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SYNTHESIS OF BICYCLIC HETEROCYCLES FROM PROPARGYL ESTERS USING A PALLADIUM CATALYST BEARING A BIDENTATE LIGAND

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Abstract- A method for synthesis of bicyclic heterocycles having functional group was developed from phenylpropargyl esters using a palladium catalyst and bidentate ligand. Isoquinoline and benzoazepine derivatives having functional groups could be synthesized using this method in high yields.

Since the reaction of allylic compounds with a palladium catalyst was discovered by Tsuji in 1965,[1] many studies on π-allylpalladium complexes have been carried out. However, there have been a few report for the reaction of propargylic compounds with a palladium catalyst.[2,3] We have reported the synthesis of carbapenam derivatives from β-lactams bearing a propargyl ester in a tether using a palladium catalyst.[4]

In this reaction, we found that carbapenam was obtained when β-lactam bearing a propargyl ester was treated with a palladium catalyst bearing a monodentate ligand. However, the use of a palladium catalyst with a bidentate ligand afforded a carbacephem derivative. On the basis of these results, we developed a ligand-controlled novel method for synthesis of heterocycles.[5] When compound (**1**) was treated with Pd(0) and P(*o*-tol)$_3$, heterocyclic compound (**2**) was obtained in a high yield. On the other hand, treatment of the same compound (**1**) with Pd(0) and DPPF afforded heterocyclic compound (**3**), which has a one carbon-elongated ring size compared with that of heterocycle (**2**). The reaction course is explained as follows. Oxidative addition of propargyl ester (**1**) to Pd(0) gives η^1-propargylpalladium complex (**I**), which is in a state of equilibrium with allenylpalladium complex (**II**). The tosylamide intramoleculary attacks the palladium metal to give paladacycle (**III**), and reductive elimination gives compound (**2**). In this reaction, a monodentate ligand is effective because one ligand on the palladium metal of **II** separates and the nitrogen of the tosylamide coordinates on the palladium metal.

On the other hand, it was shown that η^1-allenylpalladium complex (**II'**) is in a state of equilibrium with η^3-propargylpalladium complex (**IV**) when the palladium catalyst has a bidentate ligand and the

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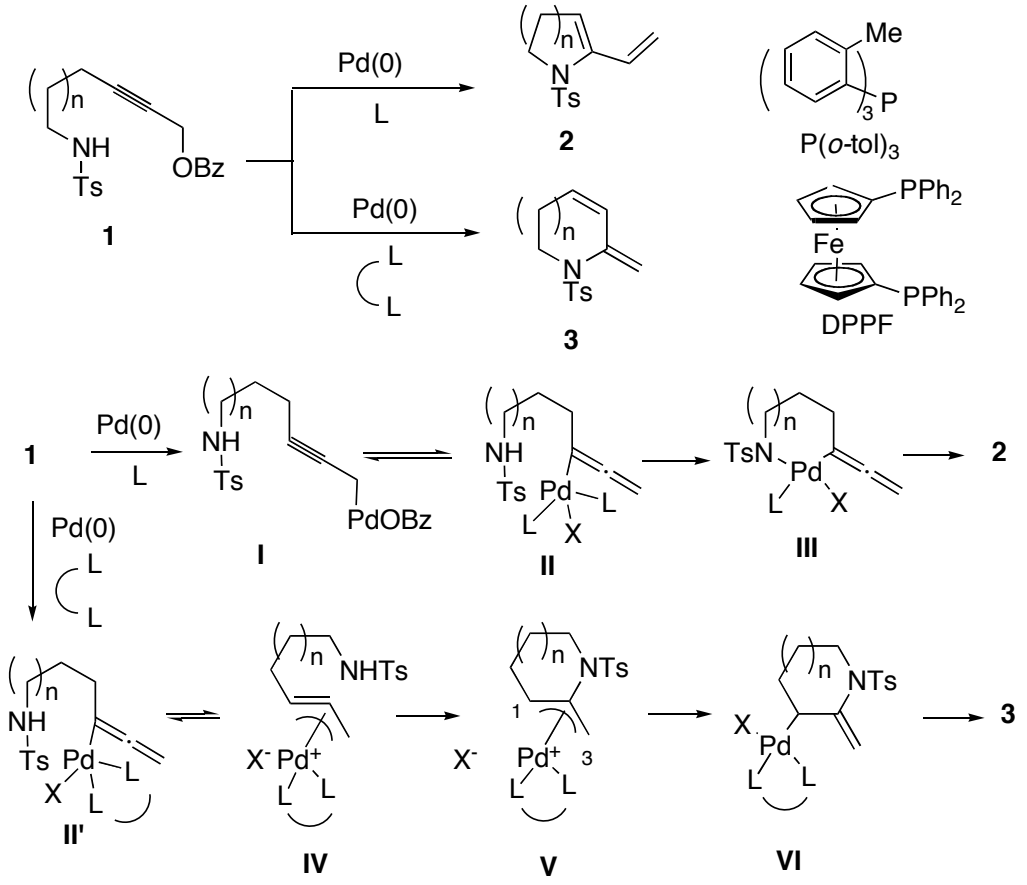
Dedicated to Dr. Potier, Emeritus Director of C. N. R. S., for the celebration of his 70th birthday.

