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Synthesis of 3-alkoxycarbonyl-1β-methylcarbapenem using palladium-catalyzed amidation of vinyl halide

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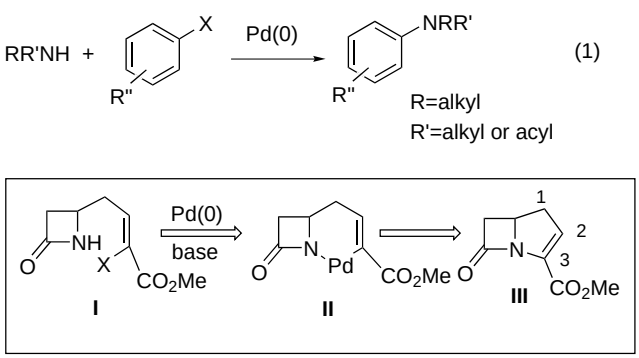
Abstract—3-Alkoxycarbonyl-1β-methylcarbapenem could be synthesized using a palladium-catalyzed C–N bond-forming reaction. In this reaction, the use of $Pd(OAc)_2$ and DPEphos gave a good result, and generation of Pd(0) in the absence of a base is necessary to increase the yield.

Development of new method for synthesizing a carbapenem skeleton is very important to gaining efficient access to new β-lactam antibiotics.[1] It is known that the 3-carboxyl group on the five-membered ring in a carbapenem skeleton is very important for antibiotic activity. We have already developed two methods for synthesizing a carbapenam skeleton using transition metals.[2] However, although a methylene or allenylidene group could be introduced at the 3-position of a carbapenam skeleton,[2b] we have not been able to introduce a carboxyl group at this position. Recent reports of Buchwald[3] and Hartwig[4] prompted us to use their C–N bond-forming reactions (Scheme 1, Eq. (1)) for the construction of a carbapenem skeleton employing a novel coupling between the β-lactam nitrogen and a vinyl halide. Our plan is shown in Scheme 1. 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.



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

Thus, we synthesized vinyl bromide **4** from 4-allyl-2-azetidinone **1**.[5] Protection of the amide nitrogen of **1** with a silyl group followed by ozonolysis gave aldehyde **2**, which was reacted with the appropriate Wittig reagent[6] to give *Z*-vinyl bromide **3** in 78% yield along with *E*-vinyl bromide in 13% yield. Deprotection of the silyl group gave **4**. To compare the reactivity of the vinyl bromide having the methoxycarbonyl group with that of the silyloxymethyl group in palladium-catalyzed C–N bond-forming reaction, vinyl bromide **6** was prepared from **3** using standard procedure.

At first, 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 **7** having the 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, $Pd(OAc)_2$-MOP and $Pd(OAc)_2$-BINAP were used as catalyst systems,[3a] but good results were not obtained (runs 2 and 3). However, surprisingly, when DPEphos was used as a ligand, the desired carbapenem **7** was obtained in 96% yield (run 4). This result established that a vinyl bromide could participate well in the palladium-catalyzed C–N bond-forming reaction.

Keywords: β-lactam; carbapenem; 3-alkoxycarbonyl-1β-methylcarbapenem; palladium-catalyzed amidation; palladium-catalyzed cyclization.

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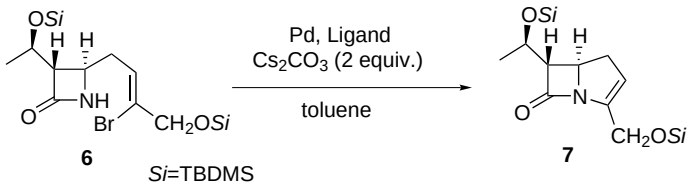
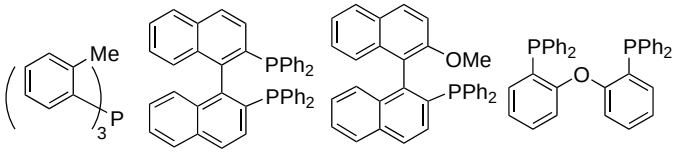
Table 1. Reaction of **6** with palladium catalysts



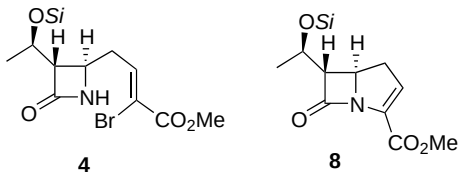
6 *Si*=TBDMS **7**

Run	Pd	Ligand	Temp. (°C)	Time (h)	Yield (%) of	
					7	**6**
1[a]	$Pd_2dba_3{\cdot}CHCl_3$	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 palladium catalyst and 20 mol% of ligand were used.
[b] 10 mol% of palladium catalyst and 15 mol% of ligand were used.



