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Synthesis of 3-Alkoxycarbonyl-1β-methylcarbapenem by Using the Palladium-Catalyzed C−N Bond-Forming Reaction between Vinyl Halide and β-Lactam Nitrogen

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3-Alkoxycarbonyl-1β-methylcarbapenem could be synthesized by using a palladium-catalyzed C−N bond-forming reaction between vinyl halide and β-lactam nitrogen. In this reaction, the use of $Pd(OAc)_2$ and DPEphos gave a good result, and the generation of Pd(0) from $Pd(OAc)_2$ in the absence of a base is necessary to increase the yield.

Introduction

Extensive and succesive works have been performed for the development of 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 and one that has strong antibiotic activity.[1] The development of a new method for forming a carbapenam skeleton is very important in establishing a method for efficient synthesis of new types of carbapenem antibiotics.[2] 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 a carbapenam skeleton because of its highly strained structure. 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 remarkable reports on the construction of carbapenam skeletons with use of organometallic reagents.[3] For example, as originally reported by Merck's group, intramolecular reaction of a rhodium−carbene complex with the N−H bond of β-lactam is often 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 metathesis reaction.[6] We have investigated the possibility of synthesizing a carbapenem skeleton using organometallic reagents.[7]

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

Our plan for the construction of a carbapenem skeleton involving the coupling of vinyl halide and amide in the presence of a palladium catalyst is shown in Scheme 2,[7c] although little is known about the reaction between vinyl

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(1) (a) Kahan, J. S.; Kahan, F. M.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiot.* **1979**, *32*, 1. (b) Albers-Schönberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491. (c) Sunagawa, M.; Sasaki, A. *Heterocycles* **2001**, *54*, 497.

(2) Berks, A. H. *Tetrahedron* **1996**, *52*, 331.

(3) Barrett, A. G. M.; Sturgess, M. A. *Tetrahedron* **1988**, *44*, 5615.

(4) (a) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31. (b) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161. (c) Williams, M. A.; Hsiao, C.-N.; Miller, M. J. *J. Org. Chem.* **1991**, *56*, 2688. (d) Kume, M.; Kubota, T.; Iso, Y. *Tetrahedron Lett.* **1995**, *36*, 8043.

(5) Trost, B. M.; Chen, S.-F. *J. Am. Chem. Soc.* **1986**, *108*, 6053.

(6) (a) Roland, S.; Durand, J. O.; Savignac, M.; Genêt, J. P. *Tetrahedron Lett.* **1995**, *36*, 3007. (b) Galland, J.-C.; Roland, S.; Malpart, J.; Savignac, M.; Genet, J.-P. *Eur. J. Org. Chem.* **1999**, 621. (c) Duboc, R.; Hénaut, C.; Savignac, M.; Genet, J.-P.; Bhatnagar, N. *Tetrahedron Lett.* **2001**, *42*, 2461.

(7) (a) Mori, M.; Kozawa, Y.; Nishida, M.; Kanamaru, M.; Onozuka, K.; Takimoto, M. *Org. Lett.* **2000**, *2*, 3245. (b) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2001**, *42*, 4869. (c) Preliminary report of this article: Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 111.

(8) (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560. (d) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423. (e) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 1232. (f) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617. (g) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367. (h) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264. (i) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307. (j) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525. (k) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35. (l) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101. (m) Shakespeare, W. C. *Tetrahedron Lett.* **1999**, *40*, 2035.

(9) (a) Madar, D. J.; Kopecka, H.; Pireh, D.; Pease, J.; Pliushchev, M.; Sciotti, R. J.; Wiedeman, P. E.; Djuric, S. W. *Tetrahedron Lett.* **2001**, *42*, 3681. (b) Cacchi, S.; Antonella Goggiamani, G. F.; Zappia, G. *Org. Lett.* **2001**, *3*, 2539. (c) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417. (d) Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1028. (e) Wagaw, S.; Rennnels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451.

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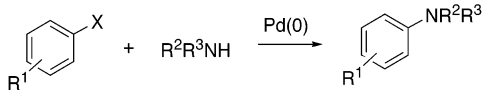
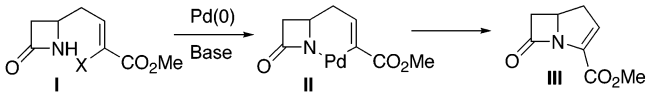
SCHEME 1. Palladium-Catalyzed C-N Bond-Forming Reaction between Aryl Halide and Amines



SCHEME 2. Our Plan for the Synthesis of a Carbapenem Skeleton



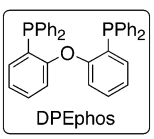
halide, instead of aryl halide, and amide in the presence of a palladium catalyst.

