

Palladium-Catalyzed C–H Homocoupling of Thiophenes: Facile Construction of Bithiophene Structure

Kentaro Masui, Haruka Ikegami, and Atsunori Mori*

Chemical Resources Laboratory, Tokyo Institute of Technology, 4259 Nagatsuta, Yokohama 226-8503, Japan

Received December 19, 2003; E-mail: amori@res.titech.ac.jp

Organic molecules bearing heteroaromatic moieties have attracted great attention recently as potential advanced materials.¹ In particular, oligothiophenes have been a major concern of excellent conductivity, electroluminescent behaviors, and characteristics as organic TFT.² A transition metal-catalyzed coupling reaction via condensation of metalated thiophene and/or thienyl halide might be a method of choice for the construction of oligothiophenes,³ however, it would be more straightforward if the carbon–carbon bond formation is achieved directly by functionalization of a C–H bond of heteroaromatics.⁴ Herein, we report that catalytic homocoupling at a C–H bond of thiophene derivatives with a palladium complex takes place in the presence of AgF or AgOCOCH₃ under mild conditions. The well-defined bithiophene unit is constructed via C–H functionalization, which is rather more atom economical than the related coupling with a halogenated or metalated derivative.

We examined the palladium-catalyzed homocoupling of 2-formylthiophene (**1a**) in the presence of several silver reagents and palladium catalysts as summarized in Table 1. The reaction was found to occur with silver(I) fluoride at 60 °C in DMSO to give 69% of 5,5'-diformyl-2,2'-bithiophene (**2a**). The product was identical with the authentic sample, which was synthesized by bromination of **1a** followed by dehalogenative homocoupling in refluxing DMF with a nickel catalyst in overall yield of ca. 30%.^{3b} The reaction with silver(I) acetate similarly effected homocoupling although it took a longer reaction period. The reaction in DMF and CH₃CN proceeded in 22% and 13% yields, respectively, while use of toluene or THF resulted in no reaction. Various palladium catalysts such as PdCl₂, PdCl₂(PhCN)₂, PdCl₂(PPh₃)₂, Pd(OAc)₂, PdCl₂(dppb), Pd₂(dba)₃, and Pd(PPh₃)₄ underwent the reaction, while no reaction was observed without palladium. The reaction in the absence of the silver reagent with catalytic or stoichiometric palladium resulted in no homocoupling. Other silver(I) reagents such as AgOTf, Ag₂CO₃, and Ag₂O were also found to be ineffective. Thus, it is considerably important to apply the combination of a palladium catalyst with a specific silver(I) reagent for the reaction at the C–H bond. In addition, other additives such as Cs₂CO₃, K₂CO₃, NaOCOCH₃, CuCl₂, and Cu(OAc)₂ did not afford **2a** at all. Such a catalytic C–H homocoupling reaction of a heteroaromatic compound involving thiophene has not been shown previously to the best of our knowledge.⁵

To study the mechanism, the reaction was carried out with various amounts of AgF. The reaction took place smoothly with 2 mol amounts of AgF toward **1a**, while the yield of **2a** diminished with decreasing the amount of employed AgF.⁶ We then performed XRD analysis of the silver residue after the reaction, the result of which showed that several peaks of the diffraction pattern were found to be identical with those of authentic silver(0).⁷

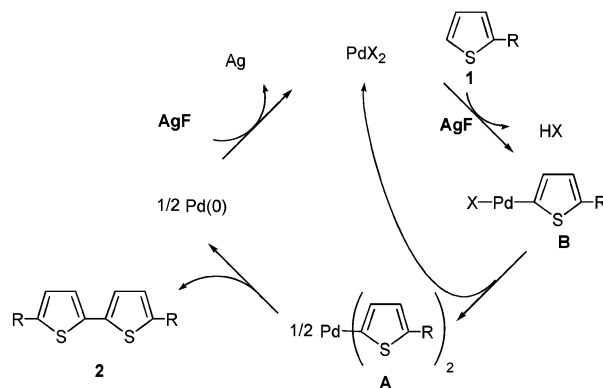
Thus, we consider that homocoupling proceeds as illustrated in Scheme 1 via reductive coupling of bis-heteroaryl palladium species

Table 1. Homocoupling of 2-Formylthiophene^a

catalyst	additive	time, h	%yield
PdCl ₂ (PhCN) ₂	AgF	5	69
PdCl ₂ (PhCN) ₂	AgF	5	45 ^b
PdCl ₂ (dppb)	AgF	5	57
none	AgF	5	0
PdCl ₂ (dppb)	none	5	0
PdCl ₂ (dppb)	AgOCOCH ₃	24	44
PdCl ₂ (PPh ₃) ₂	AgF	5	54
Pd(OAc) ₂	AgF	5	56
Pd(OAc) ₂ ^c	none	12	0
Pd(PPh ₃) ₄	AgF	5	62
Pd ₂ (dba) ₃ ·CHCl ₃ ^d	AgF	5	69

^a The reaction was carried out with 0.5 mmol of **1a**, 1.0 mmol of the additive in 3 mL of DMSO. ^b The reaction was carried out at 35 °C. ^c The reaction was carried out with catalyst loading of 100 mol %. ^d The reaction was carried out with catalyst loading of 1.5 mol %.

