

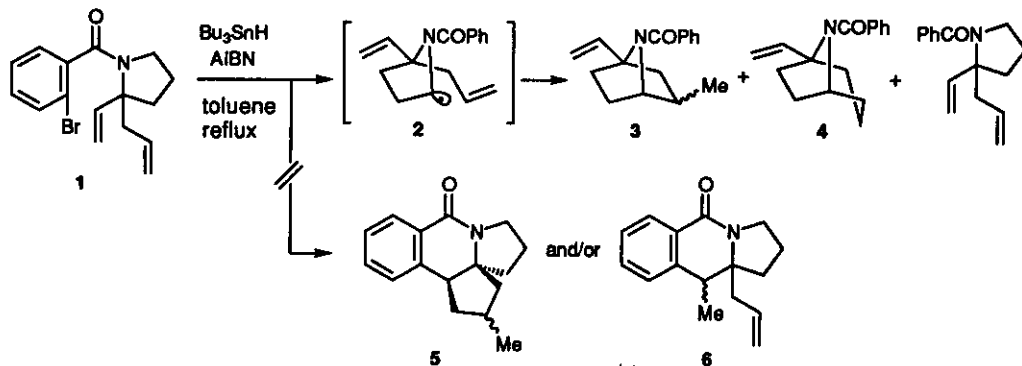
**SYNTHESIS OF TRICYCLIC NITROGEN-CONTAINING  
HETEROCYCLES BY PALLADIUM-CATALYZED  
CYCLIZATION OF 2-ALKENYL-*N*-(*o*-IODOBENZOYL)-  
AND 2-ALKENYL-*N*-(*o*-IODOPHENYLACETYL)-  
PYRROLIDINES†**

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**Abstract**—The palladium-catalyzed cyclization of the 2-alkenyl-*N*-(*o*-iodobenzoyl)- and 2-alkenyl-*N*-(*o*-iodophenylacetyl)pyrrolidines gave the tricyclic nitrogen-containing heterocycles.

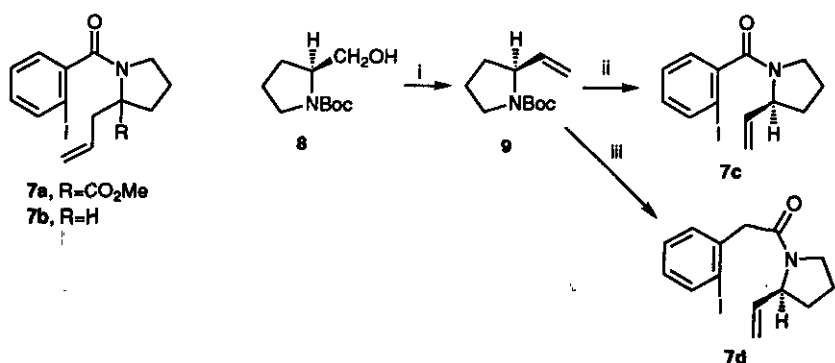
As part of our continuing studies towards the synthesis of optically active cephalotaxine,<sup>1</sup> we recently examined the tributyltin hydride-mediated cyclization of *N*-(*o*-bromobenzoyl)-2-(prop-2-enyl)-2-vinylpyrrolidine (**1**) in the hope that a route to **5** or **6** might result. In fact, this particular mode of cyclization was not observed but the 7-azabicyclo[2.2.1]heptane (**3**) (41% as a mixture of *exo* and *endo* isomers in a ratio of 2:1) and the 8-azabicyclo[3.2.1]octane systems (**4**) (16%), along with the reduction product (13%), were obtained. This reaction was



†This paper is dedicated to the memory of Professor Emeritus Yoshio Ban of Hokkaido University.

