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PALLADIUM-CATALYZED ARYLATION AT C-H AND C-C BONDS OF MASKED THIAZOLE DERIVATIVES‡

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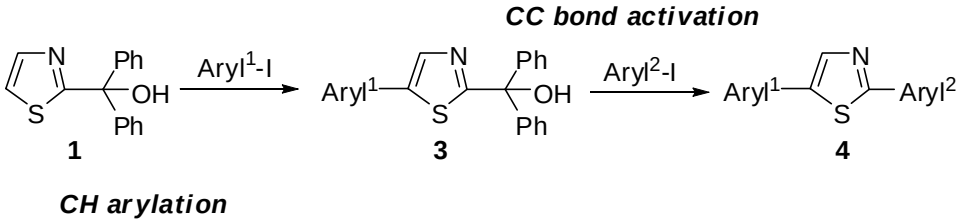
‡To the memory of Dr. John Daly.

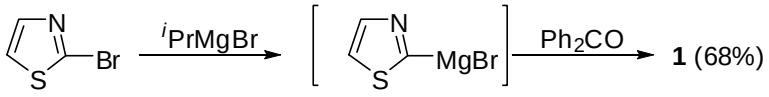
Abstract – The differently substituted 2,5-diarylthiazole derivatives are synthesized via palladium catalyzed sequential C–H arylation at the 5-position and C–C bond activation at the 2-positon with masked thiazole.

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.[1] The cross-coupling methodology with a transition metal catalyst is a tool for the introduction of a substituent into the thiazole ring.[2] 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.[3,4] 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.[5] 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.[6,7] 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.

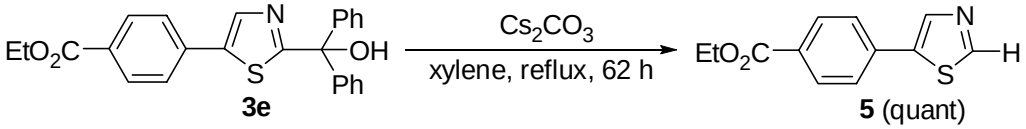
The masked thiazole **1** was prepared by the reaction of 2-bromothiazole with ^{i}PrMgBr to form the intermediate Grignard reagent[8] and following addition of benzophenone to afford the corresponding tertiary alcohol **1** in 68% yield. (Scheme 2)



Scheme 2.

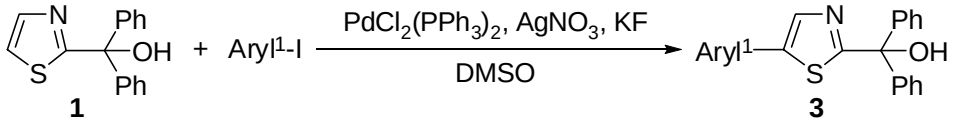
C–H arylation at the 5-position was first examined with masked thiazole **1** and an aryl iodide in the presence of a palladium catalyst and silver(I) nitrate/potassium fluoride as an activating agent. It was found to undergo the reaction affording the 5-arylated product. The reaction proceeded under 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.[5b] 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_3 (82%, entry 4) or CO_2Et (quant, entry 5) resulted in excellent yields.

Deprotection of the masked group was found to take place by treatment of **3e** with Cs_2CO_3 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,[3b,3k] the method would be a practical surrogate for the direct 5-arylation.[5b]



Scheme 3.

Table 1. Reaction with C–H arylation at the 5-position of **1**[a]



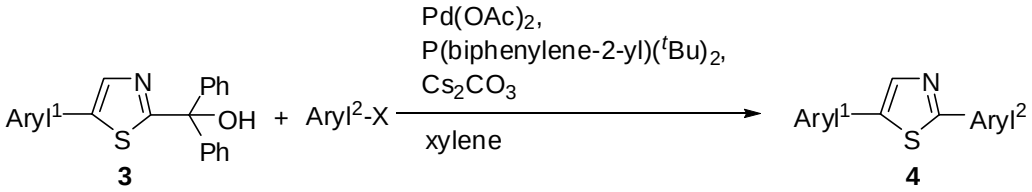
Entry	$Aryl^1$–I	Product	Yield (%)
1	C_6H_5I **(2a)**	**3a**	39
2	4-$MeOC_6H_4I$ **(2b)**	**3b**	40
3	4-MeC_6H_4I **(2c)**	**3c**	51
4	4-$CF_3C_6H_4I$ **(2d)**	**3d**	82
5	4-$EtOCOC_6H_4I$ **(2e)**	**3e**	quant

