

Palladium-Catalyzed Coupling Reactions of Bromothiophenes at the C–H Bond Adjacent to the Sulfur Atom with a New Activator System, AgNO₃/KF

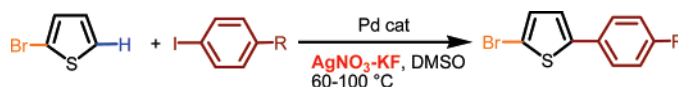
Kei Kobayashi, Atsushi Sugie, Masabumi Takahashi, Kentaro Masui, and Atsunori Mori*

Chemical Resources Laboratory, Tokyo Institute of Technology, R1-4 4259 Nagatsuta, Yokohama 226-8503, Japan

amori@res.titech.ac.jp

Received August 26, 2005

ABSTRACT



Bromothiophene derivatives react with aryl iodides catalyzed by a palladium complex in the presence of a silver(I) nitrate/potassium fluoride system to induce coupling at the C–H bond, while the carbon–bromine bond is intact. The produced coupling product bearing the C–Br bond allows further palladium-catalyzed C–C bond-forming reactions in reasonable yields.

C–H substitution reactions of aromatic compounds with organic halides are of great interest in organic synthesis compared with those of the related coupling reaction with metallic reagents, which are prepared from the corresponding halide.¹ By contrast, the direct reaction at the C–H bond would be more suitable for the synthesis of the derivatives library of various functional groups as well as the reaction would enhance atom efficiency of the synthesis.² We have recently reported that homocoupling of thiophene derivatives takes place at the carbon–hydrogen bond to form bithiophenes.³ The reaction was effectively promoted by the addition of silver(I) fluoride. Homocoupling was found to occur at the C–H bond even when the reaction was carried out with 2-bromothiophene to afford the corresponding bithiophene,

where the carbon–bromine bond was intact. Our concern has accordingly turned to the cross coupling of bromothiophene derivatives at the C–H bond to introduce a substituent into the thiophene ring. The C–H coupling of bromothiophene, if successful, further transforms the obtained coupling product by the reaction at the C–Br bond. The combination of coupling reactions at C–H and C–Br would open a new synthetic strategy for substituted thiophenes, which attracts remarkable attention in the design of advanced organic materials showing characteristics of liquid crystal, light emission, and organic semiconductors.⁴ Herein, we report that a new class of the activator system, silver(I) nitrate–potassium fluoride, undergoes palladium-catalyzed C–H substitution reactions of bromothiophene derivatives highly efficiently.

The reaction of 2-bromothiophene (**1a**) and 4-methoxy-1-iodobenzene (**2a**) was carried out with silver(I) fluoride in the presence of a palladium catalyst. The corresponding

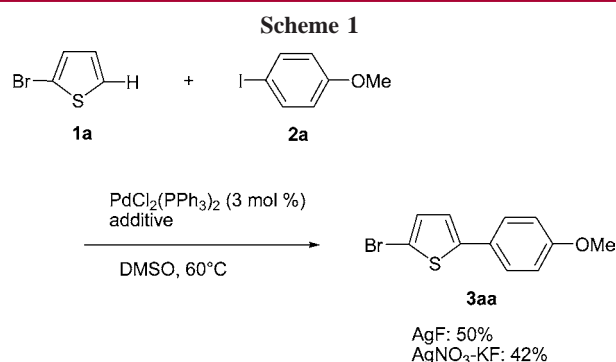
(1) *Metal-Catalyzed Cross-Coupling Reaction*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.

(2) (a) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700. (b) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467. (c) Yokooji, A.; Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2003**, *59*, 5685. (d) Kondo, Y.; Komine, T.; Sakamoto, T. *Org. Lett.* **2000**, *2*, 3111. (e) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274. (f) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 10580. (g) Sezen, B.; Sames, D. *Org. Lett.* **2003**, *5*, 3607. (h) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211.

(3) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074.

(4) (a) Masui, K.; Mori, A.; Okano, K.; Takamura, K.; Kinoshita, M.; Ikeda, T. *Org. Lett.* **2004**, *6*, 2011. (b) Briehn, C. A.; Schiedel, M.-S.; Bonsen, E. M.; Schuhmann, W.; Bäuerle, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 4680. (c) Facchetti, A.; Yoon, M.-H.; Stern, C. L.; Katz, H. E.; Marks, T. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 3900. (d) Yamamoto, T.; Arai, M.; Kokubo, H.; Sasaki, S. *Macromolecules* **2003**, *36*, 7986. (e) McCullough, R. D. *Adv. Mater.* **1998**, *10*, 93. (f) Tour, J. M. *Chem. Rev.* **1996**, *96*, 537.

coupling product was obtained in 50% yield after stirring at 60 °C for 5 h. A similar reaction with AgNO₃/KF in place of AgF was found also to afford **3aa** in 42% yield. It is remarkable that the reaction at the C–Br bond is not observed, and the reaction was shown to take place only at the C–H bond adjacent to the sulfur atom of **1a** although the yield of **3aa** was moderate (Scheme 1). Arylation of



thiophene derivatives catalyzed by a palladium complex bearing a bulky phosphine ligand has been shown recently to proceed at 150 °C in the presence of Cs₂CO₃.⁵ However, the reaction of a thiophene derivative bearing an aromatic C–Br bond would not be tolerable under such conditions.

