



# Palladium-catalyzed Arylation at C-H and C-C Bonds of Masked Thiazole Derivatives

Furukawa, Hirotoshi

Matsumura, Suguru

Sugie, Atsushi

Monguchi, Daiki

Mori, Atsunori

---

(Citation)

Heterocycles, 79(1):303-309

(Issue Date)

2009-04-01

(Resource Type)

journal article

(Version)

Version of Record

(Rights)

©Japan Institute of Heterocyclic Chemistry

(URL)

<https://hdl.handle.net/20.500.14094/90003979>



HETEROCYCLES, Vol. 79, 2009, pp. 303 - 309. © The Japan Institute of Heterocyclic Chemistry  
Received, 7th, July 2008, Accepted, 1st August, 2008, Published online, 4th August, 2008.  
DOI: 10.3987/COM-08-S(D)3

## PALLADIUM-CATALYZED ARYLATION AT C-H AND C-C BONDS OF MASKED THIAZOLE DERIVATIVES<sup>‡</sup>

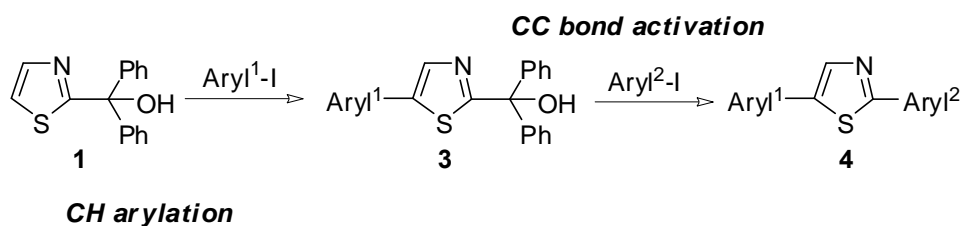
Hirotohi Furukawa, Suguru Matsumura, Atsushi Sugie, Daiki Monguchi,  
and Atsunori Mori\*

Department of Chemical Science and Engineering, Kobe University, 1-1  
Rokkodai, Nada, Kobe 657-8501, Japan  
E-mail: amori@kobe-u.ac.jp

<sup>‡</sup>To the memory of Dr. John Daly.

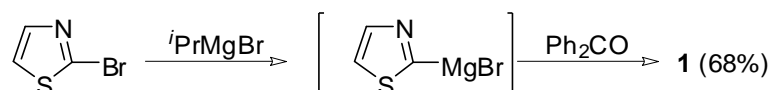
**Abstract** – The differently substituted 2,5-diarylthiazole derivatives are synthesized via palladium catalyzed sequential C–H arylation at the 5-position and C–C bond activation at the 2-position with masked thiazole.

Since 2,5-diarylated thiazoles show remarkable characteristics in photoluminescence, liquid crystal, and electrochemical redox, development of synthetic protocols for 2,5-diarylthiazoles is our major concern.<sup>1</sup> The cross-coupling methodology with a transition metal catalyst is a tool for the introduction of a substituent into the thiazole ring.<sup>2</sup> In particular, direct coupling of a thiazole derivative at the carbon–hydrogen bond by the catalysis of palladium is one of the practical way to introduce aryl and alkenyl groups via the carbon–carbon bond formation.<sup>3,4</sup> We have reported that the C–H bond at the 2- and 5-positions of thiazole is efficiently substituted by various aryl groups with a palladium catalyst.<sup>5</sup> Meanwhile, catalytic reactions via the cleavage of a C–C bond, in which a tertiary alcohol serves as a *masked* group of the corresponding C–H bond, have attracted much attention as a new class of transition metal-catalyzed carbon–carbon bond formation, and various catalytic processes involving different modes to activate the relatively inert bond have been developed.<sup>6,7</sup> Our concern has thus focused on the use of such a reaction to the functionalization of thiazole derivatives. We herein describe that a new synthetic route to introduce an aryl moiety into thiazole at the 5-position and the 2-position with a thiazole derivative masked by a tertiary alcohol **1** via the C–H bond arylation and the arylation through C–C bond activation as shown in Scheme 1.



Scheme 1.

