Ortho-selective Arylation of Arylazoles with Aryl Bromides Catalyzed by Ruthenium Complexes

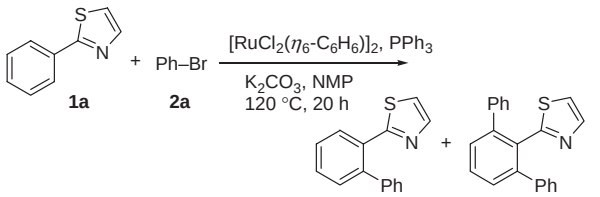
Shuichi Oi,* Hiromi Sasamoto, Raito Funayama, and Yoshio Inoue*
Department of Biomolecular Engineering, Graduate School of Engineering, Tohoku University, Sendai 980-8579

(Received June 27, 2008; CL-080646; E-mail: oishu@aporg.che.tohoku.ac.jp)

Ortho-selective direct arylation of arylazoles with aryl bromides has been accomplished in the presence of a catalytic amount of ruthenium complexes.

Transition-metal-catalyzed coupling reactions of aromatic compounds are powerful synthetic methods for the construction of biaryl structures.[1] Recently, C–C bond formation between aromatic rings including C–H bond cleavage have gained significant attention.[2] In these reactions, regioselectivity of the C–C bond formation is very important because lack of regioselectivity causes the formation of a mixture of regioisomers which are difficult to separate. Steric and electronic properties of the substituent on the aromatic rings are often effective for regioselectivity. On the other hand, functional-group-directed metalation provides only ortho selectivity. Although several functional groups, such as pyridyl,[3] imino,[4] oxazolinyl,[5] acylamino,[6] carbonyl,[7] carbamoyl,[8] carboxyl,[9] and hydroxy[10] groups have been utilized as directing groups of ortho-selective arylation reactions, expansion of the scope of the directing groups is still desired. Herein, we report on ortho arylation of arylazoles with aryl bromides catalyzed by ruthenium complexes, in which azole rings are utilized as new directing groups.[11]

As shown in Scheme 1, 2-phenylthiazole (**1a**) smoothly reacted with 1.2 equiv of bromobenzene (**2a**) in the presence of $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ (2.5 mol %), PPh_3 (10 mol %), and K_2CO_3 (200 mol %) in NMP at 120 °C for 20 h, affording 15% yield of 1:1 ortho-coupling product **3aa** and 50% yield of 1:2 coupling product **4aa**. The result indicated that the 1:2 coupling product was formed preferentially, the tendency being similar to that observed in the direct arylation of 2-aryloxazolines and -imidazolines reported before.[5a] Thus, the reaction using 2.5 equiv of bromobenzene gave **4aa** as a sole product in 97% yield. Then, scope of the directing group was examined.[12] As shown in Table 1, the reactions of 1-phenylpyrazole (**1b**) and 2-phenylbenzoxazole (**1c**) with 2.5 equiv of **2a** gave the 1:2 coupling products **4ba** and **4ca**, respectively, in good yield (Entries 1 and 2). In contrast, 1-methyl-2-phenylimidazole (**1d**) and 1-phenylindazole (**1e**) gave the 1:1 coupling products **3da** and **3ea**, respectively (Entries 3 and 4). In these cases, the methyl group of **1d** or fused benzene ring of **1e** would prevent the second coupling reaction at the alternate ortho position. Various phenylazoles bearing a methyl group at their ortho position (**1f**–**1i**) successfully underwent the ortho phenylation, affording the



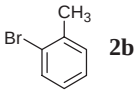
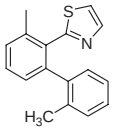
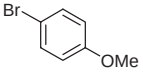
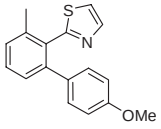
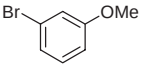
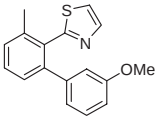
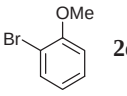
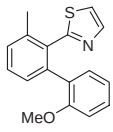
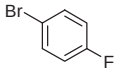
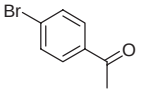
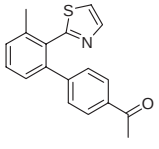
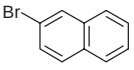
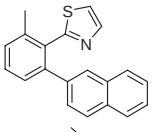
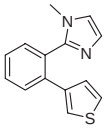
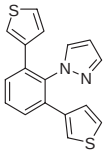
Scheme 1.

