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Palladium-Catalyzed C−H Functionalization of Heteroarenes with Aryl Bromides and Chlorides

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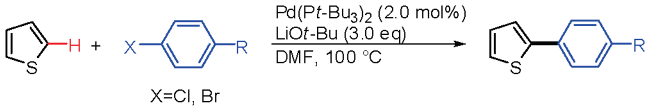
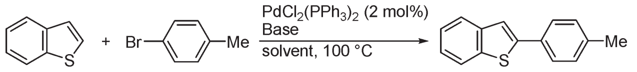


Palladium-catalyzed C−H arylation of electron-enriched heteroarenes with aryl bromides and aryl chlorides proceeds in the presence of LiO-*t*-Bu as a base. The reaction allows one-pot synthesis of differently substituted 2,5-diarylthiazole with the same catalyst system by switching the solvent and the amount of base.

The transition-metal-catalyzed C−H functionalization reaction has recently attracted much attention compared with the related cross coupling of organometallic compounds with organic halides due to its operational simplicity avoiding the preparation of corresponding organometallic reagents.[1,2] The C−H coupling reaction of heteroaromatic compounds involves a particular advantage since it is relatively easy to specify the C−H bond to be subjected to the bond formation compared with that of, for example, monosubstituted benzene. In addition, a number of heteroaromatic components are found in biologically active molecules[3] as well as advanced organic materials;[4] therefore, development of a practical synthetic strategy for such molecules is an important issue in organic synthesis. Much effort has been paid to investigate novel C−H coupling reactions of heteroaromatic compounds so far.[5]

We have shown that functionalization of an electron-deficient C−H bond such as that of azoles takes place in the presence of a weak base or fluoride ion by the catalysis of palladium/copper catalyst system,[6] while the reaction of an electron-enriched C−H bond such as the 2-position of thiophene or the 5-position of thiazole is induced by electrophilic substitution with a palladium catalyst.[6,7] An alternative strategy for the functionalization of the above C−H bond is the use of a stronger base to abstract the less acidic hydrogen atom. Dougulis and Miura recently showed that the use of a lithium salt of tertiary alcohols effectively induced the copper(I)-catalyzed arylation reaction of several heteroaromatic compounds.[8] However, the majority of the substrates employed for the coupling reaction are highly reactive aryl iodides. Accordingly, it is intriguing to explore a novel catalytic reaction that proceeds with higher performance for the C−H functionalization of heteroaromatic compounds. Herein, we describe the palladium-catalyzed

TABLE 1. Solvent Effect of the Palladium(II)-Catalyzed C−H Coupling of Benzothiophene (1) with 2a[a]



1 + **2a** → **3a**

entry	base (equiv)	solvent	yield[b] (%)
1	LiO-*t*-Bu (2)	NMP	0
2	LiO-*t*-Bu (2)	TMU	48[c]
3	LiO-*t*-Bu (2)	DMF	43
4	LiO-*t*-Bu (3)	DMF	55[c]
5	LiO-*t*-Bu (3)	toluene	0
6	LiO-*t*-Bu (3)	1,4-dioxane	0
7	KO-*t*-Bu (2)	DMF	trace
8	NaO-*t*-Bu (2)	DMF	0

[a]The reaction was performed with **1** (0.5 mmol) and **2a** (0.6 mmol) in 2 mL of solvent at 100 °C for 15 h. [b]Unless specified, the yield was estimated by ^{1}H NMR. [c]Isolated yield.

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

(2) Reviews on C−H bond arylation: (a) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (b) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382. (c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (e) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (f) Ackermann, L. *Synlett* **2007**, 507. (g) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (h) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. (i) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (j) Mori, A.; Sugie, A. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 548.

(3) For reviews: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (b) Ligault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047.

(4) For reviews, see: (a) Osaka, I.; McCullough, R. D. *Acc. Chem. Res.* **2008**, *41*, 1202. (b) Cheng, Y.-J.; Yang, S.-H.; Hsu, C.-S. *Chem. Rev.* **2009**, *109*, 5868.

(5) Selected examples of Pd-catalyzed C−H bond arylation, see: (a) Durbin, M. J.; Willis, M. C. *Org. Lett.* **2008**, *10*, 1413. (b) Yanagisawa, S.; Ueda, K.; Sekizawa, H.; Itami, K. *J. Am. Chem. Soc.* **2009**, *131*, 14622. (c) Dong, J. J.; Doucet, H. *Eur. J. Org. Chem.* **2010**, 611. (d) Miyasaka, M.; Fukushima, A.; Satoh, T.; Hirano, K.; Miura, M. *Chem.—Eur. J.* **2009**, *15*, 3674. (e) Ohnmacht, S. A.; Culshaw, A. J.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 224. (f) Gryko, D. T.; Vakuliuk, O.; Gryko, D.; Koszarna, B. *J. Org. Chem.* **2009**, *74*, 9517. (g) Pschierer, J; Plenio, H. *Angew. Chem., Int. Ed.* 10.1002/anie.201002045.

