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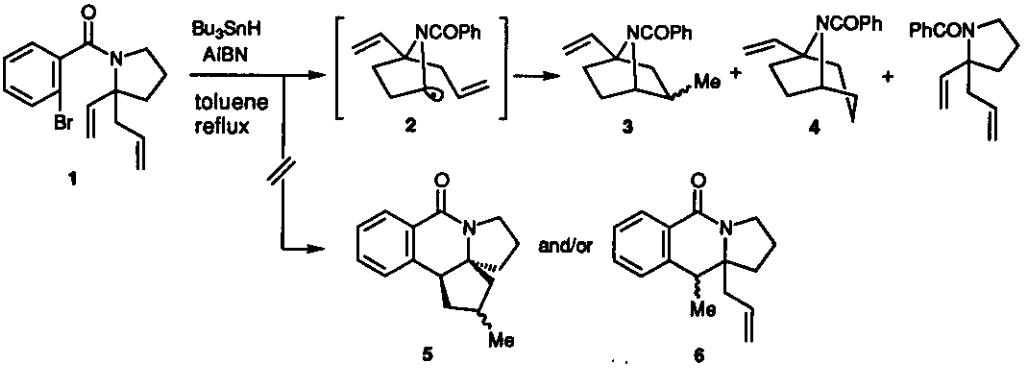
Abstract—The palladium-catalyzed cyclization of the 2-alkenyl-*N*-(*o*-iodobenzoyl)- and 2-alkenyl-*N*-(*o*-iodophenylacetyl)pyrrolidines gave the tricyclic nitrogen-containing heterocycles.

As part of our continuing studies towards the synthesis of optically active cephalotaxine,[1] 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



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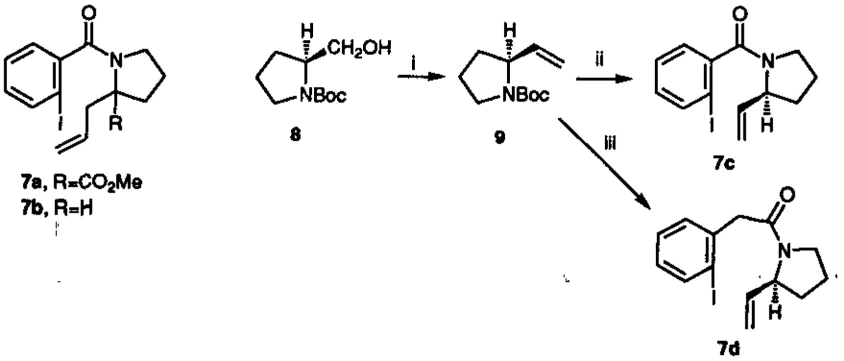
†This paper is dedicated to the memory of Professor Emeritus Yoshio Ban of Hokkaido University.

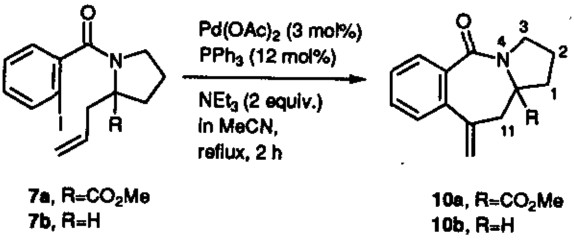
formulated as proceeding *via* the α-acylamino radical intermediate (**2**) formed by a 1,5-translocation reaction of the initially formed aryl radical.[2,3] We were then led to examine a palladium-catalyzed cyclization (intramolecular Heck reaction)[4] of the *N*-(*o*-iodobenzoyl)- and *N*-(*o*-iodophenylacetyl)-pyrrolidine derivatives (**7**).[5] 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.[3] The 2-vinyl derivatives (**7c,d**) were obtained from *N*-*tert*-butoxycarbonyl-L-prolinol (**8**) in a straightforward manner as illustrated in Scheme 1.