If vinyl halide **I** is treated with Pd(0) in the presence of a base, palladacycle **II** would be formed. Reductive elimination from **II** would give carbapenem **III** having the methoxycarbonyl group at the 3-position. Because it is known that the presence of a 3-carboxyl group on the five-membered ring in a carbapenem skeleton is very important for antibiotic activity, **III** could be a potential precursor for carbapenem having a carboxyl group at the 3-position. We report the synthesis of a carbapenem skeleton using a palladium-catalyzed intramolecular C−N bond-forming reaction.

Results and Discussion

Construction of Carbapenem Having the Silyloxymethyl Group at the 3-Position. At first, we investigated the reaction of amide nitrogen in the β-lactam ring with vinyl bromide having a silyloxymethyl group in palladium-catalyzed amidation. Vinyl bromide **6** was synthesized from 2-azetidinone **1** (Scheme 3).[10] Protection of the amide nitrogen of **1** with a silyl group followed by ozonolysis gave aldehyde **3**, which was reacted with the Wittig reagent[11] to give *Z*-vinyl bromide **4** in 78% yield along with *E*-vinyl bromide in 13% yield. Reduction of **4** by DIBAL-H gave **5**, which was converted into **6** by the usual method.

Intramolecular coupling of **6** in the presence of a palladium catalyst was examined. When a toluene solution of **6** was heated in the presence of 5 mol % of $Pd_2dba_3{\cdot}CHCl_3$, 20 mol % of P(*o*-Tol)$_3$, and 2 equiv of Cs_2CO_3 at 90 °C for 8.5 h, carbapenem **8** having a silyloxymethyl group at the 3-position was obtained, although the yield was low (Table 1, Run 1). In accordance with a recent report by Buchwald,[8k] $Pd(OAc)_2$−MOP and $Pd(OAc)_2$−BINAP were used as the catalyst systems, but good results were not obtained (Runs 2 and 3). However, surprisingly, when DPEphos was used as a ligand, the



DPEphos

desired carbapenem **8** was obtained in 96% yield (Run 4). This result showed that a vinyl bromide could participate well in a palladium-catalyzed C−N bond-forming reaction.

SCHEME 3. Synthesis of Vinyl Bromides

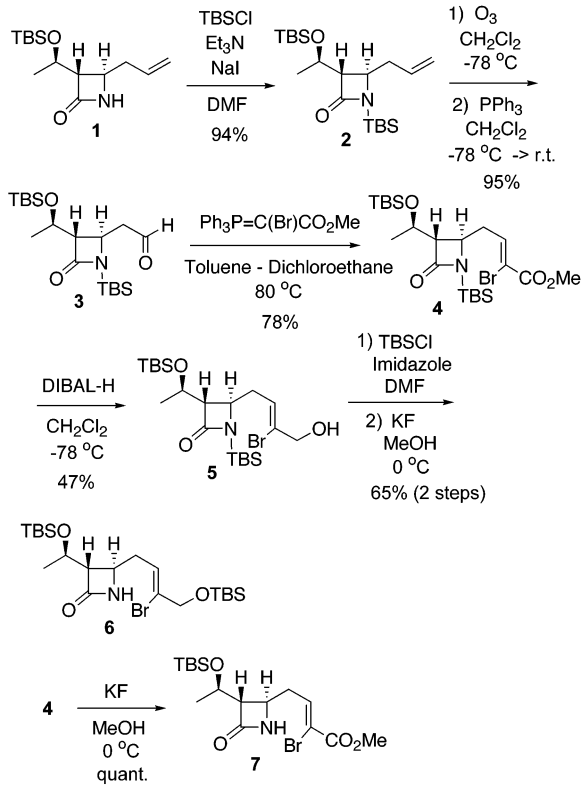
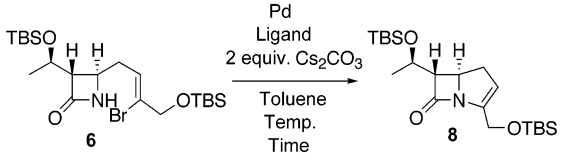