Although attempted reactions at higher temperature and for a further reaction period was examined in order to improve the yield, little progress to yield the desired product **3aa** was observed. The similar C–H arylation of 2,3-dibromothiophene (**1b**) was also examined to result in the comparable yield (41%). However, it was found that the addition of AgNO₃ in several portions dramatically improved the yield. Indeed, the yield of the reaction of **1b** with **2a** improved to 83% when 0.5 equiv of AgNO₃/KF was added in four portions with stirring for each 2 h. Further optimization revealed that the addition of AgNO₃ (0.25 equiv × 5) for 1 h × 5 afforded **3ba** in 87% yield. In addition, the addition of tetrabutylammonium fluoride (TBAF) as a solution of DMSO over a period of 5 h also furnished **3ba** in excellent yield. The results suggest that AgF formed in situ by the reaction of AgNO₃ and KF causes degradation by light or heat. Hence, a longer reaction period was not effective to achieve the higher yield when the reaction did not proceed in a reasonable reaction rate. The results are summarized in Table 1.

The reaction of several bromothiophene derivatives was examined with a variety of aromatic compounds. The results are shown in Table 2. It was found that **1a** and **1b** reacted with a variety of aryl iodides bearing an electron-donating or electron-withdrawing substituent in moderate to excellent yields. In addition, 3-methyl-2-bromothiophene (**1c**), 5-bromo-2,2'-bithiophene (**1d**), and 2,4-dibromothiophene (**1e**) also underwent the reaction. Fractional addition of AgNO₃

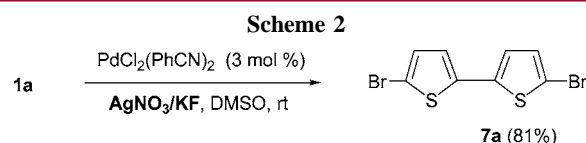
Table 1. Reaction of 2-Bromothiophene (**1a**) or 2,3-Dibromothiophene (**1b**) with 4-Methoxy-1-iodobenzene (**2a**)^a

thiophene	AgNO ₃ /eq	time	yield/ % ^b
	1.0 (AgF)	5 h ^c	50
	1.0	5 h ^c	42
	1.0	5 h	54
	1.0	24 h	57
	1.0	24 h	41
	0.5 × 4	2 h × 4	83
	0.25 × 5	1 h × 5	87
	1.0 ^d	5 h	79

^a Unless specified, the reaction was carried out at 100 °C with 0.6 mmol of **1** and 0.5 mmol of **2** in the presence of PdCl₂(PPh₃)₂ (5 mol %), AgNO₃ (0.5 mmol), and KF (1.0 mmol) in 3 mL of DMSO. ^b Isolated yield. ^c The reaction at 60 °C. ^d TBAF (1.5 wquiv) was employed in place of KF and added dropwise to the reaction mixture as a DMSO solution.

similarly improved the yield of the C–H substitution reaction when the reaction did not proceed efficiently. The reaction proceeded with aryl iodides bearing an electron-withdrawing group such as ethyl 4-iodobenzoate (**2b**), 4-iodobenzonitrile (**2c**), and 4-iodobenzotrifluoride (**2d**) in good yields. In addition, 2-iodonaphthalene (**2e**) also effected the coupling reaction to afford **3ae** and **3be** in excellent yields.

The system, AgNO₃/KF, and its fractional addition were found to be similarly effective for the homocoupling reaction. The reaction of 2-bromothiophene with a palladium catalyst (3 mol %) in the presence of AgNO₃/KF afforded the corresponding bithiophene **7a** in 81% yield when the addition of AgNO₃/KF was carried out in two portions.⁶ Compared to the reaction with AgF,³ combination of inexpensive reagents AgNO₃ and KF is noteworthy to effect the homocoupling reaction in a higher yield (Scheme 2).


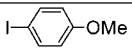
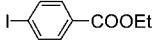
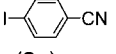
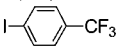



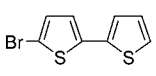
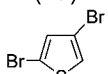


Although homocoupling and cross-coupling are competitive reactions in the presence of aryl iodide, no homocoupling is observed in the reaction of a bromothiophene **1** with aryl iodide **2** under the conditions of method A of Table 2. As we have shown previously, these reactions are completely different despite the use of the same additive, AgNO₃/KF: homocoupling afforded Ag, while AgI was obtained in the cross-coupling reaction.^{3,4a} The reaction of Pd(0) with aryl–I to give aryl–Pd–I would be the faster pathway than the reaction of Pd(0) with AgF to form Pd(II)F₂, which induces

(5) Yokooji, A.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2004**, *60*, 6757.