P(*o*-tol)$_3$ BINAP MOP DPEphos



4 **8**

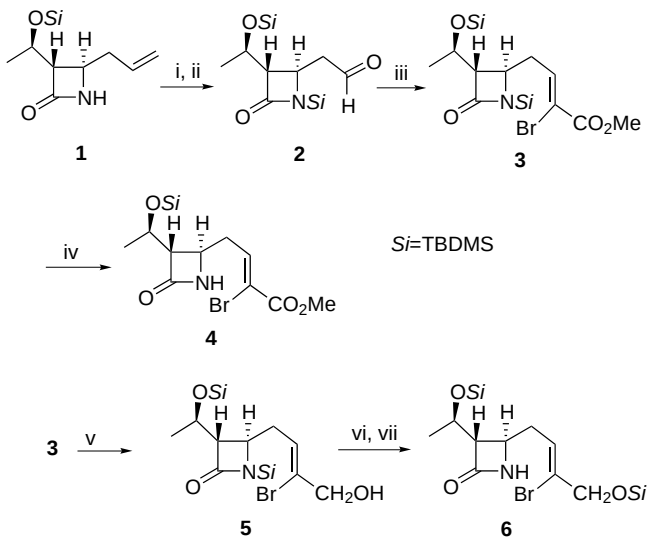
Encouraged by theses results, the palladium-catalyzed coupling of vinyl bromide **4** bearing the carbomethoxy group was attempted. However, no cyclized product **8** was produced under the same reaction conditions, and the starting material **4** was recovered in 46% yield. Various attempts were made, but the results were not satisfactory.

Subsequently, the synthesis of 1β-methylcarbapenem was investigated because it is known that a carbapenem skeleton having a 1β-methyl group is more stable than that of a non-substituted carbapenem and has unique biological properties.

Consequently, the two diastereomers of **9**[5] (Scheme 3) were separated by column chromatography on silica gel and each isomer was ozonolyzed to give an aldehyde, which was converted into the requisite vinyl halide[7] in a similar manner as for the synthesis of **4** or **6** (Scheme 2).

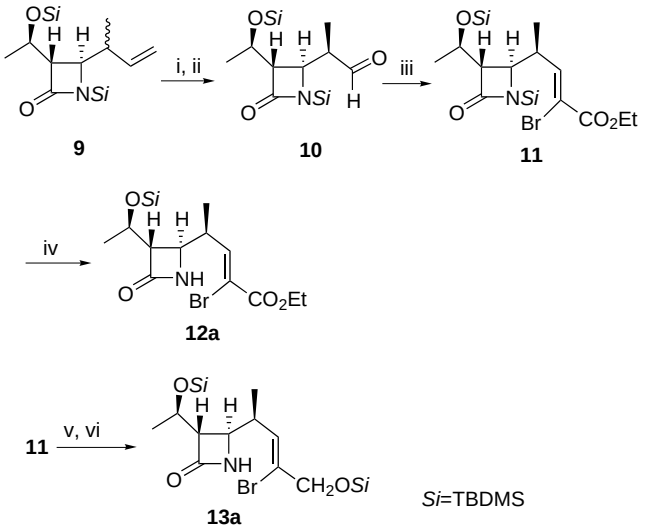
When a toluene solution of vinyl bromide **13a** having a silyloxymethyl group, $Pd(OAc)_2$, DPEphos and Cs_2CO_3 was heated at 80°C for 1.5 h, carbapenem **14** was obtained in 97% yield (Scheme 4).

Under the same reaction conditions (method A), vinyl bromide **12a** having the ethoxycarbonyl group did not

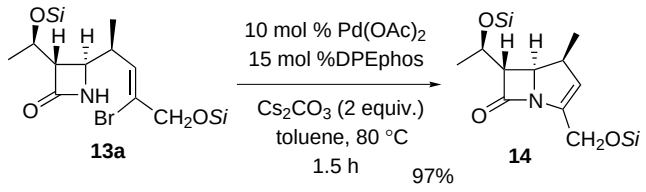


1 **2** **3** **4** **5** **6**

Scheme 2. Synthesis of vinyl bromides. (i) TBDMSCl, Et_3N, DMF, 94%; (ii) O_3, −78°C, then PPh_3, −78°C to rt, 95%; (iii) $Ph_3P{=}C(Br)COOMe$, 80°C, 78% (*E*-**3**, 13%); (iv) KF, MeOH, 0°C, quant.; (v) DIBAL-H, −78°C, 47%; (vi) TBDMSCl, imidazole, DMF; (vii) KF, MeOH, 0°C, 65% (from **5**).

