AN INTERESTING CHEMOSELECTIVITY IN PALLADATION OF AROMATIC BROMIDES[1]

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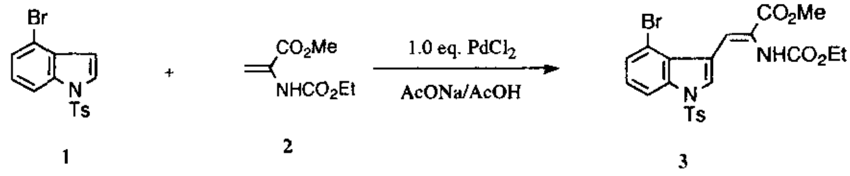
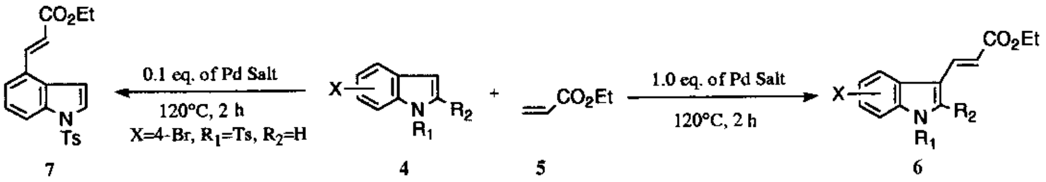
Abstract —— The reaction of various aromatic bromides with ethyl acrylate in the presence of stoichiometric amount of $Pd(OAc)_2$ gave the vinylated products without affecting the carbon-bromine bond.

In the course of our studies of direct introduction of carbon side chain at C_3-position of indole nucleus,[2] we found one-step synthesis of 4-bromodehydrotryptophan (**3**) by the vinylation of 4-bromoindole (**1**) in the presence of stoichiometric amount of palladium salt[3] (Scheme 1). The selective formation of 4-bromodehydrotryptophan (**3**) without affecting the carbon-bromine bond is synthetically useful, because bromine atom on aromatic ring might be easily converted to functionalized carbon side chain by organo-transition metal catalyst. Such a chemoselective vinylation of aromatic bromides has never been reported. In the present report, we describe the vinylation of various aromatic bromides with ethyl acrylate under the stoichiometric condition in order to find the factors for this chemoselectivity.

Table I shows the results of the reaction of various bromoindoles with ethyl acrylate using palladium salt. The vinylation of 4-bromoindole (**4a**) in the presence of 1.0 eq. of $Pd(OAc)_2$ gave the C_3-vinylated product

Scheme 1





a : X=4-Br, R_1=Ts, R_2=H
b : X=5-Br, R_1=Ts, R_2=H
c : X=7-Br, R_1=H, R_2=CO_2Et
d : X=7-OTf, R_1=H, R_2=CO_2Et

Scheme 2

Table I Vinylation of **4** with ethyl acrylate (**5**).$^{a)}$

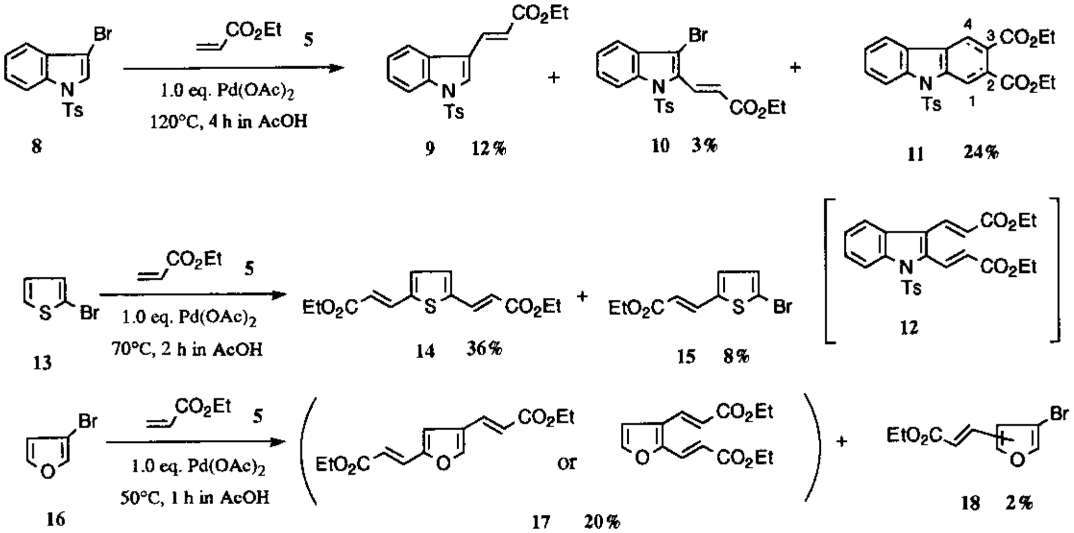
Run	indole (**4**)	Pd salt (eq.)	solvent	product (%) **6**	product (%) **7**	SM recov. (%)
1	**4a**	$Pd(OAc)_2$ (1.0)	AcOH	55	-	38
2	**4a**	$Pd(OAc)_2$ (1.0)	AcOH-Et_3N	-	trace	-$^{c)}$
3	**4a**	$PdCl_2(PPh_3)_2$ (1.0)$^{b)}$	AcOH	-	9	88$^{d)}$
4	**4a**	$PdCl_2(PPh_3)_2$ (0.1)	AcOH-Et_3N	-	82	-
5	**4b**	$Pd(OAc)_2$ (1.0)	AcOH	49	-	39
6	**4c**	$PdCl_2$ (1.0)$^{b)}$	AcOH$^{e)}$	55	-	31
7	**4d**	$Pd(OAc)_2$ (1.0)	AcOH$^{e)}$	79	-	17