(6) (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) Miyaoku, T.; Mori, A. *Heterocycles* **2009**, *77*, 151.

(7) (a) Kobayashi, K.; Sugie, A.; Takahashi, M.; Masui, K.; Mori, A. *Org. Lett.* **2005**, *7*, 5083. (b) Takahashi, M.; Masui, K.; Sekiguchi, H.; Kobayashi, N.; Mori, A.; Funahashi, M.; Tamaoki, N. *J. Am. Chem. Soc.* **2006**, *128*, 10930. (c) Masuda, N.; Tanba, S.; Sugie, A.; Monguchi, D.; Koumura, N.; Hara, K.; Mori, A. *Org. Lett.* **2009**, *11*, 2297. (d) Matsuda, S.; Takahashi, M.; Monguchi, D.; Mori, A. *Synlett* **2009**, 1941.

(8) (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (c) Matsuyama, N.; Kitahara, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2358. (d) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081. (e) Do, H.-Q.; Kashif Khan, R. M.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (f) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.

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TABLE 2. Arylation of Benzothiophene (1) with 4-Bromotoluene (2a) with Various Palladium Catalysts[a]

entry	Pd cat. (mol %)	yield[b] (%)
1	$PdCl_2(PPh_3)_2$ (2)	55
2	$PdCl_2$dppf (2)	42
3	$PdCl_2$d*t*-bpf (2)[c]	68
4	Pd(P*t*-$Bu_3)_2$ (2)	97
5	$Pd(OAc)_2$ (2)/JohnPhos (4)[d]	62
6	$Pd(OAc)_2$ (2)/*t*-Butyl XPhos (4)[e]	70

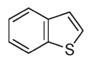
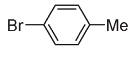
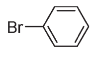
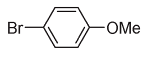
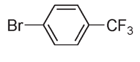
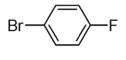
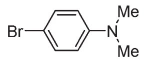
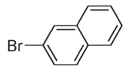
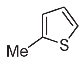
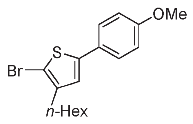
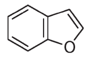
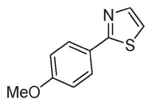
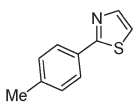
[a] The reaction was performed with **1** (0.5 mmol) and **2a** (0.6 mmol) in 2 mL of DMF at 100 °C for 15 h. [b] The yield was estimated by ^{1}H NMR yield. [c] d-*t*-bpf = 1,1′-bis(di-*tert*-butylphosphino)ferrocene. [d] JohnPhos = 2-(di-*tert*-butylphosphino)biphenyl. [e] *tert*-Butyl Xphos = 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl.

C−H arylation reactions with aryl bromides and chlorides, which occurs efficiently with LiO-*t*-Bu as an additive.[9]

We first studied the reaction of benzothiophene (**1**) with 4-bromotoluene (**2a**) in the presence of an additive and a catalytic amount of palladium(II) complex under various reaction conditions. Table 1 summarizes the results. Several bases were examined as an additive to undergo the reaction. Among those, the reaction with lithium *tert*-butoxide[10] resulted in giving 2-(4-methylphenyl)benzothiophene (**3a**) in a reasonable yield. The use of 3 equiv of LiO-*t*-Bu was found to give the coupling product **3** in a superior yield. DMF or *N*,*N*,*N*′,*N*′-tetramethylurea (TMU) was a choice of the solvent, while other polar aprotic solvents as well as less polar ones were totally ineffective. Potassium and sodium *tert*-butoxides were ineffective in undergoing the reaction. Although the reaction of several heteroaromatic compounds involving thiophene derivatives with aryl halides was shown to take place in the presence of catalytic CuI in the presence of LiO-*t*-Bu,[8] the reaction with a palladium catalyst proceeded under mild conditions with a reduced amount of aryl bromide (1.2 equiv) at 100 °C for 15 h. The reaction was found to proceed in a superior yield to that with $PdCl_2(PPh_3)_2$. Although the use of $Pd(OAc)_2$ with several other bulky phosphines also underwent the coupling reaction, the yield was slightly decreased.