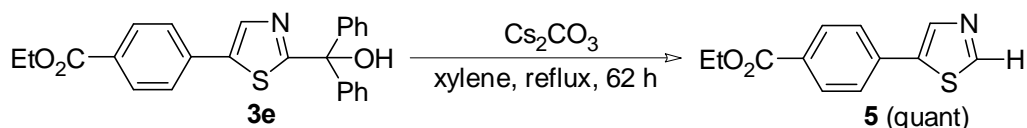
The masked thiazole **1** was prepared by the reaction of 2-bromothiazole with *i*PrMgBr to form the intermediate Grignard reagent<sup>8</sup> and following addition of benzophenone to afford the corresponding tertiary alcohol **1** in 68% yield. (Scheme 2)



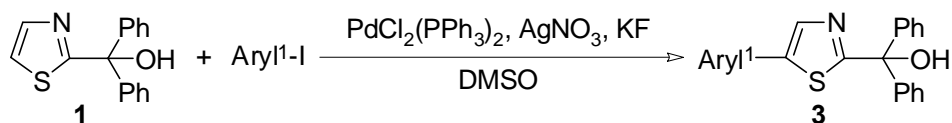
Scheme 2.

C–H arylation at the 5-position was first examined with masked thiazole **1** and an aryl iodide in the presence of a palladium catalyst and silver(I) nitrate/potassium fluoride as an activating agent. It was found to undergo the reaction affording the 5-arylated product. The reaction proceeded under similar conditions to those of 2-arylthiazole with an aryl iodide despite the presence of a hydroxy group in the molecule. Formation of the C–C bond at the 5-position of thiazole was found to occur.<sup>5b</sup> Accordingly, the masked thiazole serves as a protective group in the palladium-catalyzed reaction. The reaction with other aryl iodides was examined as shown in Table 1. Iodobenzene and aryl iodides bearing an electron-donating substituent at the 4-position afforded **3** in 39–51% yields (entries 1–3). On the other hand, iodides bearing an electron-withdrawing substituent CF<sub>3</sub> (82%, entry 4) or CO<sub>2</sub>Et (quant, entry 5) resulted in excellent yields.

Deprotection of the masked group was found to take place by treatment of **3e** with Cs<sub>2</sub>CO<sub>3</sub> under reflux in xylene to afford the corresponding 5-arylated thiazole in a quantitative yield. (Scheme 3) Since few example on regioselective arylation at the 5-position of unsubstituted thiazole is reported,<sup>3b,3k</sup> the method would be a practical surrogate for the direct 5-arylation.<sup>5b</sup>



Scheme 3.

Table 1. Reaction with C–H arylation at the 5-position of **1**<sup>a</sup>

Entry	Aryl <sup>1</sup> -I	Product	Yield (%)
1	C <sub>6</sub> H <sub>5</sub> I ( <b>2a</b> )	<b>3a</b>	39
2	4-MeOC <sub>6</sub> H <sub>4</sub> I ( <b>2b</b> )	<b>3b</b>	40
3	4-MeC <sub>6</sub> H <sub>4</sub> I ( <b>2c</b> )	<b>3c</b>	51
4	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> I ( <b>2d</b> )	<b>3d</b>	82
5	4-EtOCOC <sub>6</sub> H <sub>4</sub> I ( <b>2e</b> )	<b>3e</b>	quant

<sup>a</sup> The reaction was carried out with **1** (0.5 mmol) and **2** (0.6 mmol) in the presence of 5 mol% of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, AgNO<sub>3</sub> (0.6 mmol) and KF (1.0 mmol) in DMSO (3 mL) at 100 °C for 5 h.

We then carried out the palladium-catalyzed reaction at the 2-position through the C–C bond activation in the presence of Cs<sub>2</sub>CO<sub>3</sub> to undergo the 2-arylation (Table 2). The reaction of **3e** with various aryl halides **2** (Cl, Br, and I) was employed for the reaction to obtain **4a** to bring about similar yields (entry 1-3). It should be pointed out that aryl bromides and chlorides reacted similarly to aryl iodides when a bulky phosphine was employed as a ligand of palladium catalyst.<sup>7f,10</sup> The masked thiazole bearing an electron-withdrawing substituent was found to undergo the reaction smoothly. Indeed, the reaction of **3e** proceeded with both electron-rich iodides **2a,b** and those having an electron-withdrawing substituent **2d-e** to give **4a-d**. The reaction of **3b**, which possesses an electron-enriched aryl group as a substituent at the 5-position, with electron-deficient aryl iodide **2e** proceeded in a good yield (entry 7), while the reaction of electron-enriched **2b** resulted in a poor yield (entry 8).

With differently substituted 2,5-diarylthiazole **4b** and **4e** in hand, we then compared characteristics of these isomers. Figure 1 shows fluorescence spectra of the obtained 2,5-diarylthiazoles. Both compounds showed photoluminescence. The quantum yield of **4e** was found to be  $\Phi = 0.56$ , which was ca. twice higher than that of **4b** ( $\Phi = 0.24$ ).