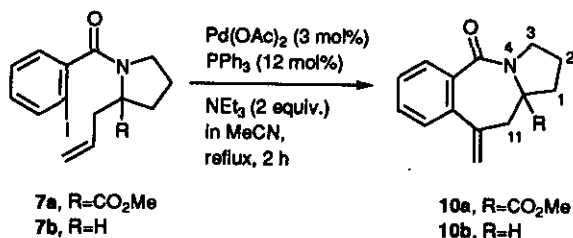
formulated as proceeding *via* the  $\alpha$ -acylamino radical intermediate (**2**) formed by a 1,5-translocation reaction of the initially formed aryl radical.<sup>2,3</sup> We were then led to examine a palladium-catalyzed cyclization (intramolecular Heck reaction)<sup>4</sup> of the *N*-(*o*-iodobenzoyl)- and *N*-(*o*-iodophenylacetyl)-pyrrolidine derivatives (**7**).<sup>5</sup> In this paper we report our preliminary studies on this cyclization.

The precursors (**7a,b**) were prepared by essentially the same reaction sequence used for the synthesis of the corresponding *N*-(*o*-bromobenzoyl)pyrrolidine derivatives.<sup>3</sup> The 2-vinyl derivatives (**7c,d**) were obtained from *N*-*tert*-butoxycarbonyl-L-prolinol (**8**) in a straightforward manner as illustrated in Scheme 1.

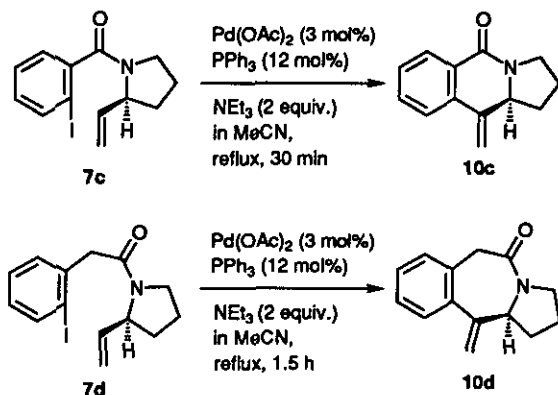


**Scheme 1.** Reagents and conditions: i, (a) DMSO, (COCl)<sub>2</sub>, NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; (b) Ph<sub>3</sub>P<sup>+</sup>Me Br<sup>-</sup>, NaH, DMSO (41%); ii, (a) CF<sub>3</sub>CO<sub>2</sub>H, CH<sub>2</sub>Cl<sub>2</sub>; (b) *o*-iodobenzoyl chloride, NEt<sub>3</sub>, DMAP, CH<sub>2</sub>Cl<sub>2</sub> (quant.); iii, (a) CF<sub>3</sub>CO<sub>2</sub>H, CH<sub>2</sub>Cl<sub>2</sub>, (b) *o*-iodophenylacetyl chloride, NEt<sub>3</sub>, DMAP, CH<sub>2</sub>Cl<sub>2</sub> (47%)

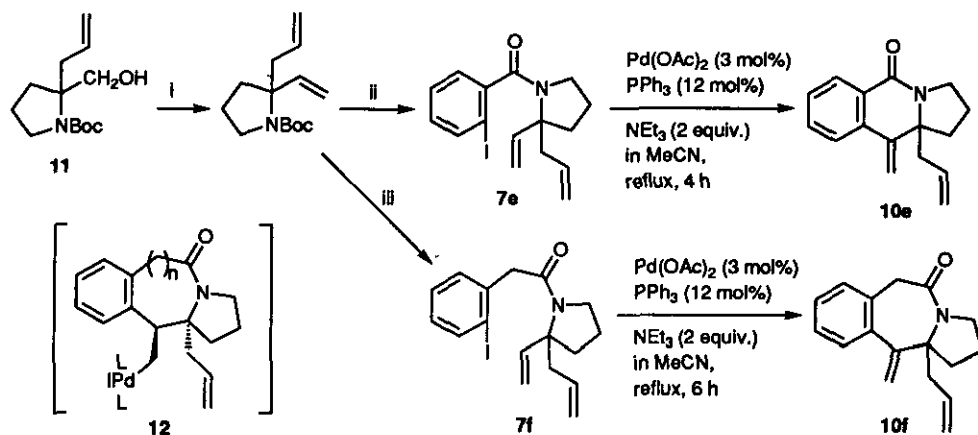
When **7a** was treated with palladium(II) acetate (3 mol%), triphenylphosphine (12 mol%), and triethylamine (2 equiv.) in boiling acetonitrile under an argon atmosphere for 2 h, the hexahydro-1*H*-pyrrolo[1,2-*b*][2]-benzazepin-5-one (**10a**), mp 92-93 °C, was obtained in 94% yield. The structure of **10a** was derived from the spectroscopic evidence [ir (CHCl<sub>3</sub>): 1740, 1640 cm<sup>-1</sup>; <sup>1</sup>H-nmr (CDCl<sub>3</sub>, 270 MHz)  $\delta$ : 2.92 (1H, d, *J*=15.8 Hz, one of 11-H), 3.24 (3H, s, OMe), 3.84 (1H, dt, *J*=15.8 and 2.6 Hz, one of 11-H), 5.03-5.09 and 5.17-5.21 (1H each, br, vinylic protons)]. Similarly, **7b** gave the corresponding tricyclic heterocycle (**10b**) as an oil in 97% yield.<sup>6</sup>