TABLE 3. Pd-Catalyzed C−H Arylation of Heteroarenes with Aryl Bromides[a]

$$\text{Heteroaryl−H} + \text{Br−Aryl} \xrightarrow[\text{DMF, 100 °C}]{\text{Pd(P}t\text{-Bu}_3)_2\text{ (2 mol\%)},\ \text{LiO}t\text{-Bu (3 equiv)}} \text{Heteroaryl−Aryl}$$

entry	Heteroaryl−H	Br-Aryl		yield[b] (%)
1	 **1**		**2a**	**3a**, 97
2	**1**		**2b**	**3b**, 91
3	**1**		**2c**	**3c**, 85
4	**1**		**2d**	**3d**, 69
5	**1**		**2e**	**3e**, 82
6	**1**		**2f**	**3f**, 48
7	**1**		**2g**	**3g**, 71
8[c]	 **5**		**2a**	**6a**, 65
9	**5**		**2h**	**6h**, 60
10	 **7**		**2a**	**8a**, 47
11	**7**		**2c**	**8c**, 34
12	 **9**		**2a**	**10a**, 73
13	 **11**		**2c**	**12c**, 63

[a] Unless noted, the reaction was performed with **1** (0.5 mmol) and **2a** (0.6 mmol) in 2 mL of DMF at 100 °C for 15 h. [b] Isolated yield. [c] Reaction temperature: 60 °C.

The reaction conditions found in Table 2 were applied to the reaction of several heteroaromatic compounds and aryl bromides as summarized in Table 3. Various aryl bromides bearing an electron-withdrawing or -donating substituent reacted with benzothiophene (**1**) to afford the coupling products **3a**−**g** in good to excellent yields. In addition, the reaction with other thiophene derivatives proceeded similarly to afford the corresponding C−H arylation products. Furthermore, other heteroaromatic compounds such as furan and thiazole (at the 5-position) also underwent the reaction.

It is also remarkable that the reaction with aryl chlorides (**4**) proceeded under similar conditions. As shown in Table 4, several unactivated and activated aryl chlorides such as **4a**−**d**

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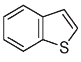
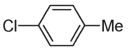
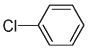
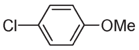
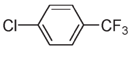
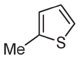
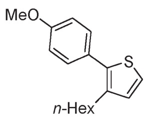
[9] Selected examples of Pd-catalyzed C−H bond arylation with aryl chlorides: (a) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (b) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (c) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449. (d) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (e) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097.

[10] For recent examples using *tert*-butoxides in C−H coupling reactions, see: (a) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (b) Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673. (c) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733. (d) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737. (e) Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 4156. (f) Kim, S. H.; Chang, H. *Org. Lett.* **2010**, *12*, 1868. (g) Kawano, T.; Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2010**, *75*, 1764. (h) Vechorkin, O.; Proust, V.; Hu, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3061.

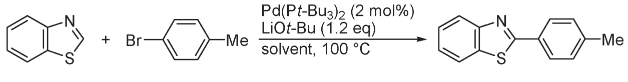
TABLE 4. Pd-Catalyzed C–H Arylation of Heteroarenes with Aryl Chlorides[a]

$$\text{Heteroaryl–H} + \text{Cl–Aryl} \xrightarrow[\text{DMF, 100 °C}]{\text{Pd(P}t\text{-Bu}_3)_2\text{ (2 mol\%)},\ \text{LiO}t\text{-Bu (3 equiv)}} \text{Heteroaryl–Aryl}$$

entry	Heteroaryl–H	Cl-Aryl		yield[b] (%)
1	 **1**		**4a**	**3a**, 92
2	**1**		**4b**	**3b**, 91
3[c]	**1**		**4c**	**3c**, 62
4	**1**		**4d**	**3d**, 67
5	 **5**		**4a**	**6a**, 88
6	 **13**		**4a**	**14a,** 58

[a] Unless noted, the reaction was performed with **1** (0.5 mmol) and **2a** (0.6 mmol) in 1 mL of DMF at 100 °C for 15 h. [b] Isolated yield. [c] A mixture of DMF (1 mL) and 1,4-dioxane (1 mL) was employed as a solvent system.

SCHEME 1

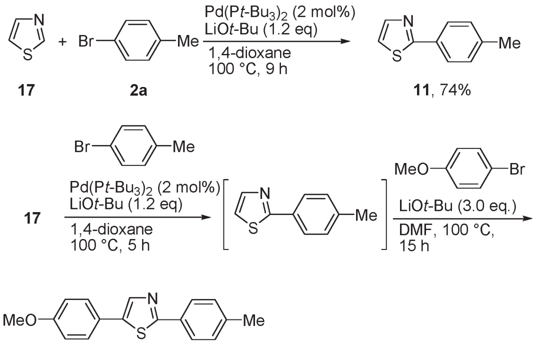


15 **2a** **16a**, trace (in DMF) 96% (in 1,4-dioxane)

reacted smoothly with thiophene derivatives **1**, **5**, and **13** to afford the corresponding coupling product in good to excellent yields.

