Nucleophilic Allylation-Heterocyclization *via* Bis-π-allylpalladium Complexes: Synthesis of Five- and Six-Membered Heterocycles

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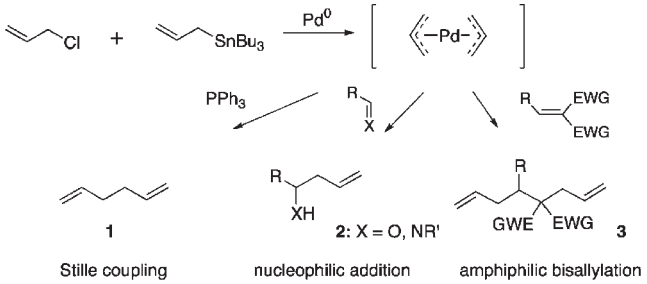
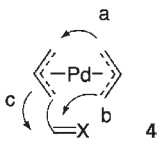
The reaction of the allylic halides **5**–**9** having an aldehyde or an imine moiety in the molecule with allyltributylstannane proceeded smoothly in the presence of Pd_2•dba_3•$CHCl_3$ (5 mol%) in DMF or THF, giving the corresponding heterocycles **10**–**14** in good to high yields. The Stille coupling product was not obtained under these reaction conditions.

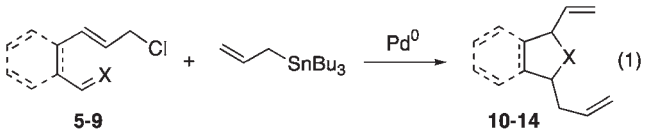
Bis-π-allylpalladium complexes are known as an intermediate in Stille coupling reaction between allylic halides and allylic stannanes and reductive coupling of these two π-allyl groups on palladium affords hexadiene derivatives **1** (Scheme 1).[1] In the meantime, bis-π-allylpalladium complexes react with electrophiles such as aldehydes and imines to give the corresponding homoallyl alcohols and amines **2**,[2] or react with Michael acceptors in an amphiphilic bisallylation manner to give the octadiens **3**.[3,4] Ligands on the palladium such as triphenylphosphine[5a,b] and maleic anhydride[5c,d] have an important role for the coupling reaction.[5] The mere presence or absence of triphenylphosphine suffices to control bis-π-allylpalladium complexes in the presence of aldehydes (or imines).[6] In the absence of triphenylphosphine, bis-π-allylpalladium complexes react with aldehydes or imines chemoselectively, even in the presence of allylic chlorides, whereas in the presence of triphenylphosphine the Stille coupling reaction takes place chemoselectively, even in the presence of aldehydes or imines. Our interest in the reaction course of the complexes led us to introduce aldehydes and imines into one of allyl groups on the bis-π-allylpalladium as shown in the complex **4**. Three reaction pathways, (a)–(c), would be envisioned from the unsymmetric bis-π-allylpalladium complex **4**: (a) the Stille-type reductive coupling pathway; (b) the intermolecular allylic addition; (c) intramolecular allylic addition.



Scheme 1.



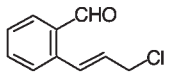
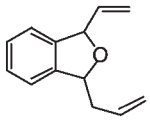
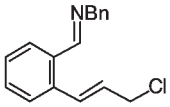
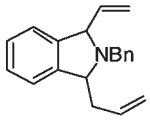
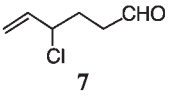
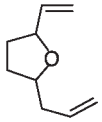
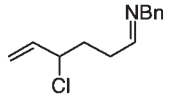
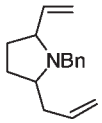
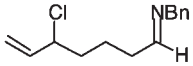
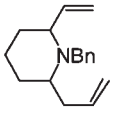
Therefore, we examined the palladium-catalyzed reaction of allyltributylstannane with an aldehyde (or an imine) containing allylic halide in the same molecule and found that the nucleophilic allylation of C = X group (path b) followed by heterocyclization through the coupling reaction between the resulting X^- and the remaining allyl group gives five- and six-membered heterocycles in good to high yields (eq 1).



2-(3-Chloropropenyl)benzaldehyde **5** was synthesized from phthalaldehyde and used for the preliminary experiments. The reaction of **5** with allyltributylstannane was catalyzed by Pd_2•dba_3•$CHCl_3$ (5 mol%) in THF at room temperature to give 1-[2-(3-chloropropenyl)phenyl]but-3-en-1-ol in 88% yield in the absence of triphenylphosphine (path b), or 2-hexa-1,5-dienylbenzaldehyde in 70% yield with a small amount of regioisomer (3%) in the presence of triphenylphosphine (path a).[6] However, the heterocyclization took place, when the reaction was carried out in DMF at 50 °C in the absence of triphenylphosphine, to afford 1-allyl-3-vinyl-1,3-dihydroisobenzofuran **10** in 88% yield with a 60/40 ratio of *cis*- and *trans* isomers (eq 1 and entry 1 in Table 1). The reaction of the imine **6**, which was derived from benzylamine and **5**, with allyltributylstannane was also catalyzed by Pd_2•dba_3•$CHCl_3$ (5 mol%) in THF at room temperature to give 1-allyl-2-benzyl-3-vinyl-2,3-dihydro-1*H*-isoindole **11** in 56% yield with a 61/39 ratio of *cis*- and *trans* isomers (entry 2). Although longer reaction time (140 h) was needed at room temperature, the reaction was completed for 46 h at 50 °C (entry 3). Next, the linear substrates were examined. 4-chloro-5-hexenal **7** underwent the heterocyclization in DMF to give 2-allyl-5-vinyltetrahydrofuran **12** in 64% yield[7] with a 58/42 ratio of *cis*- and *trans* isomers (entry 4). The reaction of the imine **8** derived from **7** also proceeded very smoothly even at 0 °C in THF to give 2-allyl-1-benzyl-5-vinylpyrrolidine **13** in 50% yield (entry 5). The *trans* isomer was obtained as a major product (*cis/trans* = 40/60). The yield and the diasteroselectivity of **13** were increased when the reaction was carried out in DMF, and thus, **13** was obtained in 67% yield with a 25/75 ratio of *cis*- and *trans* isomers (entry 6). Benzyl-(5-chloro-hept-6-enylidene)amine **9** underwent the nucleophilic allylation followed by the heterocyclization in DMF at 0 °C to afford 2-allyl-1-benzyl-6-vinylpiperidine **14** in 67% yield with higher diastereoselectivity (*cis/trans* = 20/80, entry 7). In all cases, the stereochemistry of the cyclic products was determined by NOE experiments.[8]

