Observation of Sequential Electrophilic Substitution of Bromothiophene and Immediate Reductive Elimination of Arylpalladium Complexes

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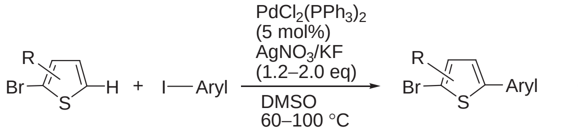
(Received July 10, 2006; CL-060777; E-mail: amori@kobe-u.ac.jp)

The reaction of aryl(iodo)palladium(II)(bpy) complex with 2,3-dibromothiophene in the presence of $AgNO_3/KF$ as an activator induces CH arylation in 64–78% yields. These results suggest that palladium-catalyzed CH arylation of bromothiophene derivatives proceeds through the electrophilic substitution of aryl(iodo)palladium(II) complex triggered by $AgNO_3/KF$ to form the aryl(thienyl)palladium(II) complex, which readily undergoes reductive elimination to give the CH arylation product.

Transition metal-catalyzed reactions at the CH bond of organic molecules attract considerable attention due to the great advantage in atom economy compared with the corresponding coupling reaction with organometallic reagents.[1] In particular, such a CH substitution reaction of a heteroaromatic compound is of much interest[2] since heteroaromatic molecules with certain substituents are found in a wide range of advanced organic materials as well as biologically active compounds.[3] In order to develop further practical and efficient catalytic reaction, the mechanistic aspect becomes quite important. We have been studying palladium-catalyzed cross-coupling and homocoupling reactions of thiazole and thiophene derivatives.[4] Especially, the reactions of a 2-bromothiophene derivative **1** induce cross coupling with aryl iodide **2** to produce arylthiophene **3** (eq 1) and homocoupling at the carbon–hydrogen bond while the carbon–bromine bond is completely intact even in the presence of a palladium complex.[5] We have also shown that certain additives such as silver(I) compounds play a significant role for the smooth reaction. Accordingly, our interest has been centered to the understanding of the reaction mechanism of the CH substitution reaction. We herein describe studies on the palladium-catalyzed CH substitution reaction of bromothiophene derivatives using a stoichiometric amount of organopalladium complexes bearing 2,2′-bipyridine (bpy) ligand[6] **4** in the presence of silver(I) nitrate/KF, which is shown to be an efficient activator for the CH substitution reaction.

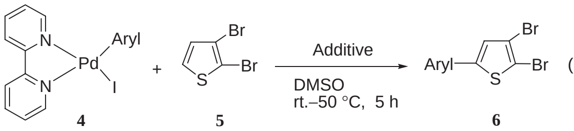


(1)

1 (1.2 eq) **2** (1.0 eq) **3**

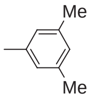
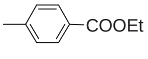
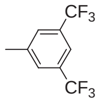
The reaction was carried out with arylpalladium(II) iodide **4** and 2.4 equivalents of 2,3-dibromothiophene **5** in DMSO for 5 h (eq 2).[5b,7] The results are summarized in Table 1. Treatment of palladium complex **4a** (Aryl = C_6H_3-3,5-Me_2)[8] and **5** with $AgNO_3/KF$ at 50 °C gave the corresponding coupling product **6a** in 71% yield, while no reaction was found to occur in the absence of $AgNO_3/KF$. The reaction with either $AgNO_3$ or KF also gave no coupling product **6a**. It should be pointed out that the reaction took place at room temperature although the yield was slightly inferior. The reaction with other palladium complexes like **4b** (Aryl = C_6H_4-4-COOEt) and **4c** (Aryl = C_6H_3-3,5-$(CF_3)_2$) with **5** in the presence of $AgNO_3/KF$ similarly proceeded to give **6b** and **6c**.