Table 1. Ortho-selective arylation of arylazoles **1** with bromobenzene (**2a**)[a]

Entry	1	Equiv of 2a	Product	Yield/%
1	**1b**	2.5	**4ba**	97
2	**1c**	2.5	**4ca**	55
3	**1d**	1.2	**3da**	84
4	**1e**	1.2	**3ea**	70
5	**1f**	1.2	**3fa**	96
6	**1g**	1.2	**3ga**	66
7	**1h**	1.2	**3ha**	92
8	**1i**	1.2	**3ia**	82
9	**1j**	2.5	**3ja**	10
10[b]	**1k**	1.2	**3ka**	43

[a]Reactions were carried out using 0.5 mmol of **1**, 0.6 or 1.25 mmol of **2a**, 0.0125 mmol of $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$, 0.05 mmol of PPh_3, and 1.0 or 2.0 mmol of K_2CO_3 in 1 mL of NMP at 120 °C for 20 h under N_2. [b]Reaction at 140 °C for 48 h.

Table 2. Ortho-selective arylation of **1f**, **1d**, and **1b** with various aryl bromides **2**[a]

Entry	1	2	Product	Yield/%
1	**1f**	 **2b**	 **3fb**	93
2	**1f**	 **2c**	 **3fc**	98
3	**1f**	 **2d**	 **3fd**	91
4	**1f**	 **2e**	 **3fe**	84
5	**1f**	 **2f**	 **3ff**	63
6	**1f**	 **2g**	 **3fg**	71
7	**1f**	 **2h**	 **3fh**	93
8	**1d**	 **2i**	 **3di**	83
9	**1b**	**2i** (2.5 equiv)	 **4bi**	96

[a]Reactions were carried out using 0.5 mmol of **1**, 0.6 mmol of **2**, 0.0125 mmol of $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$, 0.05 mmol of PPh_3, and 1.0 mmol of K_2CO_3 in 1 mL of NMP at 120 °C for 20 h under N_2.

corresponding 1:1 phenylated products (Entries 5 to 8). On the other hand, the reaction of 1-phenyl-1,2,4-triazole (**1j**) with **2a** proceeded sluggishly, affording 1:1 coupling product **3ja** in a low yield of 10% under the same reaction conditions as above (Entry 9). Similarly, the reaction rate of 1-methyl-5-phenyltetrazole (**1k**) with **2a** was sluggish, however, 43% yield of the coupling product **3ka** was obtained under harsher reaction conditions (140 °C, 48 h, Entry 10).

The present direct coupling reaction showed a broad scope for aryl bromides. Typical results are shown in Table 2. Bromobenzenes having either an electron-donating or -withdrawing group (**2b**–**2g**, 1.2 equiv) and 2-bromonaphthalene (**2h**, 1.2 equiv) all reacted well with **1f**, giving the corresponding 1:1 coupled products in good to excellent yield (Entries 1 to 7). Furthermore, heteroaryl bromides can be also used in this reaction. A slightly excess amount of 3-bromothiophene (**2i**) successfully reacted with **1d** to afford the 1:1 coupling product **3di** in 83% yield (Entry 8), while 2.5 equiv of **2i** reacted with **1b** to afford the 1:2 coupling product **4bi** in an excellent yield of 96% (Entry 9).

In conclusion, efficient and regioselective direct arylation of arylazoles with aryl bromides catalyzed by ruthenium complexes has been stated. The present reaction provides a powerful method for the synthesis of azole derivatives in combination with the palladium-catalyzed direct arylation of azoles.[2a,2c] The reaction pathway would involve the nitrogen-directed ortho ruthenation and oxidative addition of aryl halides to a ruthenium complex as was discussed before.[3h]

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" from MEXT, Japan.

