## PALLADIUM-CATALYZED CROSS-COUPLING REACTION: DIRECT ALLYLATION OF ARYL BROMIDES WITH ALLYL ACETATE

Yuusaku Yokoyama, Sadao Ito, Yumi Takahashi, and Yasuoki Murakami\*

School of Pharmaceutical Science, Toho University 2-2-1, Miyama, Funabashi, Chiba 274, Japan

Abstract: Various aryl bromides underwent a palladium-catalyzed cross-coupling reaction with allyl acetate in the presence of hexa-n-butylditin to give the allylated products in very high yields.

The palladium-catalyzed cross-coupling reaction of an organotin reagent with an organic halide or its equivalent has been extensively studied<sup>1,2)</sup> in recent years. Although it takes place under mild condition and tolerates a wide variety of functional groups, there are some limitations for synthesizing various organic frameworks, since the organometallic partner cannot conveniently be synthesized in some cases. On the other hand, there are only a few methods<sup>3)</sup> for the direct cross-coupling reaction which does not involve an organometallic reagent as a coupling partner.

Previously we reported<sup>4)</sup> the regioselective vinylation at the C<sub>3</sub>-position of indole nucleus using palladium. In this communication, we describe that ethyl N-tosyl-3-bromoindole-2-carboxylate (<u>1a</u>) was directly coupled with allyl acetate (<u>2</u>) in the presence of hexa-n-butylditin (<u>3</u>) and palladium catalyst to give C<sub>3</sub>-allylated product (<u>4a</u>) in high yield (Scheme 1), and this one-step-allylation was applicable to various aryl bromides.



The typical experimental procedure is as follows. A mixture of bromide  $(\underline{1a}, 1 \text{ mmol})$ , allyl acetate  $(\underline{2}, 1.5 \text{ mmol})$ , ditin  $(\underline{3}, 1.5 \text{ mmol})$ , and palladium catalyst  $(\underline{9}, 0.1 \text{ mmol})$  in DMF (1 ml) was heated at  $120^{\circ}$ C for 1.0 hr. The resulting black solution was worked up and purified by column chromatography on alumina to give the product  $(\underline{4a})$  in 88% yield as a colorless solid. The results are summarized in Table I. The use of palladium catalysts coordinated by bidentate ligands such as  $\underline{9}, \underline{10}$ , and  $\underline{11}$  gave the product  $(\underline{4a})$  in very high yields (runs 1, 2, and 3),  $5^{\circ}$  but the use of monodentate phosphine palladium  $(\underline{12})$  was less effective (run 4). The N-unprotected indole (1b) and 5-bromo-

		<b>N</b> .	$Bu_3SnSnBu_3$ ( <u>3</u> )			
Ar-Br + <u>5</u> Table I		$\frac{2}{2}$ OAc -	Palladium Catalyst DMF, 120 <sup>°</sup> C	$\rightarrow$ Ar $\underline{\underline{6}}$		
Run	Ar-Br	Palladium	Reaction <sup>a)</sup>	$Product(\underline{6})^{d}$		
		Catalyst	Time (hr)	Yield(%)	mp( <sup>O</sup> C)	
1	<u>1a</u>	9	1.0	88	68.5-71.5	
2	<u>1a</u>	<u>10</u>	1.5	84	-	
3	<u>1a</u>	<u>11</u>	1.0	81		
4	<u>1a</u>	<u>12</u>	2.0	47		
5	<u>1b</u>	9	0.5 <sup>b</sup> )	49	85-87	
6	<u>7</u>	9	4.5 <sup>b)</sup>	59	oil	
7	<u>8a</u>	9	0.5 <sup>b)</sup>	86	137-139	
8	8b	9	0.5 <sup>c)</sup>	86	oil	
9	8c	9	0.5	69	89-92	

a) Ar-Br: Allyl acetate :  $Bu_3SnSnBu_3$ : Catalyst = 1 : 1.5 : 1.5 : 0.1 b) Ar-Br : Allyl acatate :  $Bu_3SnSnBu_3$ : Catalyst = 1 : 2 : 3 : 0.1 c) Toluene was used as a solvent at reflux temperature. d) All new compounds were satisfactorily identified by spectral data and elemental analyses.



indole derivative  $(\underline{7})$  also gave the allylated products  $(\underline{6})$  in moderate yields (runs 5 and 6). Furthermore this reaction could be applied to the bromobenzene derivatives  $(\underline{8a-c})$  with electron-withdrawing or electron-donating groups (runs 7, 8, and 9).