Table 1. The reaction of aryl(iodo)palladium(II)(bpy) complex **4** with 2,3-dibromothiophene **5**[a]



(2)

4 **5** **6**

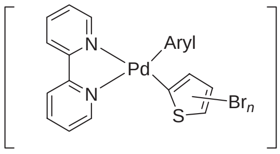
Aryl	Temp/°C	Additive	Product **6**/%
 **4a**	50	$AgNO_3/KF$	71
4a	50	none	0
4a	50	$AgNO_3$	0
4a	50	KF	0
4a	rt.	$AgNO_3/KF$	67
 **4b**	rt.	$AgNO_3/KF$	66
4b	50	$AgNO_3/KF$	78
 **4c**	rt.	$AgNO_3/KF$	64

[a]The reaction was carried out with aryl(iodo)palladium(II)(bpy) complex **4** (0.05 mmol) and 2,3-dibromothiophene **5** (0.12 mmol) in the presence of additive (0.2 mmol) in DMSO for 5 h.

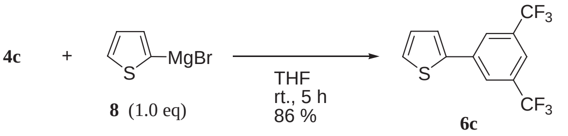
Since the catalytic CH arylation is considered to proceed through an aryl(iodo)palladium(II) complex **4**, the reaction of a palladium complex **4** with **5** would be a part of the catalytic cycle, which is a class of electrophilic substitution of **5** with **4** leading to the aryl(thienyl)palladium(II) complex **7**. The complex would be converted to the product **6** through reductive elimination. The results suggest that the $AgNO_3/KF$ system serves as an effective activator in the electrophilic substitution reaction of the palladium complex **4**, where both $AgNO_3$ and KF are necessary to undergo the reaction. Since a cationic arylpalladium complex has been shown to undergo immediate disproportionation leading to the formation of biaryl,[8] the reaction with $AgNO_3$

would not induce substitution with bromothiophene derivatives smoothly. Although the advantage of the $AgNO_3/KF$ system as an activator has not been clear yet, strong affinity between silver and iodine atoms as well as an effect of fluoride ion would play a key role for the reaction.

Attempted detection of aryl(thienyl)palladium complex **7** was found to be unsuccessful even in the use of electron-deficient palladium complex **4b** (Aryl = C_6H_4-4-COOEt) and **4c** (Aryl = C_6H_3-3,5-$(CF_3)_2$) at room temperature. Immediate reductive elimination of **7** which once formed would occur to produce the arylation product **6**.[9] Indeed, the reaction of the palladium complex **4c** with Grignard reagent **8** also afforded **6c** in 86% yield at room temperature (eq 3). The reaction of aryl(halo)palladium(II) with a Grignard reagent is the well-known transmetalation step of Kumada–Tamao–Corriu coupling[10] that gives **7**. Further reductive elimination leading to **6c** would take place despite the use of 3,5-bis(trifluoromethyl)-phenyl group of **4c** bearing a more electron-deficient substituent that retards reductive elimination. Accordingly, the result suggests that reductive elimination occurs regardless of the use of $AgNO_3/KF$ and that the step has been inevitable in the electrophilic substitution of 2,3-dibromothiophene **5** shown in eq 2.



7



(3)

In summary, we observed that the reaction of arylpalladium iodide **4** with 2,3-dibromothiophene **5** gave the coupling product **6**. These findings suggest that the catalytic reaction involves the sequential reaction pathway of electrophilic substitution-reductive elimination and that $AgNO_3/KF$ is the activator system for the electrophilic substitution of the arylpalladium complex **4** and bromothiophene derivatives.

This work was partially supported by a Grant-in-Aid for Scientific Research on Priority Areas, "Advanced Molecular Transformation of Carbon Resources" by Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and Notes

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6 The CH arylation reaction of 2,3-bromothiophene catalyzed by $PdCl_2(bpy)$ was also shown to proceed similarly to that using $PdCl_2(PPh_3)_2$ as a catalyst.

7 Since the catalytic CH arylation with **5** resulted in highest yield among bromothiophene derivatives employed, the reaction with stoichiometric palladium complex was also studied using **5**.

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