References and Notes

1 a) *Cross-Coupling Reactions*, ed. by N. Miyaura, Springer, Berlin, **2002**. b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., ed. by A. de Meijere, F. Diederich, Wiley-VCH, Weinheim, **2004**.

2 Reviews: a) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173. b) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174. c) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200.

3 a) S. Oi, S. Fukita, N. Hirata, N. Watanuki, S. Miyano, Y. Inoue, *Org. Lett.* **2001**, *3*, 2579. b) S. Oi, K. Sakai, Y. Inoue, *Org. Lett.* **2005**, *7*, 4009. c) D. Shabashov, O. Daugulis, *Org. Lett.* **2005**, *7*, 3657. d) D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330. e) K. L. Hull, E. L. Lanni, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 14047. f) Y. Matsuura, M. Tamura, T. Kochi, M. Sato, N. Chatani, F. Kakiuchi, *J. Am. Chem. Soc.* **2007**, *129*, 9858. g) I. Ozdemir, S. Demir, B. Cetinkaya, C. Gourlaouen, F. Maseras, C. Bruneau, P. H. Dixneuf, *J. Am. Chem. Soc.* **2008**, *130*, 1156. h) S. Oi, R. Funayama, T. Hattori, Y. Inoue, *Tetrahedron* **2008**, *64*, 6051.

4 S. Oi, Y. Ogino, S. Fukita, Y. Inoue, *Org. Lett.* **2002**, *4*, 1783.

5 a) S. Oi, E. Aizawa, Y. Ogino, Y. Inoue, *J. Org. Chem.* **2005**, *70*, 3113. b) S. Oi, H. Sato, S. Sugawara, Y. Inoue, *Org. Lett.* **2008**, *10*, 1823.

6 a) O. Daugulis, V. G. Zaitsev, *Angew. Chem., Int. Ed.* **2005**, *44*, 4046. b) A. Lazareva, O. Daugulis, *Org. Lett.* **2006**, *8*, 5211. c) S. Yang, B. Li, X. Wan, Z. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 6066. d) Z. Shi, B. Li, X. Wan, J. Cheng, Z. Fang, B. Cao, C. Qin, Y. Wang, *Angew. Chem., Int. Ed.* **2007**, *46*, 5554.

7 a) T. Satoh, Y. Kametani, Y. Terao, M. Miura, M. Nomura, *Tetrahedron Lett.* **1999**, *40*, 5345. b) F. Kakiuchi, Y. Matsuura, S. Kan, N. Chatani, *J. Am. Chem. Soc.* **2005**, *127*, 5936. c) D. Shabashov, O. Daugulis, *Org. Lett.* **2006**, *8*, 4947.

8 Y. Kametani, T. Satoh, M. Miura, M. Nomura, *Tetrahedron Lett.* **2000**, *41*, 2655.

9 H. A. Chiong, Q.-N. Pham, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 9879.

10 a) T. Satoh, J.-I. Inoh, Y. Kawamura, Y. Kawamura, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239. b) Y. Terao, H. Wakui, M. Nomoto, T. Satoh, M. Miura, M. Nomura, *J. Org. Chem.* **2003**, *68*, 5236. c) R. B. Bedford, M. E. Limmert, *J. Org. Chem.* **2003**, *68*, 8669. d) S. Oi, S. Watanabe, S. Fukita, Y. Inoue, *Tetrahedron Lett.* **2003**, *44*, 8665.

11 Limited examples of arylation of 1-arylpyrazoles with aryl tosylates or halides have been reported: a) L. Ackermann, A. Althammer, R. Born, *Angew. Chem., Int. Ed.* **2006**, *45*, 2619. b) L. Ackermann, A. Althammer, R. Born, *Synlett* **2007**, 2833, and Ref. 3c. Rhodium-catalyzed arylation of arylazoles with tetraarylborates has been also reported: c) S. Miyamura, H. Tsurugi, T. Satoh, M. Miura, *J. Organomet. Chem.* **2008**, *693*, 2438.

12 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

Published on the web (Advance View) August 27, 2008; doi:10.1246/cl.2008.994