1318 (M − ^{t}Bu)$^+$, found 296.1314.

Supporting Information Available: Information on experimental procedures, spectral data for substrate **2**−**9**, **15**−**21**, **27**−**32**, and **36**−**39** and for carbapenams and carbacephams **10**, **11**, **22**−**25**, **33**−**35**, **40**, **41**, and **43**. This material is available free of charge via the Internet at http://pubs.acs.org.

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