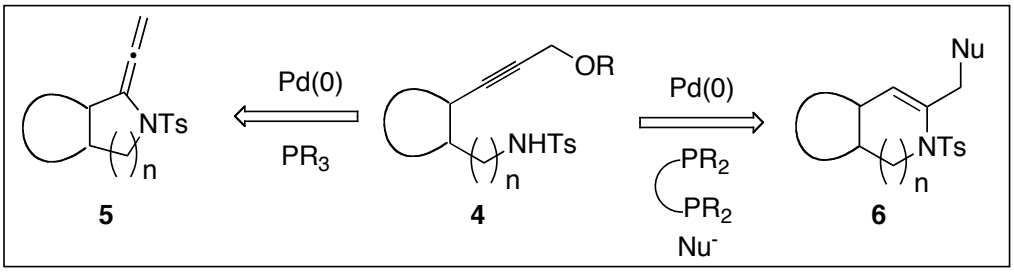
Scheme 1. Plan for Ligand-Controlled Synthesis of Bicyclic Heterocycles.



nucleophile attacks the central carbon of **IV** to give π-allylpalladium complex (**V**),[6] which is in a state of equilibrium with σ-allylpalladium complex (**VI**). Thus, β-hydrogen elimination gives compound (**3**).

We planned to extend this reaction to the synthesis of bicyclic heterocycles as shown in Scheme 2. That is, when propargyl ester (**5**) is treated with Pd(0) and a monodentate ligand, bicyclic heterocycles (**4**) would be formed, while a palladium catalyst bearing a bidentate ligand should afford heterocycles (**6**) which has a one-carbon elongated ring size.

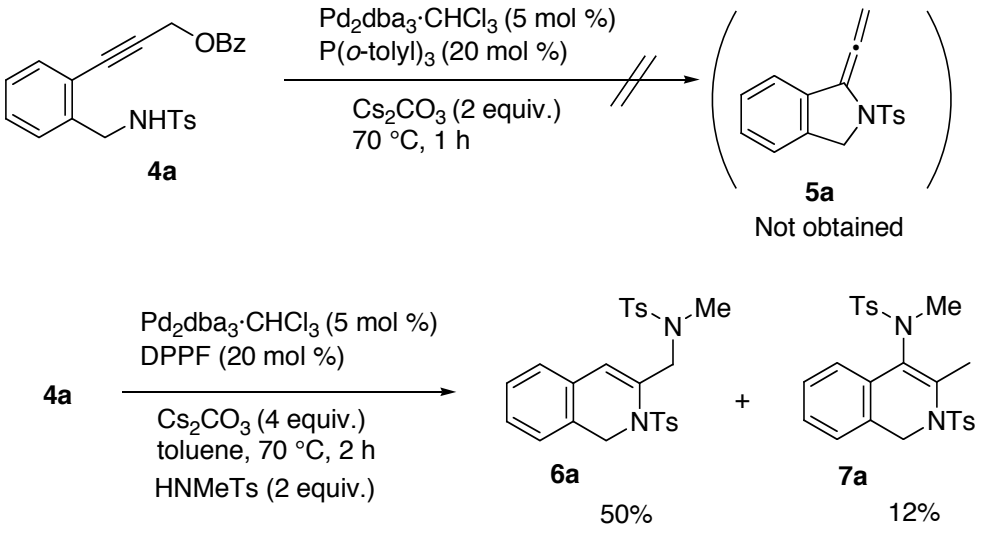
Scheme 2. Plan for Synthesis of Bicyclic Heterocycles



When a toluene solution of phenylpropargyl benzoate (**4a**) bearing a tosylaminomethyl group at the 2-position, 5 mol % of $Pd_2dba_3{\cdot}CHCl_3$ and 20 mol % of P(o-tol)$_3$ was stirred in the presence of Cs_2CO_3 at 70 °C for 1 h, the spot of the starting material (**4a**) disappeared on TLC, but no product was formed.