TABLE 1. Reaction of 6 with Palladium Catalysts



run	Pd	ligand	temp (°C)	time (h)	yield (%) 8	yield (%) 6
1[a]	$Pd_2(dba)_3CHCl_3$	P(*o*-Tol)$_3$	90	8.5	16	75
2[b]	$Pd(OAc)_2$	(S)-MOP	80	11	3	65
3[b]	$Pd(OAc)_2$	BINAP	80	11	trace	76
4[b]	$Pd(OAc)_2$	DPEphos	80	6	96	−

[a] 5 mol % of $Pd_2(dba)_3CHCl_3$ and 20 mol % of a ligand were used. [b] 10 mol % of $Pd(OAc)_2$ and 15 mol % of a ligand were used.

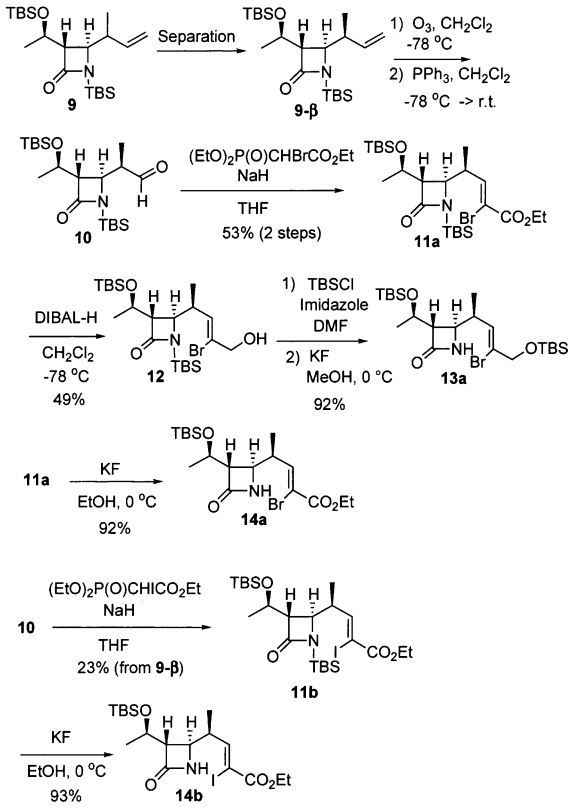
Subsequently, the synthesis of 1β-methylcarbapenem was investigated. In general, it is known that a carbapenem skeleton having a 1β-methyl group is both biologically and chemically more stable than is a nonsubstituented carbapenem skeleton and attention is currently focused on its unique biological properties.[1c,12]

Consequently, the two diastereomers of **9**[10] were separated by column chromatography on silica gel, and isomer **9**-β was ozonolyzed to give aldehyde **10**, which was converted into vinyl bromide **13a** in a similar manner as that for the synthesis of **6**[13] (Scheme 4).

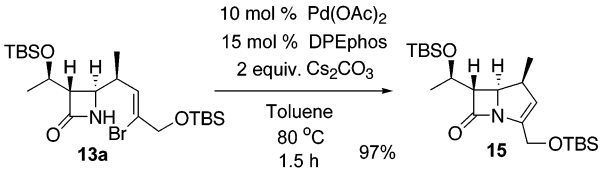
The coupling reaction of vinyl bromide **13a** having a silyloxymethyl group was examined. When a toluene

(10) Imuta, M.; Itani, H.; Ona, H.; Hamada, Y.; Uyeo, S.; Yoshida, T. *Chem. Pharm. Bull.* **1991**, *39*, 663.
(11) Märkl, G. *Chem. Ber.* **1962**, *95*, 3003.
(12) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29.
(13) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

SCHEME 4. Substrates for Synthesis of 1β-Methylcarbapenem



SCHEME 5. Reaction of 13a with a Palladium Catalyst



solution of **13a**, $Pd(OAc)_2$, DPEphos, and Cs_2CO_3 was heated at 80 °C, carbapenem **15** was obtained in 97% yield after only 1.5 h, at which time TLC analysis showed complete consumption of starting material **13a** (Scheme 5). The reaction of methyl-substituented **13a** progressed faster than that of nonsubstituented **6**.