Table 2. Reaction at the 2-position through the C–C bond activation of **3** with aryl halide **2**

Entry	<b>3</b>	Aryl <sup>2</sup> -X	Product	Time (h)	Yield (%)
1	<b>3e</b>	C <sub>6</sub> H <sub>5</sub> Cl ( <b>2f</b> )	<b>4a</b>	33	49 <sup>a</sup>
2	<b>3e</b>	C <sub>6</sub> H <sub>5</sub> Br ( <b>2g</b> )	<b>4a</b>	11	66 <sup>a</sup>
3	<b>3e</b>	C <sub>6</sub> H <sub>5</sub> I ( <b>2a</b> )	<b>4a</b>	11	55 <sup>a</sup>
4	<b>3e</b>	4-MeOC <sub>6</sub> H <sub>4</sub> I ( <b>2b</b> )	<b>4b</b>	22	61 <sup>a</sup>
5	<b>3e</b>	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> I ( <b>2d</b> )	<b>4c</b>	15	45 <sup>b</sup>
6	<b>3e</b>	4-EtOCOC <sub>6</sub> H <sub>4</sub> I ( <b>2e</b> )	<b>4d</b>	80	48 <sup>b</sup>
7	<b>3b</b>	<b>2e</b>	<b>4e</b>	60	54 <sup>a</sup>
8	<b>3b</b>	<b>2b</b>	<b>4f</b>	12	15 <sup>a</sup>

<sup>a</sup> The reaction was carried out with **3** (0.1 mmol) and **2** (0.12 mmol) in the presence of 5 mol% of Pd(OAc)<sub>2</sub>, 10 mol% of P(biphenylene-2-yl)(<sup>t</sup>Bu)<sub>2</sub> and Cs<sub>2</sub>CO<sub>3</sub> in xylene (1.6 mL) at 150 °C. <sup>b</sup> CuI (10 mol%) was used as a cocatalyst. PPh<sub>3</sub> was employed in place of P(biphenylene-2-yl)(<sup>t</sup>Bu)<sub>2</sub>.

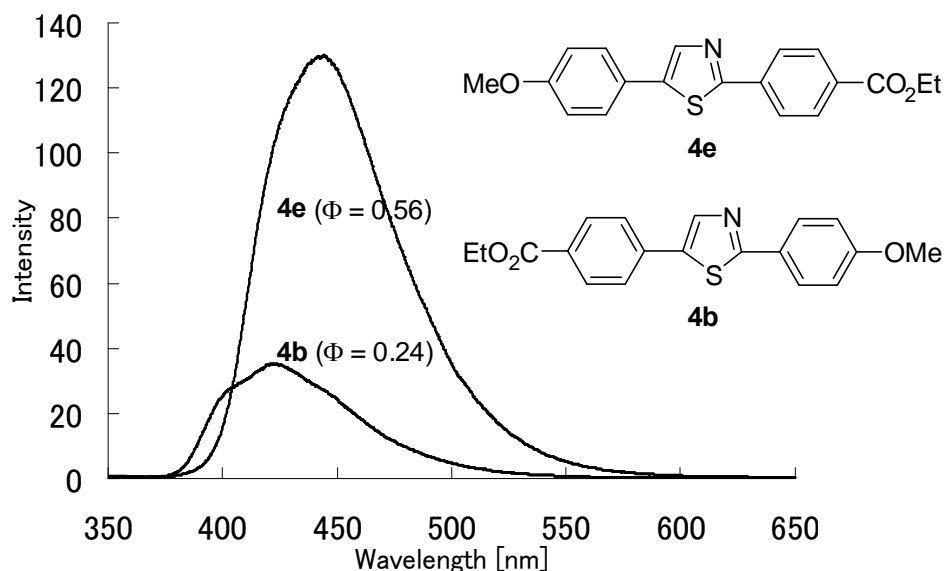


Figure 1. Fluorescence spectra of **4b** and **4e** as  $1 \times 10^{-5}$  and  $1 \times 10^{-6}$  M solutions of chloroform, respectively.

In summary, we showed that palladium-catalyzed arylation reactions of masked thiazole took place at the C–H bond of the 5-position of thiazole and at the C–C bond of the 2-position. The masked group was found to serve as a functional group to promote C–C bond formation via C–C bond activation at the 2-position of thiazole, as well as a protective group in the 5-arylation reaction with a palladium catalyst

and a silver salt. The protocols allow the introduction of the substituent in an opposite order, which reacts at the 5-position and then at the 2-position, to our conventional 2-arylation and the following 5-arylation sequence.<sup>10</sup>

## ACKNOWLEDGEMENT

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 (MEXT), Japan.