a) 2.0 eq. of **5** was used. b) 4.0 eq. of AcONa was added. c) Debrominated product (**4e**, X=H, R_1=Ts, R_2=H) was obtained in 78% yield. d) A trace amount of debrominated product (**4e**) was contaminated. e) Reaction temperature: 100 °C.

selectively (Run 1), whereas only C_4-vinylated product (**7**) was obtained when the catalytic amount of $PdCl_2(PPh_3)_2$ was used in AcOH-Et_3N (Run 4). Those selectivities were in striking contrast, so some control experiments were accomplished to find the factors for those selectivities. The addition of Et_3N or exchange of the palladium salt from $Pd(OAc)_2$ to $PdCl_2(PPh_3)_2$ completely suppressed the formation of **6** and gave only little amount of the C_4-vinylated product (**7**) (Runs 2 and 3). From those results, it was clear that the Et_3N and PPh_3 played an important role for this chemoselectivity. Et_3N might reduce Pd(II) to Pd(0);[4] therefore, the addition of Et_3N suppressed the palladation by Pd(II) at the C_3-position of the indole (**4**), while Et_3N was required for the catalytic vinylation. The co-ordination of PPh_3 to Pd (II) might decrease its electrophilicity, and also Pd (0) was precipitated as Pd-black without the co-ordination of PPh_3; therefore, PPh_3 would suppress the nucleophilic attack of Pd (II) at the C_3-position, and Pd(0) could not attack at the C_4-position of **4a**.[5]

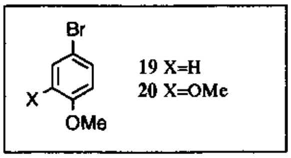
The vinylation of 5-bromo-1-tosylindole (**4b**) and ethyl 7-bromo- (**4c**) or 7-trifluoromethanesulfonyloxy(OTf)-indole-2-carboxylate (**4d**) gave C_3-vinylated products (**6b-d**) in moderate to good yields under the same stoichiometric condition as shown in runs 5, 6, and 7 of Table I. However, the same reaction of 3-

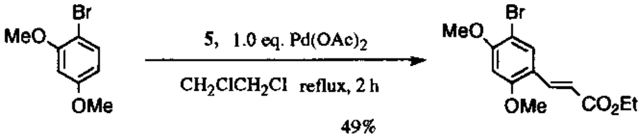
Scheme 3



bromoindole (**8**) gave two monovinylated indoles (**9** and **10**) and dihydrocarbazole derivative (**11**)[6] which should be derived from 2,3-divinyl product (**12**) by electrocyclic reaction. The non-chemoselective vinylation also occurred on 2-bromothiophene (**13**) and 3-bromofuran (**16**); divinyl products (**14** and **17**) were mainly obtained in 36 and 20% yields respectively, accompanied with small amount of expected monovinyl product (**15** and **18**)[7] (Scheme 3). Those results showed that the chemoselectivity was lost when the bromine atom was attached at electron-rich position in heteroaromatic ring.