Two possible pathways for this reaction are considered as shown in Scheme 2. The aryl- $\pi$ -allyl palladium complex (<u>17</u>), which would give the allylated products (<u>6</u>) by the reductive elimination, may be produced by two routes; i.e. i) transmetallation of aryl-palladium complex (<u>13</u>) with allyltin (<u>16</u>) which would be produced from  $\pi$ -allyl-palladium acetate (<u>15</u>) and ditin (<u>3</u>) (Path A), and ii) transmetallation of <u>15</u> with aryltin (<u>14</u>) which would be produced from  $\sigma$ -complex (<u>13</u>) and ditin (<u>3</u>) (path B). Both reaction pathways seem to be equally possible, because C<sub>3</sub>-stannylated indole derivative (<u>18</u>) and allyltin (<u>16</u>), both of which would be considered as possible intermediates in the allylation of the 3-bromoindole (<u>1a</u>), could be obtained by the reactions of allyl acetate (<u>2</u>) and 3-bromoindole (<u>1a</u>) with ditin (<u>3</u>), respectively (Scheme 3). However, it is interesting that the total yields of these two-step-synthesis (Scheme 3) were much lower than those of the one-step-synthesis (Table I, run 1).





Although palladium-catalyzed allylation using allyltin  $(\underline{16})^{2a}$  or aryltin  $(\underline{14})^{2d}$  has been already reported, there is no literature concerning the direct allylation like our present work. Consequently we believe that this reaction could be classified as a new type of cross-coupling reaction and provide a new methodology for carbon-carbon bond formation. Further investigation for the mechanistic detail and application of this direct cross-coupling are now in progress.

## References and Notes

This paper forms Part XIII of "Synthetic Studies on Indoles and Related Compounds"

- a) M. Kosugi, Y. Shimizu, and T. Migita, Chem. Lett., 1423 (1977). b) D. Milstein and J. K. Stille, J. Amer. Chem. Soc., <u>100</u>, 3636 (1978). c) M. W. Logue and K. Teng, J. Org. Chem., <u>47</u>, 2549 (1982). d) K. Kikukawa, K. Kono, F. Wada, and T. Matsuda, J. Org. Chem., <u>48</u>, 1333 (1983). e) E. Keinan and M. Peretz, J. Org. Chem. <u>48</u>, 5302 (1983). f) W. F. Goure, M. E. Wright, P. D. Davis, S. S. Labadie, and J. K. Stille, J. Amer. Chem. Soc., 106, 6417 (1984).
- 2) a) M. Kosugi, K. Sasazawa, Y. Shimizu, and T. Migita, Chem. Lett., 301 (1977). b) B. M. Trost and E. Keinan, Tetrahedron Lett., <u>21</u>, 2595 (1980).
  c) J. P. Godschalx and J. K. Stille, Tetrahedron Lett., <u>21</u>, 2599 (1980).
  d) F. K. Sheffy, J. P. Godschalx, and J. K. Stille, J. Amer. Chem. Soc., 106, 4833 (1984).
- 3) For example, copper-promoted Ullmann reaction is known to be slow and often results in extensive homo-coupling. W. Carruthers, In "Comprehensive Organometallic Chemistry"; G. Wilkinson, et al., Ed.; Pergaman Press: New York, 1982; Vol. 7, p 661.
- 4) Y. Murakami, Y. Yokoyama, and T. Aoki, Heterocycles, <u>22</u>, 1493(1984).
- 5) It has been reported that <u>9</u> is the most effective catalyst among these palladium complexes. T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, and K. Hirotsu, J. Amer. Chem. Soc., <u>106</u>, 158 (1984).

(Received in Japan 12 October 1985)