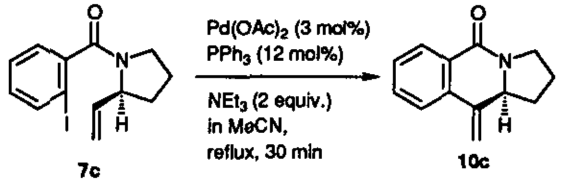


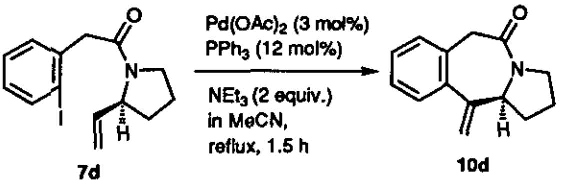
Scheme 1. *Reagents and conditions*: i, (a) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2; (b) $Ph_3P^+Me\ Br^-$, NaH, DMSO (41%); ii, (a) CF_3CO_2H, CH_2Cl_2; (b) *o*-iodobenzoyl chloride, NEt_3, DMAP, CH_2Cl_2 (quant.); iii, (a) CF_3CO_2H, CH_2Cl_2, (b) *o*-iodophenylacetyl chloride, NEt_3, DMAP, CH_2Cl_2 (47%)

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 (CHCl3): 1740, 1640 cm^{-1}; ^1H-nmr ($CDCl_3$, 270 MHz) δ: 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 tricylic heterocycle (**10b**) as an oil in 97% yield.[6]

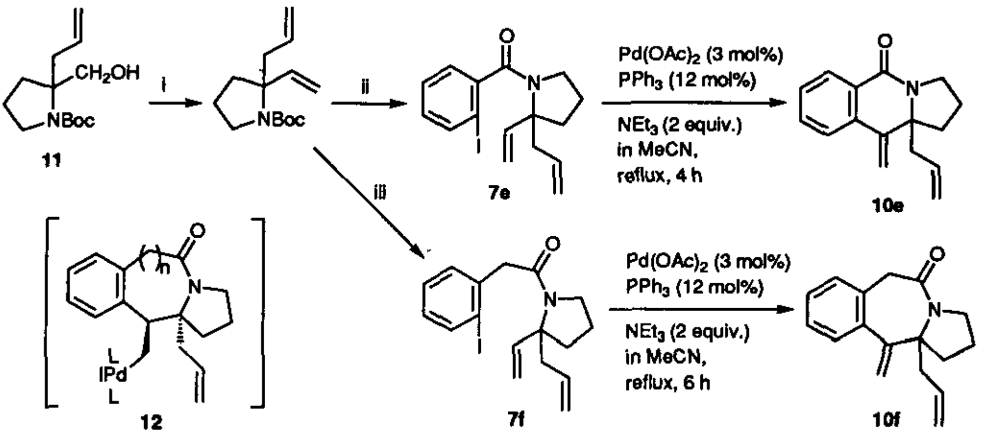


The same type of reaction was also observed with the 2-vinylpyrrolidines (**7c,d**), which afforded the hexahydropyrrolo[1,2-*b*]isoquinolin-5-one (**10c**), mp 158-159 °C, and the hexahydro-1*H*-pyrrolo[2,1-*b*][3]benzazepin-5-one (**10d**), an oil, in 67 and 25% yields, respectively.





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**)[1c] in four steps as shown in Scheme 2. The Heck reaction of **7e,f** using Pd(PPh$_3$)$_4$/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, (COCl)$_2$, NEt$_3$, CH$_2$Cl$_2$, (b) Ph$_3$P$^+$Me Br$^-$, NaH, DMSO (88%); ii, (a) CF$_3$CO$_2$H, CH$_2$Cl$_2$; (b) *o*-iodobenzoyl chloride, NEt$_3$, DMAP, CH$_2$Cl$_2$ (65%); iii, (a) CF$_3$CO$_2$H, CH$_2$Cl$_2$, (b) *o*-iodophenylacetyl chloride, NEt$_3$, DMAP, CH$_2$Cl$_2$ (91%)

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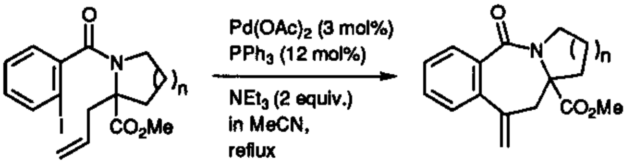
5. The bromo analog of **7a** also gave the same product (**10a**) but the cyclization reaction was very slow.
6. The Heck reaction of the piperidine (**13a**) and azetidine derivatives (**13b**), which were synthesized by alkylation of methyl *N*-(*o*-iodobenzoyl)piperidine-2-carboxylate and its azetidine 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.



13a, n=2
13b, n=0

14a, n=2
14b, n=0

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