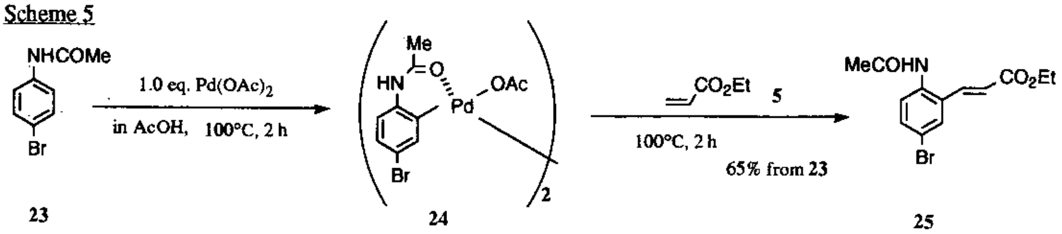
The vinylation of 4-bromoanisole (**19**) or 3,4-dimethoxybromobenzene (**20**) under the stoichiometric condition did not give the product at all to recover the starting material, but 2,4-dimethoxybromobenzene (**21**) selectively gave the C_5-vinylated product (**22**)[8] as shown in Scheme 4. Since acetanilide was known[9] to form a stable *ortho*-palladated σ-complex through coordination of Pd(II) to acetamide group, the vinylation of *p*-bromoacetanilide (**23**) was attempted. When the reaction was carried out by the stepwise manner in one-pot in order to prepare the *ortho*-palladated intermediate (**24**) *in situ*, the vinylation proceeded smoothly to give the product (**25**) vinylated regioselectively at *ortho* position (scheme 5).





21 Scheme 4 **22**

Scheme 5



We believe that the present investigation provides a useful regioselective synthetic method of polysubstituted aromatic compounds. We are now trying to apply the present reaction to the total synthesis of indole alkaloids.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. This paper is the XXXII of Synthetic Studies of Indoles and Related Compounds. Part XXXI: T. Watanabe, C. Miyagi, and Y. Murakami, *J. Heterocycl. Chem.,* 1993, **30**, 317.

2. a)Y. Murakami, Y. Yokoyama, and T. Aoki, *Heterocycles*, 1984, **22**, 1493. b) Y. Yokoyama, S. Ito, Y. Takahashi, and Y. Murakami, *Tetrahedron Lett.*, 1985, **23**, 6457. c) Y. Yokoyama, M. Ikeda, M. Saito, T. Yoda, H. Suzuki, and Y. Murakami, *Heterocycles*, 1990, **31**, 1505. d) Y. Yokoyama, H. Suzuki, S. Matsumoto, S. Sunaga, M. Tani, and Y. Murakami, *Chem. Pharm. Bull.*, 1991, **39**, 2830.

3. Y. Yokoyama, M. Takahashi, Y. Kohno, K. Kataoka, Y. Fujikawa, and Y. Murakami, *Heterocycles*, 1990, **31**, 803.

4. When the brown mixture of $Pd(OAc)_2$ and Et_3N in DMF was heated at 120 °C, the mixture was turned to black within 5 min by the precipitation of Pd-metal. *cf.* M. E. Kuehne and T. C. Hall, *J. Org. Chem.*, **1976**, 2742.

5. It is known that the palladium-catalyzed vinylation of aromatic bromide does not occur without PPh_3. R. F. Heck, "Organic Reactions," Vol. 27, John Wiley and Sons, Inc., New York, 1982, pp. 345-390.

6. The position of double bond (1, 2- or 3, 4-position) could not be determined from nmr spectrum.

7. It has been reported that the vinylation of thiophene or furan itself gave the mixture of 2-monovinyl and 2,5-divinyl products in the presence of stoichiometric amount of $Pd(OAc)_2$. Y. Fujiwara, O. Maruyama, M. Yoshidomi, and H. Taniguchi, *J. Org. Chem.,* 1981, **46**, 851.

8. The reactivity for palladation by Pd(II) is known to increased with the increase of electron density of aromatic ring. Y. Fujiwara, R. Asano, I. Moritani, and S. Teranishi, *J. Org. Chem.,* 1976, **41**, 1681.

9. H. Horino and N. Inoue, *J. Org. Chem.,* 1981, **46**, 4416; S. J. Tremont and H. U. Rahman, *J. Am. Chem. Soc.,* 1984, **106**, 5759.

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