ORGANIC LETTERS

2001
Vol. 3, No. 16
2579−2581

Ruthenium Complex-Catalyzed Direct Ortho Arylation and Alkenylation of 2-Arylpyridines with Organic Halides

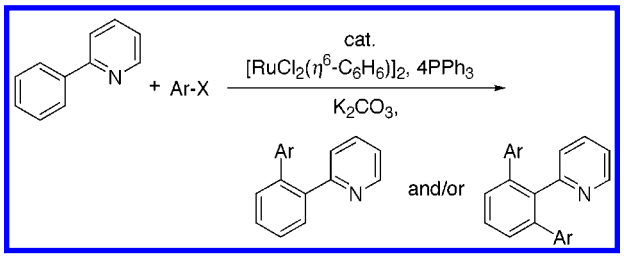
Shuichi Oi,*,† Susumu Fukita,† Naoki Hirata,† Noboru Watanuki,† Sotaro Miyano,‡ and Yoshio Inoue*,†

Department of Materials Chemistry and Department of Biomolecular Engineering, Graduate School of Engineering, Tohoku University, Sendai 980-8579, Japan

oishu@aporg.che.tohoku.ac.jp

Received June 11, 2001

ABSTRACT



The ortho position of the aromatic ring of pyridyl group-substituted aromatic compounds is directly arylated or alkenylated with organic halides in the presence of a catalytic amount of a ruthenium(II)-phosphine complex.

Transition metal-catalyzed cross-coupling reactions of aromatic compounds have recently been recognized to be of genuine synthetic utility. Reactions of various arylated metal compounds, such as Mg, Zn, B, Si, and Sn, with aryl halides or their synthetic equivalents, such as aryl triflates, catalyzed by nickel or palladium complexes are widely employed for preparations of unsymmetrical biaryls.[1] However, these reactions require each reactant to have a reacting point, such as a halogen or a metal functionalized group. Recently, there has been much interest in transition metal-catalyzed direct C−C bond formation of aromatic compounds involving the activation of normally unreactive aromatic C−H bond, in terms of synthesis efficiency and minimization of atomic waste.[2] Examples of these reactions include ruthenium-catalyzed ortho alkylation of acetophenones with terminal alkenes[3] and ortho carbonylation of pyridylbenzenes with CO and terminal alkenes,[4] rhodium-catalyzed ortho alkylation of pyridylbenzenes with terminal alkenes[5] and multiple alkylation of arylboronic acids with norbornene,[6] and palladium-catalyzed alkenylation of benzene derivatives with

* To whom correspondence should be addressed.
† Department of Materials Chemistry.
‡ Department of Biomolecular Engineering.

(1) (a) Knight, D. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 481−520. (b) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669. (c) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (e) Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.*, **1994**, *66*, 1471. (f) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (g) Mitchell, T. N. *Synthesis* **1992**, 803.

(2) (a) Shilov, E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Kakiuchi, F.; Murai, S. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; pp 47−79. (c) Fujiwara, Y.; Jintoku, T.; Takaki, K. *CHEMTECH* **1990**, 636. (d) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (e) Trost, B. M. *Science* **1991**, *278*, 1471.

(3) (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. (b) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M,; Chatani, N. *Pure Appl. Chem.* **1994**, *66*, 1527. (c) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62. (d) Kakiuchu, F.; Tanaka, Y.; Sato, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 679. (e) Kakiuchi, F.; Yamamoto, Y.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 781. (f) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *J. Organomet. Chem.* **1995**, *504*, 151.

(4) Chatani, N.; Ie, Y.; Kakiuchi F.; Murai, S. *J. Org. Chem.* **1997**, *62*, 2604.

(5) (a) Lim, Y.-G.; Kim, Y. H.; Kang, J.-B. *J. Chem. Soc., Chem. Commun.* **1994**, 2267. (b) Lim, Y.-G.; Kang, J.-B.; Kim, Y. H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2201.

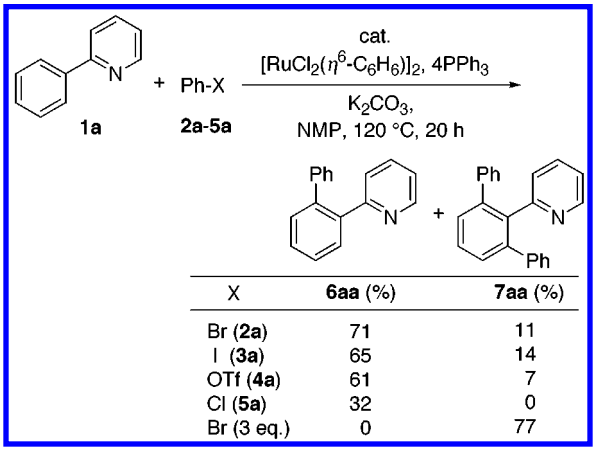
(6) Oguma, K.; Miura, M.; Satoh, T.; Nomura M. *J. Am. Chem. Soc.* **2000**, *122*, 10464.