A plausible mechanism which accounts for this chemoselective bis-π-allylpalladium reaction is shown in Scheme 2. Oxidative addition of palladium(0) to **5** would give the π-

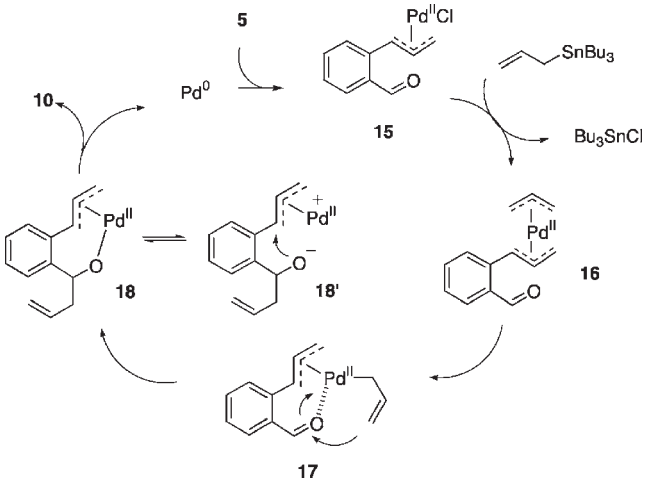
Table 1. Heterocyclization of allyltributylstannane with allylic halides catalyzed by palladium(0)[a]

Entry	Allylic halide	Solv. / Temp. / Time	Product	Yield/% (*cis* / *tans*) [b]
1	 **5**	DMF / 50 °C 18 h	 **10**	88 (60/40)
2	 **6**	THF / rt 140 h	 **11**	56 (61/39)
3	**6**	THF / 50 °C 46 h	**11**	63 (73/27)
4	 **7**	DMF / 50 °C 24 h	 **12**	64 (58/42)
5	 **8**	THF / 0 °C 83 h	 **13**	50 (40/60)
6	**8**	DMF / 0 °C 63 h	**13**	67 (25/75)
7	 **9**	DMF / 0 °C 45 h	 **14**	67 (20/80)

[a]All reactions were carried out in the presence of Pd_2dba_3•$CHCl_3$ (5 mol%). [b]Isolated yield based on the parent allylic halide. The ratio of *cis*- and *trans* isomers was indicated in parentheses.

allylpalladium chloride complex **15** and then transmetalation of **15** with allyltributylstannane would give the bis-π-allylpalladium complex **16**. An aldehyde group in the complex **16** would coordinate to the palladium in an intramolecular manner to form the π-allyl-σ-allylpalladium **17** in which the σ-allyl group on the palladium is transferred to give **18**. There could be an equilibrium between **18** and **18'**. The *anti* attack of the alkoxy anion to the π-allyl group on the palladium **18'** would afford **10** and palladium(0) would be regenerated. This step might be accelerated in polar solvents such as DMF since the ionic intermediate **18'** is formed prior to **18** in those solvents.

The representative procedure is indicated as follows. To a solution of Pd_2•dba_3•$CHCl_3$ (26 mg, 0.025 mmol) in DMF (3 mL) were added **5** (90 mg, 0.5 mmol) and allyltributylstannane (166 mg, 0.5 mmol) at room temperature under argon atmosphere, and then the mixture was stirred at 50 °C for 18 h. The reaction was quenched with water and the mixture was extracted with ether. The organic layer was washed with a saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$ and then concentrated. Purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **10** in 88% yield. The ratio of



Scheme 2.

cis- and *trans* isomers was determined by ^{1}HNMR. The separation of the *cis*– and *trans* isomers was carried out by HPLC using LiChrosorb® Si 60 (7 μm) column (hexane/ethyl acetate = 100/1, flow rate = 5 mL/min): t_R = 10.6 min (*trans* isomer), t_R = 11.6 min (*cis* isomer).

In conclusion, not only ligands but also solvents exert an important influence on the reaction course of bis-π-allylpalladium complexes. The nucleophilic allylation followed by heterocyclization can be conducted in one shot by a proper choice of solvents, providing a convenient procedure for the synthesis of five- and six-membered cyclic ethers and amines.

This paper is dedicated to Prof. Teruaki Mukaiyama on the occasion of his 75th birthday.

References and Notes

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4 Recently, the theoretical study for the reactivity of bis-π-allylpalladium complexes was reported: K. J. Szabo, *Chem. Eur. J.*, **6**, 4413 (2000).
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6 H. Nakamura, M. Bao, and Y. Yamamoto, *Angew. Chem., Int. Ed.*, **40**, 3208 (2001).
7 The NMR yield was 76%.
8 For example, the stereochemistry of *cis*-**10** and *trans*-**10** was determined as follows: NOEs were observed between H^a and H^b in *cis*-**10** and between H^a and H^c in *trans*-**10**, respectively.