Various attempts were made, but the desired product (**5a**) was not obtained. Presumably, since the product has a phenylallenyl moiety and an allenamide moiety, the product (**5a**) would be unstable under the reaction conditions. Subsequently, when a toluene solution of **4a**, 5 mol % of $Pd_2dba_3{\cdot}CHCl_3$, 20 mol % of DPPF and Cs_2CO_3 was stirred at 70 °C for 2 h in the presence of N-methyltosylamide (4 equiv) as a nucleophile,[5] isoquinoline derivatives (**6a**) and (**7a**) were obtained in 50% and 12% yields, respectively. These compounds should be obtained from π-allylpalladium complex (**V**) *via* η^3-propargyl palladium complex (**IV**).

Scheme 3. Investigation of Ligand-Controlled Synthesis of Isoindoline and Isoquinoline.

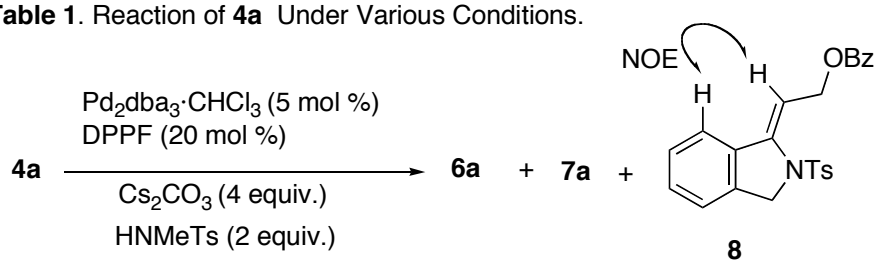


To increase the yield of the desired isoquinoline derivative (**6a**) or (**7a**), the reaction was carried out at room temperature, but the yield was decreased to 36% and five-membered ring compound (**8**) was obtained in 7% yield (Table 1, run 1). When the reaction was carried out at 50 °C, the yields of isoquinolines were slightly increased (run 2). THF could be used as a solvent, but the yields were not improved (run 3).

Since compound (**8**) has a five-membered ring, it was thought that **8** was formed *via* allenylpalladium complex (**III**). However, the benzoate group was placed at the allylic position. A NOE experiment on compound (**8**) indicated that *Z*-olefin is formed. Although the reason for formation of **8** having *Z*-olefin is not clear, one possibility is that an alkyne part of **4a** coordinates to the divalent hydridepalladium complex and the tosylamide nitrogen attacks an alkyne part to give **VII** and reductive elimination would give compound (**8**).

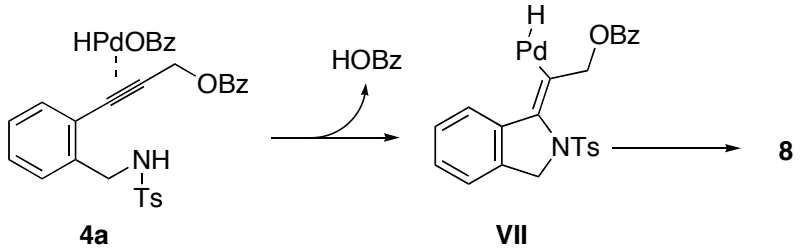
Subsequently, the nucleophile was changed to methyl malonate. When the propargyl carbonate (**4b**) was treated with $Pd_2dba_3{\cdot}CHCl_3$ and DPPF in the presence of methyl malonate at room temperature for 3 h, isoquinoline derivative (**6b**) was formed as a sole product in 75% yield. It was interesting that an isoquinoline derivative having a functional group was obtained by a one-step reaction.

Table 1. Reaction of **4a** Under Various Conditions.

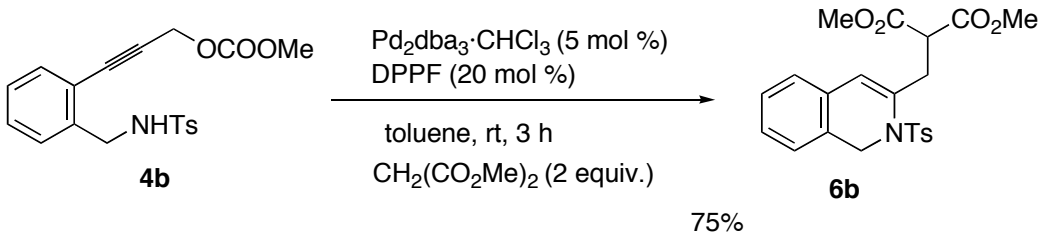


run	solvent	temp. (°C)	time (h)	yield (%)			
				6a	**7a**	**8**	**4a**
1	toluene	rt	22	36	—	7	38
2	toluene	50	2	53	13	10	—
3	THF	50	2	39	9	10	—

Scheme 4. Reaction Course for Formation of **8**.