10.1021/ol016257z CCC: $20.00
Published on Web 07/17/2001

alkynes[7] and alkylation of aromatic halides with alkyl halides.[8] For the cases of the arylation of aromatic compounds, we have reported that, in the presence of a catalytic amount of a rhodium(I)-phosphine complex, pyridylbenzenes are directly arylated in the ortho position with tetraarylstannanes.[9] Coordination by the pyridyl group is presumed to direct the rhodium complex during the cleavage of the ortho C−H bond. Arylations with aryl halides were also reported; for example, phenolic compounds such as 1-naphthols and 2-phenylphenols,[10] benzyl phenyl ketones,[11] and benzanilides[12] were arylated with aryl halides in the presence of palladium catalyst. It is considered that the coordination between the phenolate or enolate oxygen of the substrates and the arylpalladium intermediate plays a key role in these reactions. In our previous report, the arylrhodium species generated by the transmetalation with tetraarylstannane is assumed to be a key intermediate. The oxidative addition of aryl halides to transition metal complexes would also yield the arylated transition metal species, which was thus expected to act similarly as an intermediate for the arylation of pyridylbenzenes. Herein we report that, in the presence of a catalytic amount of a ruthenium(II)-phosphine complex, the aromatic rings of pyridyl group-substituted aromatic compounds were directly arylated or alkenylated, in the ortho position, with the corresponding organic halides.

2-Phenylpyridine (**1a**, 0.5 mmol) was treated with an equimolar amount of bromobenzene (**2a**, 0.5 mmol) in the presence of $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ (0.0125 mmol), PPh_3 (0.05 mmol, P/Ru ratio = 2), and K_2CO_3 (1.0 mmol) in *N*-methylpyrrolidinone (NMP) at 120 °C for 20 h to yield the monophenylated product **6aa** (71% yield) and a small amount of the diphenylated product **7aa** (11% yield, Scheme 1).

Scheme 1



X	**6aa** (%)	**7aa** (%)
Br (**2a**)	71	11
I (**3a**)	65	14
OTf (**4a**)	61	7
Cl (**5a**)	32	0
Br (3 eq.)	0	77

$RuCl_2(PPh_3)_3$ or $[RuCl_2(cod)]_2$-4PPh_3 catalytic systems also showed good activities in affording the products in similar yields, which indicate that the preceding three catalytic systems generate analogous active catalytic species. However, various phosphine ligands other than PPh_3, such as alkyl phosphines, phosphites, and bidentate diphosphines, were examined in combination with $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$, and did not exhibit comparably favorable results. Wilkinson complex ($RhCl(PPh_3)_3$), which was most effective in arylation reaction with tetraarylstannanes,[9] showed a lower catalytic activity in the present reaction system, affording product **6aa** in merely 22% yield. Other PPh_3- and chlorine-coordinated complexes of Fe, Co, Pd, and Pt did not demonstrate any catalytic activities. Aprotic polar solvents were suitable for the reaction, of which NMP exhibited the best results. Iodobenzene (**3a**) and phenyltriflate (**4a**) were also used as phenylating reagents; reaction of the former gave 65% yield of product **6aa** and 14% yield of product **7aa**, while the latter gave 61% yield of product **6aa** and 7% yield of product **7aa**. The reaction of chlorobenzene (**5a**) was slower; 32% yield of product **6aa** was obtained from the reaction after 20 h. When reactant **1a** (0.5 mmol) was treated with an excess amount of bromobenzene (**2a**, 1.5 mmol) under similar reaction conditions, except the increased amount of K_2CO_3 (3.0 mmol), the diphenylated product **7aa** was obtained exclusively in 77% yield.

Table 1 summarizes the representative results for the reactions of arylpyridines **1** with equimolar amounts of bromides **2**.[13] The arylation of 2-phenylpyridine (**1a**) with substituted bromobenzenes **2b**, **2c**, or 1-bromonaphthalene (**2d**) proceeded comparably as in the case of bromobenzene (**2a**), affording the monoarylated products **6ab**−**ad** in 60−64% yields and the diarylated products **7ab**−**ad** in 16−18% yields (entries 1−3). The reaction of **1a** with a hetero-aryl bromide, bromopyridine (**2e**), yielded products **6ae** and **7ae** in 40% and 14% yields, respectively (entry 4). Alkenylation was also observed when **1a** was treated with β-bromostyrene (**2f**) to afford the monoalkenylated product **6af** in 62% yield and the dialkenylated product **7af** in 17% yield (entry 5). 3-Methyl-2-phenylpyridine (**1b**) selectively gave the monophenylated product (**6ba**) in 90% yield in the reaction with bromobenzene (**2a**, entry 6). As was described in the literatures,[4,5] the steric interaction between the phenyl group and the methyl group in **6ba** would prevent the second phenylation. Meta substituted phenylpyridines underwent the arylation only at the less hindered ortho position. Thus, the

(7) (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (b) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252.