## REFERENCES AND NOTES

1. (a) K. Dölling, H. Zäschke, and H. Schubert, *J. Prakt. Chem.*, 1979, **321**, 643. (b) A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, 'Comprehensive Heterocyclic Chemistry II,' Pergamon, Oxford, 1996. (c) Y. Shirota, *J. Mater. Chem.*, 2000, **10**, 1.
2. F. Diederich and P. J. Stang, 'Metal-Catalyzed Cross-Coupling Reaction,' Wiley-VCH, Weinheim, 1998.
3. (a) S. Pivsa-Art, T. Satoh, Y. Kawamura, M. Miura, and M. Nomura, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 467. (b) G. Bold, A. Fässler, H.-G. Capraro, R. Cozens, T. Klimkait, J. Lazdins, J. Mestan, B. Poncioni, J. Rösel, D. Stover, M. Tintelnot-Blomley, F. Acemoglu, W. Beck, E. Boss, M. Eschbach, T. Hürlimann, E. Masso, S. Roussel, K. Ucci-Stoll, D. Wyss, and M. Lang, *J. Med. Chem.*, 1998, **41**, 3387. (c) A. Yokooji, T. Okazawa, T. Satoh, M. Miura, and M. Nomura, *Tetrahedron*, 2003, **59**, 5685. (d) G. L. Turner, J. A. Morris, and M. F. Greaney, *Angew. Chem. Int. Ed.*, 2007, **46**, 7996. (e) F. Bellina, C. Calandri, S. Cauteruccio, and R. Rossi, *Tetrahedron*, 2007, **63**, 1970. (f) F. Bellina, S. Cauteruccio, and R. Rossi, *Eur. J. Org. Chem.*, 2006, **6**, 1379. (g) D. Alagille, R. M. Baldwin, and G. D. Tamagnan, *Tetrahedron Lett.*, 2005, **46**, 1349. (h) H. A. Chiong and O. Daugulis, *Org. Lett.*, 2007, **9**, 1449. (i) Y. Kondo, T. Komine, and T. Sakamoto, *Org. Lett.*, 2000, **2**, 3111. (j) A. L. Gottumukkala and H. Doucet, *Eur. J. Inorg. Chem.*, 2007, **23**, 3629. (k) M. Parisien, D. Valette, and K. Fagnou, *J. Org. Chem.*, 2005, **70**, 7578.
4. For reviews: (a) A. Mori and A. Sugie, *Bull. Chem. Soc. Jpn.*, 2008, **81**, 548. (b) T. Satoh and M. Miura, *Chem. Lett.*, 2007, **36**, 200. (c) I. V. Seregin and V. Gevorgan, *Chem. Soc. Rev.*, 2007, **36**, 1173. (d) D. Alberico, M. E. Scott, and M. Lautens, *Chem. Rev.*, 2007, **107**, 174. (e) L. C. Campeau, D. R. Stuart, and K. Fagnou, *Aldrichimica Acta*, 2007, **40**, 35. (f) C. A. Zifcsak and D. J. Hlasta, *Tetrahedron*, 2004, **60**, 8991.
5. (a) A. Mori, A. Sekiguchi, K. Masui, T. Shimada, M. Horie, K. Osakada, M. Kawamoto, and T. Ikeda, *J. Am. Chem. Soc.*, 2003, **125**, 1700. (b) K. Masui, A. Mori, K. Okano, K. Takamura, M.