[a] The reaction was carried out with **1** (0.5 mmol) and **2** (0.6 mmol) in the presence of 5 mol% of $PdCl_2(PPh_3)_2$, $AgNO_3$ (0.6 mmol) and KF (1.0 mmol) in DMSO (3 mL) at 100 ºC 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_2CO_3 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.[7f,10] The masked thiazole bearing a 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 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	**3**	$Aryl^2$-X	Product	Time (h)	Yield (%)
1	**3e**	C_6H_5Cl **(2f)**	**4a**	33	49[a]
2	**3e**	C_6H_5Br **(2g)**	**4a**	11	66[a]
3	**3e**	C_6H_5I **(2a)**	**4a**	11	55[a]
4	**3e**	4-$MeOC_6H_4I$ **(2b)**	**4b**	22	61[a]
5	**3e**	4-$CF_3C_6H_4I$ **(2d)**	**4c**	15	45[b]
6	**3e**	4-$EtOCOC_6H_4I$ **(2e)**	**4d**	80	48[b]
7	**3b**	**2e**	**4e**	60	54[a]
8	**3b**	**2b**	**4f**	12	15[a]

[a] The reaction was carried out with **3** (0.1 mmol) and **2** (0.12 mmol) in the presence of 5 mol% of $Pd(OAc)_2$, 10 mol% of P(biphenylene-2-yl)(^{t}Bu)$_2$ and Cs_2CO_3 in xylene (1.6 mL) at 150 ºC. [b] CuI (10 mol%) was used as a cocatalyst. PPh_3 was employed in place of P(biphenylene-2-yl)(^{t}Bu)$_2$.

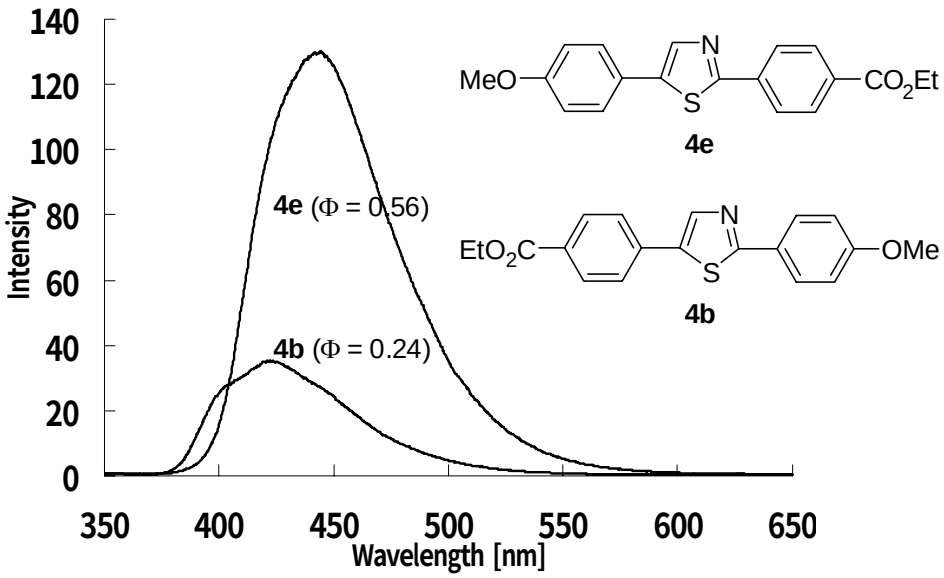


Figure 1. Fluorescence spectra of **4b** and **4e** as 1×10^{-5} and 1×10^{-6} M solutions of chloroform, respectively.

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.[10]

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REFERENCES AND NOTES

1. (a) K. Dölling, H. Zaschke, 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. Zificsak 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. Suzaki, 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*, in press.

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_2CO_3 (39.1 mg, 0.12 mmol), $Pd(OAc)_2$ (1.42 mg, 0.005 mmol), P(biphenylene-2-yl)(^{t}Bu)$_2$ (2.98 mg, 0.01 mmol), xylene (1.6 mL), ethyl 4-iodobenzoate **2e** (33 mg, 20 μL, 0.12 mmol), and **3e** (41.6 mg, 0.1 mmol). The reaction mixture was stirred at 150 ^{o}C under N_2 atmosphere for 80 h. After cooling to rt, the mixture was poured onto saturated aqueous NH_4Cl 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%).[5a]