Scheme 1. Plausible Reaction Mechanism of Homocoupling



A, which is formed by electrophilic C–H substitution of Pd^{II}X₂ with **1** to give **B** and following disproportionation. AgF would serve as an effective promoter (although it is not incorporated into the stoichiometry) in forming the intermediate **B** through a specific interaction with the palladium catalyst and the sulfur atom of **1**. Silver fluoride then serves as an oxidizing agent of the formed Pd(0) species also to regenerate the Pd(II) catalyst. Hence, use of more than a stoichiometric amount of AgF toward **1a** would be required for the effective homocoupling reaction.

Hydrogen fluoride, which would be formed during homocoupling, neither inhibited the catalytic reaction nor damaged the glassware significantly, probably due to the formation of a stabilizing complex with DMSO, whose signal in the ¹⁹F NMR spectrum appeared at –164.2 ppm as singlet.^{8,9} (**CAUTION!** The reaction should be carried out in a well-ventilated hood with gloves throughout the procedure.)

Table 2. Palladium-Catalyzed Homocoupling of Heteroaromatic Compounds^a

product	time, h	yield
	(2b)	5 85%
	(2c)	5 69%
	(2d)	5 43%
	(2e)	5 58%
	(2f)	5 41%
	(6)	5 63%
		24 83% ^b

^a The reaction was carried out under similar conditions shown in Table 1. ^b AgOCOCH₃ and PdCl₂(dppb) were employed instead of AgF and PdCl₂(PhCN)₂.

On the other hand, C–H cross coupling was found to occur when the palladium-catalyzed reaction of **1a** in the presence of AgF was carried out with iodobenzene (**3**), affording the coupling product **4** in 58% yield (eq 1). Worthy of note is that AgF played a markedly different role from homocoupling. XRD analysis of the silver residue in the cross-coupling reaction indicated the formation of AgI.⁷ It is also a remarkably mild C–H functionalization reaction that takes place at the 5-position of thiophene derivatives.¹⁰

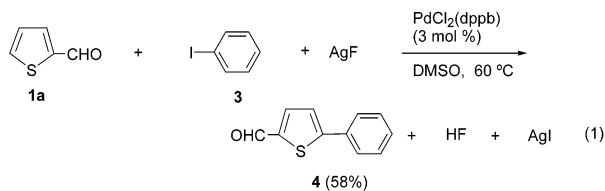
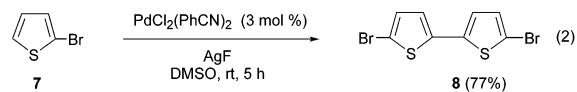


Table 2 shows results of homocoupling with various thiophene derivatives. The reaction of ethyl thiophene-2-carboxylate (**1b**) and 2-acetylthiophene (**1c**) similarly proceeded. In addition to electron-deficient thiophene derivatives **1a–1c**, thiophenes bearing alkyl and aryl groups effected homocoupling. Benzothiophene (**1f**) also furnished **2f** in 41% yield. It was found that homocoupling of 2-(4-methoxyphenyl)thiazole (**5**) took place at the 5-position to afford the corresponding bithiazole **6** in a good yield. Both additives AgF and AgOCOCH₃ effected homocoupling smoothly.

It should be pointed out that the reaction of 2-bromothiophene (**7**) afforded 5,5'-dibromo-2,2'-bithiophene (**8**) as shown in eq 2.



The reaction took place at room temperature within 5 h to give the coupling product at the 5-position in 77% isolated yield, while the bromo group did not react at all. On the other hand, synthesis of **8** has been conventionally carried out with nickel-catalyzed dehalogenative homocoupling of **7** followed by re-bromination.¹¹ Accordingly, a direct and practical synthesis of dihalogenated bithiophene via C–H homocoupling is extremely noteworthy since **8** is a key intermediate of a variety of oligothiophene derivatives, which are widely applied as advanced organic materials.²

Supporting Information Available: Experimental details and characterization of coupling products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (7) See Supporting Information.
- (8) The ¹⁹F NMR spectrum of commercially available Et₃N·3HF in DMSO appeared at δ –158.7 ppm. The reaction mixture in the presence of Et₃N, which also effected homocoupling of **1a** in 51% yield, showed the corresponding signal at –152.1 ppm.
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