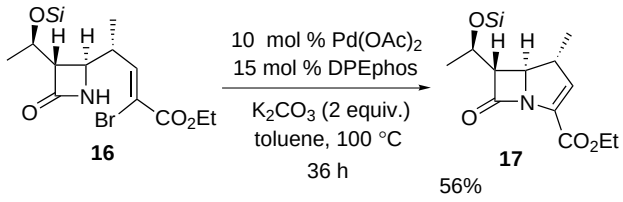


Scheme 3. Substrate for synthesis of 1β-methylcarbapenem. (i) Separation; (ii) O_3, −78°C, then PPh_3, −78°C to rt; (iii) $(EtO)_2P(O)CH(Br)COOEt$,[7] NaH, 53% (two steps); (iv) KF, EtOH, 0°C, 92%; (v) DIBAL-H, −78°C, 49%; (vi) TBDMSCl, imidazole and then KF, MeOH, 0°C, 65%.



Scheme 4. Synthesis of the 1β-methylcarbapenem derivative.

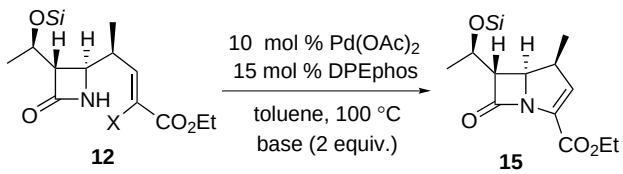
produce carbapenem **15** (Table 2, run 1). However, we were very pleased to find that **15** was obtained in 59% yield when K_2CO_3 was used instead of Cs_2CO_3 (run 2). Under the same conditions, vinyl iodide **12b** gave **15** in only 20% yield (run 3), although, in general, the reactivity of vinyl iodide is higher than that of vinyl bromide in the oxidative addition to Pd(0). Buchwald has carried out careful generation of Pd(0) in palladium-catalyzed C–N bond-forming reaction.[3a] 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, and then the base was added at 0°C. The toluene solution was then heated at an appropriate temperature (method B). Surprisingly, the yield of **15** increased to 90% when vinyl iodide **12b** was reacted with $Pd(OAc)_2$ and DPEphos using method B (run 5). Treatment of vinyl bromide **12a** using method B also increased the yield of the desired product (run 4). On the other hand, the use of Na_2CO_3 as a base or (*S*)-BINAP, DPPF, and PPh_3 as a ligand using method B gave only a trace amount of **15**. Synthesis of 3-ethoxycarbonyl-1α-methylcarbapenem **17** from vinyl bromide **16** was carried out using method B, and **17** was obtained in 56% yield (Scheme 5).



Scheme 5. Synthesis of 1α-methylcarbapenem.

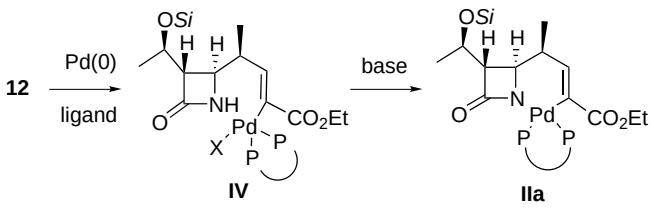
The difference between method A and method B in this reaction is the presence or absence of a base in the generation of Pd(0). In this reaction, Pd(0) is generated from $Pd(OAc)_2$ and DPEphos. In the absence of a base (method B), Pd(0) reacts with vinyl halide to produce vinylpalladium halide **IV** coordinated by DPEphos upon heating. After cooling, the base is added and palladacycle **IIa** would be formed (Scheme 6). On the other hand, in the case of method A, since the genera-

Table 2. Synthesis of 1β-methylcarbapenem



Run	Substrate	X	Base	Method[a]	Time (h)	Yield (%) of	
						15	**12**
1	**12a**	Br	Cs_2CO_3	A	22	Trace	10
2	**12a**	Br	K_2CO_3	A	36	59	12
3	**12b**	I	K_2CO_3	A	10	20	63
4	**12a**	Br	K_2CO_3	B	48	74	19
5	**12b**	I	K_2CO_3	B	22	90	2

[a] **Method A**: A toluene solution of **12**, $Pd(OAc)_2$, the ligand, and the base was heated at an appropriate temperature. **Method B**: A toluene solution of **12**, $Pd(OAc)_2$, and the ligand was heated at 100°C for 2 min. The solution was added to a base in toluene at 0°C and then the whole toluene solution was heated at an appropriate temperature.



Scheme 6. Possible reaction course.

tion of the nitrogen anion by the base and the generation of Pd(0) from $Pd(OAc)_2$[8] by DPEphos occur simultaneously upon heating at 100°C, various palladium species would be produced under the reaction conditions.

In conclusion, 1α- and 3-alkoxycarbonyl-1β-methylcarbapenem could be synthesized using a palladium-catalyzed C–N bond-forming reaction. In this reaction, the effect of the palladium catalyst is significant; that is, the use of $Pd(OAc)_2$ and DPEphos is suitable, and generation of Pd(0) in the absence of a base is necessary to increase the yield. Moreover, these results indicate that vinyl bromide or iodide could be used for a palladium-catalyzed C–N bond-forming reaction. Further studies are in progress.

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