- Kinoshita, and T. Ikeda, [\*Org. Lett.\*, 2004, \*\*6\*\*, 2011](#). (c) K. Masui, H. Ikegami, and A. Mori, [\*J. Am. Chem. Soc.\*, 2005, \*\*126\*\*, 5074](#). (d) K. Kobayashi, A. Sugie, M. Takahashi, K. Masui, and A. Mori, [\*Org. Lett.\*, 2005, \*\*7\*\*, 5083](#). (e) A. Sugie, K. Kobayashi, Y. Suzuki, and K. Osakada, [\*Chem. Lett.\*, 2006, \*\*35\*\*, 1100](#). (f) K. Kobayashi, M. S. Mohamed Ahmed, and A. Mori, [\*Tetrahedron\*, 2006, \*\*62\*\*, 9548](#). (g) M. Takahashi, K. Masui, H. Sekiguchi, N. Kobayashi, A. Mori, M. Funahashi, and N. Tamaoki, [\*J. Am. Chem. Soc.\*, 2006, \*\*128\*\*, 10930](#). (h) N. Arai, M. Takahashi, M. Mitani, and A. Mori, [\*Synlett\*, 2006, 3170](#). (i) J. Shikuma, A. Mori, K. Masui, R. Matsuura, A. Sekiguchi, H. Ikegami, M. Kawamoto, and T. Ikeda, [\*Chem. Asian J.\*, 2007, \*\*2\*\*, 301](#). (j) A. Mori, J. Shikuma, M. Kinoshita, T. Ikeda, M. Misaki, Y. Ueda, M. Komura, S. Asaoka, and T. Iyoda, [\*Chem. Lett.\*, 2008, \*\*37\*\*, 272](#). (k) N. Arai, T. Miyaoku, S. Teruya, and A. Mori, [\*Tetrahedron Lett.\*, 2008, \*\*49\*\*, 1000](#). (l) T. Miyaoku and A. Mori, [\*Heterocycles\*, 2009, \*\*77\*\*, 151](#).
6. For reviews: (a) T. Mitsudo and T. Kondo, [\*Synlett\*, 2001, 309](#). (b) T. Nishimura and S. Uemura, [\*Synlett\*, 2004, 201](#). (c) T. Kondo and T. Mitsudo, [\*Chem. Lett.\*, 2005, \*\*34\*\*, 1462](#).
7. (a) Y. Terao, H. Wakui, T. Satoh, M. Miura, and M. Nomura, [\*J. Am. Chem. Soc.\*, 2001, \*\*123\*\*, 10407](#). (b) Y. Terao, H. Wakui, M. Nomoto, T. Satoh, M. Miura, and M. Nomura, [\*J. Org. Chem.\*, 2003, \*\*68\*\*, 5236](#). (c) Y. Terao, M. Nomoto, T. Satoh, M. Miura, and M. Nomura, [\*J. Org. Chem.\*, 2004, \*\*69\*\*, 6942](#). (d) A. Yokooji, T. Satoh, M. Miura, and M. Nomura, [\*Tetrahedron\*, 2004, \*\*60\*\*, 6757](#). (e) S. Hayashi, K. Hirano, H. Yorimitsu, and K. Oshima, [\*J. Am. Chem. Soc.\*, 2006, \*\*128\*\*, 2210](#). (f) M. Nakano, T. Satoh, and M. Miura, [\*J. Org. Chem.\*, 2006, \*\*71\*\*, 8309](#). (g) T. Niwa, H. Yorimitsu, and K. Oshima, [\*Angew. Chem. Int. Ed.\*, 2007, \*\*46\*\*, 2643](#). (h) T. Nishimura, T. Katoh, K. Takatsu, R. Shintani, and T. Hayashi, [\*J. Am. Chem. Soc.\*, 2007, \*\*129\*\*, 14158](#). (i) Y. Sumida, S. Hayashi, K. Hirano, H. Yorimitsu, and K. Oshima, [\*Org. Lett.\*, 2008, \*\*10\*\*, 1629](#). See also: (j) T. Ooi, T. Miura, and K. Maruoka, [\*J. Am. Chem. Soc.\*, 1998, \*\*120\*\*, 10790](#). (k) M. Csékei, Z. Novák, and A. Kotschy, [\*Tetrahedron\*, 2008, \*\*64\*\*, 975](#) and references therein.
8. M. Abarbri, J. Thibonnet, L. Bérillon, F. Dehmel, M. Rottländer, and P. Knochel, [\*J. Org. Chem.\*, 2000, \*\*65\*\*, 4618](#).
9. (a) J. L. Rutherford, M. P. Rainka, and S. L. Buchwald, [\*J. Am. Chem. Soc.\*, 2002, \*\*124\*\*, 15168](#). (b) D. Zim and S. L. Buchwald, [\*Org. Lett.\*, 2003, \*\*5\*\*, 2413](#). (c) R. Martin and S. L. Buchwald, [\*J. Am. Chem. Soc.\*, 2007, \*\*129\*\*, 3844](#).

10. **Arylation of 3e at the 2-position through the C–C bond activation with 2e (Table 2, Entry 6)** To a 25 mL Schlenk tube equipped with a magnetic stirring bar were added Cs<sub>2</sub>CO<sub>3</sub> (39.1 mg, 0.12 mmol), Pd(OAc)<sub>2</sub> (1.42 mg, 0.005 mmol), P(biphenylene-2-yl)(<sup>t</sup>Bu)<sub>2</sub> (2.98 mg, 0.01 mmol), xylene (1.6 mL), ethyl 4-iodobenzoate **2e** (33 mg, 20  $\mu$ L, 0.12 mmol), and **3e** (41.6 mg, 0.1 mmol). The reaction mixture was stirred at 150 °C under N<sub>2</sub> atmosphere for 80 h. After cooling to rt, the mixture was poured onto saturated aqueous NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel to afford 18.3 mg of **4d** (48%).<sup>5a</sup>