The same type of reaction was also observed with the 2-vinylpyrrolidines (**7c,d**), which afforded the hexahydropyrrolo[1,2-*b*]isoquinolin-5-one (**10c**), mp 158-159 °C, and the hexahydro-1*H*-pyrrolo[2,1-*b*][3]benzazepin-5-one (**10d**), an oil, in 67 and 25% yields, respectively.



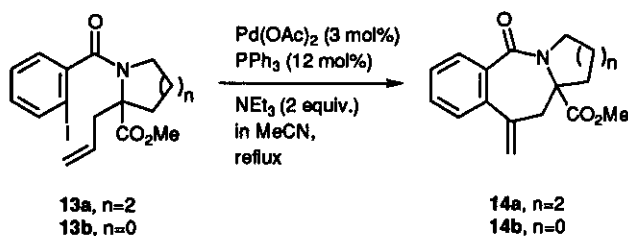
Based on these results, we have then investigated the possibility of a tandem cyclization of the 2-(prop-2-enyl)-2-vinylpyrrolidine derivatives (**7e,f**), which were prepared from the alcohol (**11**)<sup>1c</sup> in four steps as shown in Scheme 2. The Heck reaction of **7e,f** using  $\text{Pd}(\text{PPh}_3)_4/\text{NEt}_3$  gave only the monocyclization products (**10e**) and (**10f**) in 75 and 21% yields, respectively. Even under the reaction conditions in the presence of hydride ion source such as sodium formate, essentially the same results were obtained. A possible explanation for the failure of the double cyclization is that the intermediate (**12**) formed after the first cyclization might have a *trans*-diaxial stereochemical relationship between the Pd moiety and propenyl group, which is unsuitable for the second cyclization.



**Scheme 2.** Reagents and conditions: i, (a) DMSO,  $(\text{COCl})_2$ ,  $\text{NEt}_3$ ,  $\text{CH}_2\text{Cl}_2$ , (b)  $\text{Ph}_3\text{P}^+\text{Me Br}$ ,  $\text{NaH}$ , DMSO (88%); ii, (a)  $\text{CF}_3\text{CO}_2\text{H}$ ,  $\text{CH}_2\text{Cl}_2$ ; (b) *o*-iodobenzoyl chloride,  $\text{NEt}_3$ , DMAP,  $\text{CH}_2\text{Cl}_2$  (65%); iii, (a)  $\text{CF}_3\text{CO}_2\text{H}$ ,  $\text{CH}_2\text{Cl}_2$ , (b) *o*-iodophenylacetyl chloride,  $\text{NEt}_3$ , DMAP,  $\text{CH}_2\text{Cl}_2$  (91%)

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- The bromo analog of **7a** also gave the same product (**10a**) but the cyclization reaction was very slow.
- The Heck reaction of the piperidine (**13a**) and azetidine derivatives (**13b**), which were synthesized by alkylation of methyl *N*-(*o*-iodobenzoyl)piperidine-2-carboxylate and its azetidine congener with prop-2-enyl bromide, gave the octahydropyrido[1,2-*b*][2]benzazepin-6-one (**14a**), mp 54.5 °C, and the hexahydroazeto[1,2-*b*][2]benzazepin-4-one (**14b**), mp 119-120 °C, in 84 and 93% yields, respectively.



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