(6) The addition of AgNO₃/KF in one portion resulted in giving 52% of **7a**.

Table 2. Reaction of Bromothiophene Derivatives with Various Aryl Iodides^a

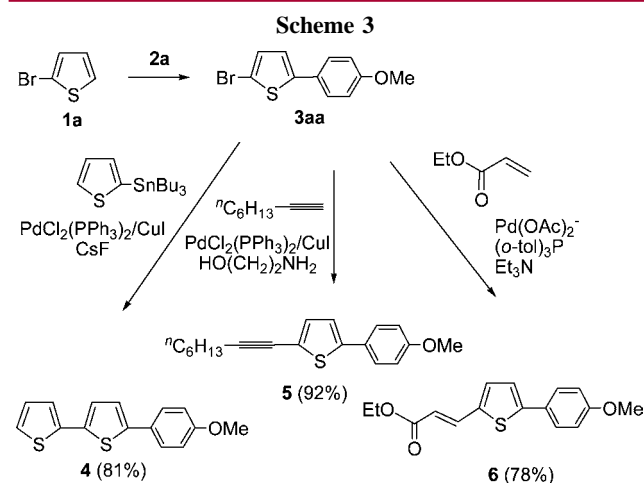
thiophene	Aryl-I	method ^b	yield/ % ^c
 (1a)	 (2a)	B	60
	 (2b)	B	93
	 (2c)	B	64
	 (2d)	B	(75)
	 (2e)	B	(79)
 (1b)	2a	A	87
	2b	A	72
	2c	A	68
	2d	A	(67)
	2e	A	(86)
 (1c)	2a	B	61
	2b	A	51
	2c	A	53
 (1d)	2a	B	48
 (1e)	2a	B	65

^a Unless specified, the reaction was carried out at 100 °C with 0.6 mmol of **1**, 0.5 mmol of **2** in the presence of PdCl₂(PPh₃)₂ (5 mol %), AgNO₃ (0.5 mmol), and KF (1.0 mmol) in 3 mL of DMSO. ^b Method A: AgNO₃ (0.25 equiv, 1 h × 5); Method B: AgNO₃ (0.5 equiv, 2 h × 4). ^c Isolated yield. The yield based on NMR is shown in parentheses.

homocoupling of thiophene. Formation of bithiophene would subsequently be suppressed in the presence of aryl iodide **2**.⁷

Since the obtained C–H substitution reaction products **3** possess a carbon–bromine bond, **3** allows further substitution reactions with several nucleophilic reagents. Hence, bromothiophenes **1** serve as a chameleon substrate that brings about sequential electrophilic and nucleophilic substitutions, without a protective group, at C–H and C–Br bonds, respectively. Indeed, when **3aa** was treated with (2-thienyl)-tributyl tin in the presence of a palladium/copper catalyst,

the corresponding bithiophene **4** was obtained in 81% yield.⁸ The reaction of 1-octyne using 2-ethanolamine as an activator⁹ also underwent the Sonogashira coupling to afford **5** in a reasonable yield and Mizoroki–Heck reaction¹⁰ with ethyl acrylate afforded **6** as summarized in Scheme 3.



In summary, palladium-catalyzed arylation reaction of bromothiophene derivatives was shown to take place at the carbon–hydrogen bond adjacent to the sulfur atom, while the coupling reaction at the carbon–bromine bond did not occur at all. Such a C–H arylation without affecting the bromo group by the palladium catalyst can be accomplished because the reaction using a AgNO₃/KF system proceeds under mild conditions compared with other C–H arylations.^{2,5} Since the obtained arylation product still possesses a carbon–bromine bond, further functionalization with transition-metal-catalyzed bond-forming reactions such as various cross-coupling reactions with main group reagents, terminal alkynes, or activated or unactivated double bonds may be applicable.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research (No. 16550092) by the Japan Society for the Promotion of Science and by The Sumitomo Foundation.

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

OL052063Y

(7) Since the lifetime of in situ formed AgF is not long enough, slightly excess amounts of bromothiophene **1** would not be converted to the corresponding bithiophene via homocoupling.

(8) (a) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132. (b) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301. (c) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

(9) (a) Mohamed Ahmed, M. S.; Sekiguchi, A.; Masui, K.; Mori, A. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 160. (b) Mohamed Ahmed, M. S.; Mori, A. *Tetrahedron* **2004**, *66*, 9977. (c) Mori, A.; Mohamed Ahmed, M. S.; Sekiguchi, A.; Masui, K.; Koike, T. *Chem. Lett.* **2002**, 756. (d) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(10) (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320. (c) Heck, R. F. *Org. React.* **1982**, *27*, 345.