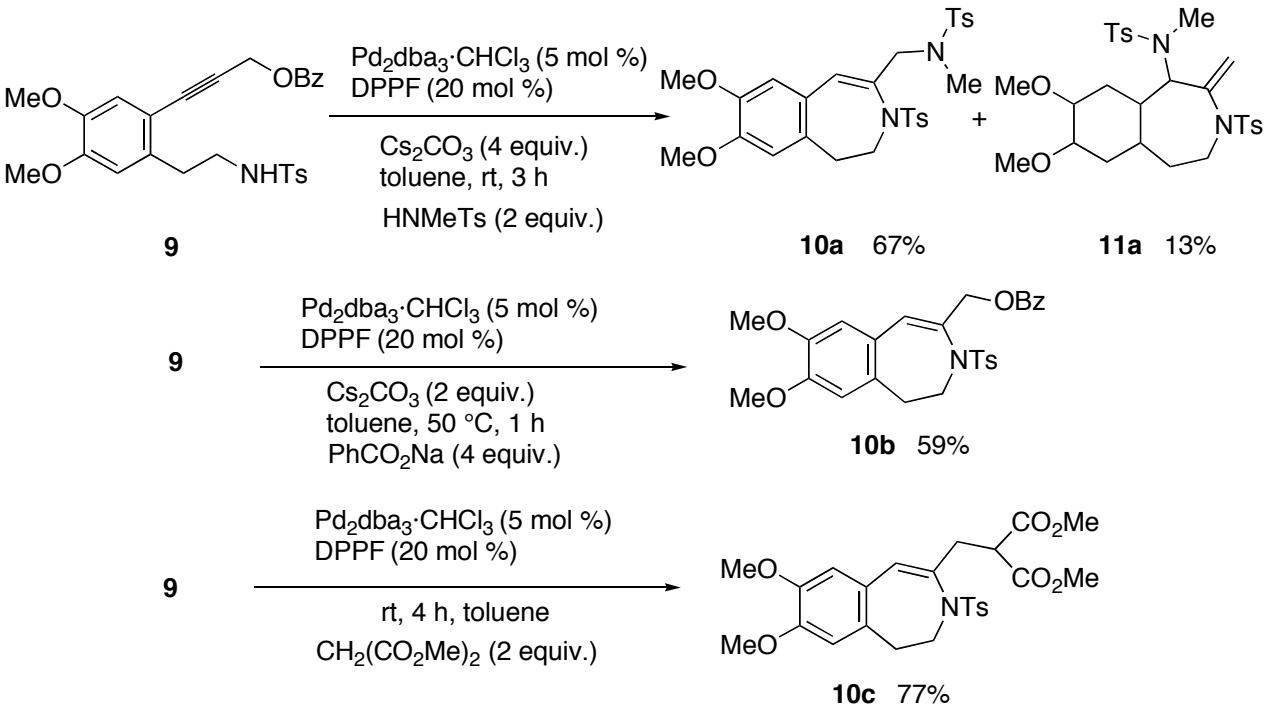
Scheme 5. Synthesis of an Isoquinoline Derivative.



The synthesis of benzoazepine derivatives was examined. When a toluene solution of **9**, 5 mol % of $Pd_2dba_3{\cdot}CHCl_3$, 20 mol % of DPPF and $CsCO_3$ was stirred in the presence of *N*-methyltosylamide at room temperature for 3 h, benzoazepine derivatives (**10a**) and (**11a**) were obtained in 67% and 13% yields, respectively.[7] In a similar manner, sodium benzoate or methyl malonate was used as a nucleophile, and the desired benzodiazepine derivative (**10b**) or (**10c**) was obtained in high yield. These results indicated that benzoazepine derivatives having various functional groups could be synthesized by one-pot reactions.

The results indicated that the reaction of propargyl ester with a palladium catalyst bearing a bidentate ligand in the presence of various nucleophiles gave bicyclic heterocycles in high yields by one-step reactions. Further studies are in progress.

Scheme 7. Synthesis of Various Benzoazepine Derivatives.



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7. In this reaction, the use of monodentate ligand, P(*o*-tol)$_3$, did not give a desired isoquinoline.