The C–H functionalization reaction with LiO-*t*-Bu as a base was found to proceed not only at the C–H bond of a relatively electron-enriched carbon atom such as thiophene but also at an electron-deficient C–H bond. The reaction of benzothiazole (**15**) with 4-bromotoluene (**2a**) did not proceed when DMF was employed as a solvent; however, it was found to occur smoothly by switching the employed solvent to less polar. The reaction in 1,4-dioxane at 100 °C afforded the coupling product **16a** in 96% yield. In contrast to our previous case using NaOH or TBAF as an additive, where Pd/Cu catalyst system was effective, the reaction was found to proceed without copper cocatalyst.[6a,b] It is also remarkable that the reaction of **15** was performed with a smaller amount of base (Scheme 1).

SCHEME 2



17 **2a** **11**, 74%

12c, 56%

This solvent effect was successfully applied to the regioselective C–H arylation reaction of thiazole (**17**). The reaction of 4-bromotoluene (**2a**) and **17** took place at the 2-position selectively when the reaction was carried out in 1,4-dioxane as a solvent. As suggested by the results of the entry 6 of Table 1, the use of a less polar solvent is completely ineffective for the reaction of an electron-enriched C–H bond such as the 2-position of thiophene. Indeed, the reaction at the 5-position of thiazole, which is a typical electron-enriched carbon atom, hardly occurred in 1,4-dioxane.[11]

Thus, the regioselective C–H arylation reaction lead to facile synthesis of 2,5-diarylthiazole derivatives[6a,12] by one-pot iterative 2-arylation and following 5-arylation with thiazole. Unsubstituted thiazole **17** was first subjected to the reaction of 4-bromotoluene (**2a**) in 1,4-dioxane with 1.2 equiv of LiO-*t*-Bu at 100 °C for 5 h to undergo the 2-arylation. It is remarkable to observe 2-position selective arylation without copper cocatalyst.[13] Following addition of DMF, 3.0 equiv of LiO-*t*-Bu and 4-bromoanisole (**2c**) afforded 2,5-diarylthiazole **12c** in 56% overall yield (Scheme 2).

In summary, we have shown a facile palladium-catalyzed C–H arylation reaction of heteroaromatic compounds with aryl bromides and chlorides. The reaction proceeded smoothly to afford the corresponding coupling products in reasonable yields. It was also found that regioselective C–H arylation of thiazole took place at the 2-position of thiazole by judicious choice of solvent. Differently substituted 2,5-diarylthiazole was thereby obtained in a facile manner.

Experimental Section

General Procedure for C–H Coupling of Thiophene Derivatives with Aryl Halide Representative for the Preparation of 2-(4-Trifluoromethyl)benzo[*b*]thiophene (3d). To a 20 mL Schlenk tube equipped with a magnetic stirring bar was added a 2.2 M THF solution of LiO-*t*-Bu (1.5 mmol, 0.68 mL) under nitrogen atmosphere. The solvent was removed under reduced pressure. To the residue were successively added Pd(P*t*-Bu$_3$)$_2$ (5.1 mg, 0.01 mmol), benzo[*b*]thiophene **1** (68 mg, 0.5 mmol), 4-bromobenzotrifluoride (**2d**) (135 mg, 0.6 mmol), and DMF (2.0 mL). The mixture was stirred at 100 °C for 15 h. After being cooled to room temperature, the reaction mixture was poured into water, and the organic materials were extracted with diethyl ether. The organic layer was washed with water twice and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to leave a crude oil, which was purified by

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[11] The reaction in DMF gave unidentified side products.

[12] (a) Shikuma, J.; Mori, A.; Masui, K.; Matsuura, R.; Sekiguchi, A.; Ikegami, H.; Kawamoto, M.; Ikeda, T. *Chem. Asian J.* **2007**, *2*, 301. (b) Mori, A.; Shikuma, J.; Kinoshita, M.; Ikeda, T.; Misaki, M.; Ueda, Y.; Komura, M.; Asaoka, S.; Iyoda, T. *Chem. Lett.* **2008**, *37*, 272.

[13] Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467. Also see ref 6a.

column chromatography on silica gel using hexane as an eluent to afford 96 mg of **3d** as a colorless solid (69% yield): mp 195.2−196.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.34 (2H, m), 7.56 (1H, s), 7.60 (2H, d, J = 8.2 Hz), 7.72−7.76 (3H, m), 7.78 (1H, dd, J = 7.9, 0.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ121.03, 122.35, 123.95, 124.13 (q, J_{C-F} = 279 Hz), 124.80, 124.98, 125.93 (q, J_{C-F} = 4 Hz), 126.59, 130.00 (q, J_{C-F} = 35 Hz), 137.72, 139.79, 140.40, 142.28; IR (neat) 824, 1070, 1111, 1168, 1330; HRMS (EI+) calcd for $C_{15}H_9F_3S$ 278.0377, found m/z 278.0377.

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