Construction of Carbapenem Having a Carbalkoxy Group at the 3-Position. Encouraged by the excellent results obtained by using the substrates **6** and **13a** having a silyloxymethyl group at the 3-position, palladium-catalyzed coupling of vinyl bromide **7** having a carbomethoxy group was attempted. Synthesis of **7** is shown in Scheme 3. The reaction of **7** with $Pd(OAc)_2$ and DPEphos was carried out under the same reaction conditions, but no cyclized product **16** was produced, and the starting material **7** was recovered in 46% yield (Scheme 6). The reaction was attempted under various conditions, but the results were not satisfactory.

Next, with use of substrates **14a** and **14b** having β-methyl and the carbethoxy groups at the 1- and 3-positions, synthesis of 3-ethoxycarbonyl-1β-methylcarbapenem was attempted. Synthesis of substrates **14a** and **14b** is shown in Scheme 4. Under the same reaction conditions (method A), vinyl bromide **14a** having an

SCHEME 6. Reaction of 7 with a Palladium Catalyst

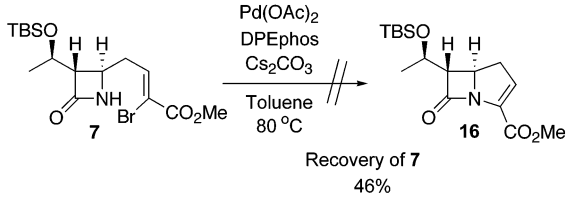
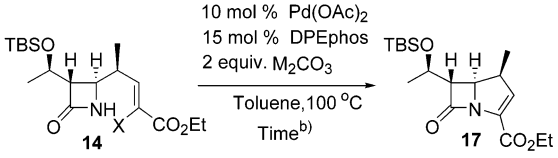


TABLE 2. Reaction of 14 with a Palladium Catalyst

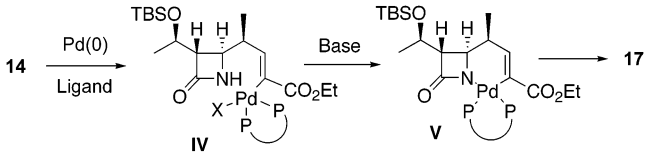


Run	Substrate	X	Base	Method[a]	Time (h)	Yield (%) 17	Yield (%) 14
1	**14a**	Br	Cs_2CO_3	A	22	Trace	10
2	**14a**	Br	K_2CO_3	A	36	59	12
3	**14b**	I	K_2CO_3	A	10	20	63
4	**14c**	OTf	K_2CO_3	B	22	14	-
5	**14b**	I	K_2CO_3	B	22	90	2
6	**14a**	Br	K_2CO_3	B	48	74	19
7	**14a**	Br	Cs_2CO_3	B	22	Trace	10
8	**14a**	Br	Na_2CO_3	B	48	11	74

[a] Method A: A toluene solution of **14**, $Pd(OAc)_2$, DPEphos, and M_2CO_3 was heated at 100 °C. Method B: A toluene solution of **14**, $Pd(OAc)_2$, and DPEphos was heated at 100 °C for 2 min and was added to a suspension of K_2CO_3 in toluene. Then the toluene solution was heated at 100 °C. [b] The reaction mixture was stirred until the starting material **14** had been completely consumed as judged by TLC analysis.

ethoxycarbonyl group did not produce carbapenem **17** (Table 2, Run 1). However, when K_2CO_3 was used instead of Cs_2CO_3, we were very pleased to find that **17** was obtained in 59% yield (Run 2). The reaction rate of **14a** was much slower than that of **13a**. Under the same conditions, vinyl iodide **14b** gave **17** in only 20% yield (Run 3), although, in general, the reactivity of vinyl iodide is higher than that of vinyl bromide in the oxidative addition to Pd(0). To generate Pd(0) in a palladium-catalyzed C−N bond-forming reaction, Buchwald has carried out a special procedure. That is, a toluene solution of the substrate, $Pd(OAc)_2$, and the ligand was heated in the absence of a base at 100 °C for 2 min to dissolve the catalysts, and then the base was added at 0 °C. Then the toluene solution was heated at an appropriate temperature (method B).[8k] Our next trials were carried out using this method (method B) reported by Buchwald. When vinyl triflate **14c** was used, **17** was obtained in only low yield, although the starting material was consumed (Run 4). However, surprisingly, the yield of **17** increased to 90% when vinyl iodide **14b** was reacted with $Pd(OAc)_2$ and DPEphos, using method B (Run 5). Treatment of vinyl bromide **14a** by using method B also increased the yield of **17** (Run 6). On the other hand, the use of Na_2CO_3 or Cs_2CO_3 as a base gave only a trace amount of **17** (Runs 7 and 8). When BINAP or DPPF or PPh_3 as a ligand was used, the yields were very low. These results

SCHEME 7. Possible Reaction Course



suggest that K_2CO_3 as a base and DPEphos as a ligand would be the best combination in intramolecular palladium-catalyzed coupling of **14a**.

The difference between methods A and B in this reaction is the presence or absence of a base in the generation of Pd(0). In this reaction, Pd(0) would be generated from $Pd(OAc)_2$ and DPEphos.[14] In the case of method B, when the solution is heated for 2 min in the absence of a base, $Pd(OAc)_2$ is dissolved by the coordination of the ligand and then Pd(0) would be formed. In the absence of a base, only DPEphos would completely coordinate to the palladium metal. Then the base is added and the nitrogen anion is produced to form palladacycle **V** (Scheme 7).

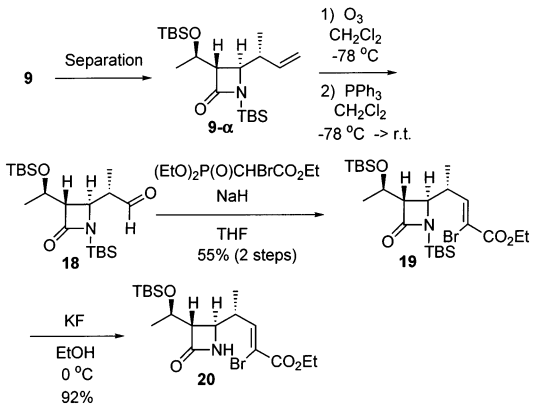
However, in the case of method A, since the generation of the nitrogen anion by the base and the generation Pd(0) from $Pd(OAc)_2$ occur simultaneously upon heating at 100 °C, various palladium species involving the coordination of the nitrogen anion on palladium metal would be produced under the reaction conditions, because the palladium catalyst should not form an eight-membered ring by coordination of DPEphos. As result, the yields of **17** would be decreased.

Next, to compare the reactivity of vinyl bromide having a 1β-methyl group with that of vinyl bromide having a 1α-methyl group in the palladium-catalyzed C−N bond-forming reaction, 3-ethoxycarbonyl-1α-methylcarbapenem **21** was synthesized from vinyl bromide **20**. Vinyl bromide **20** was also synthesized in a similar manner with **14a** (Scheme 8).

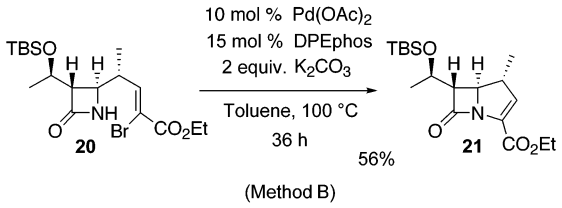
When **20** was treated following method B under similar reaction conditions, **21** was obtained in 56% yield (Scheme 9). However, when **7**, which has no substituent at the 1-position, was treated in a similar manner, no cyclized product **16** was produced. This means that the substituent at the 1-position is important for this cyclization.

In conclusion, 3-alkoxycarbonyl-1β-methylcarbapenem and 3-alkoxycarbonyl-1α-methylcarbapenem could be

SCHEME 8. Substrate for Synthesis of 1α-Methylcarbapenem



SCHEME 9. Synthesis of 1α-Methylcarbapenem



synthesized by using a palladium-catalyzed C−N bond-forming coupling of vinyl halide and β-lactam nitrogen. In this reaction, the use of $Pd(OAc)_2$−DPEphos as a catalyst system and the use of K_2CO_3 as a base are suitable, and the generation of Pd(0) in the absence of a base is necessary to increase the yield. Although only aryl halide has been used for C−N bond-forming reactions, our results also indicated that vinyl bromide or vinyl iodide can be used for a palladium-catalyzed C−N bond-forming reaction. This new efficient method for the construction of a carbapenem skeleton with a palladium catalyst is expected to be a powerful tool for research on next-generation carbapenem antibiotics.

Supporting Information Available: Information on experimental procedures, spectral data for substrate **2**−**8, 11a, 11b, 12**, **13a**, **14a**, **14b**, **15**, **17**, **19**, **20**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177.