(8) (a) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119. (b) Catellani, M.; Cugini, F. *Tetrahedron* **1999**, *55*, 6595.

(9) Oi, S.; Fukita, S.; Inoue, Y. *Chem. Commun.* **1998**, 2439.

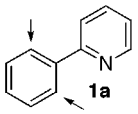
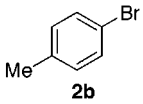
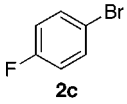
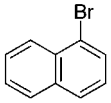
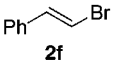
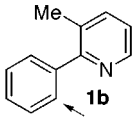
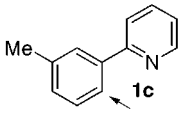
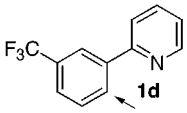
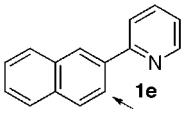
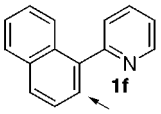
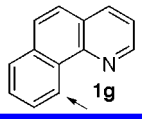
(10) (a) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740. (b) Satoh, T.; Inoh, J.-I.; Kawamura, Y.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239. (c) Kawamura, Y.; Satoh, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 961.

(11) Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1999**, *40*, 5345.

(12) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655.

(13) A following procedure is representative. A mixture of **1a** (77.6 mg, 0.5 mmol), **2a** (78.6 mg, 0.5 mmol), K_2CO_3 (138 mg, 1.0 mmol), PPh_3 (13.1 mg, 0.05 mmol), and $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ (6.3 mg, 0.0125 mmol, available from Aldrich) in 1 mL of dried NMP was stirred at 120 °C for 20 h under a N_2 atmosphere in a Schlenk tube. The reaction mixture was diluted with 50 mL of EtOAc, washed with water (20 mL × 3), and dried over $MgSO_4$. After the solvent was evaporated in vacuo, the residue was purified by flash chromatography (hexanes−EtOAc, 5: 1) to give the phenylated products **6aa** (82.1 mg, 71%) and **7aa** (16.9 mg, 11%).

Table 1. Ruthenium-Catalyzed Ortho Arylation and Alkenylation of 2-Arylpyridines **1** with Organic Halides **2**[a]

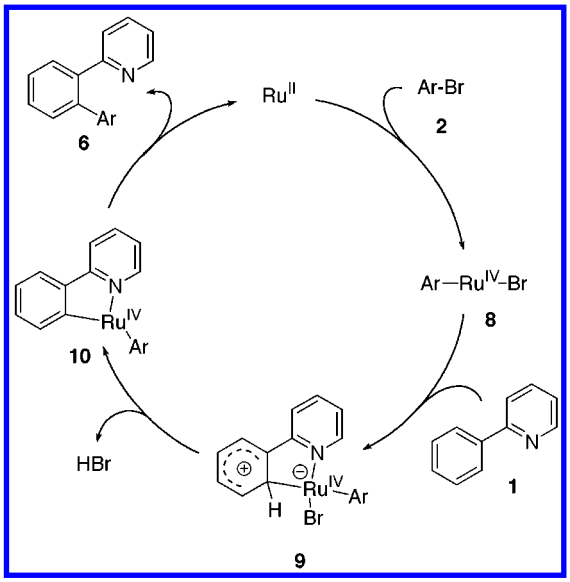
entry	**1**[b]	**2**	yield (%)[c] mono (**6**)	di (**7**)
1	 **1a**	 **2b**	60 (**6ab**)	18 (**7ab**)
2	**1a**	 **2c**	64 (**6ac**)	16 (**7ac**)
3	**1a**	 **2d**	60 (**6ad**)	16 (**7ad**)
4	**1a**	 **2e**	40 (**6ae**)	14 (**7ae**)
5	**1a**	 **2f**	62 (**6af**)	17 (**7af**)
6	 **1b**	 **2a**	90 (**6ba**)	0
7	 **1c**	**2a**	95 (**6ca**)	0
8	 **1d**	**2a**	90 (**6da**)	0
9	 **1e**	**2a**	81 (**6ea**)	0
10	 **1f**	**2a**	76 (**6fa**)	-
11	 **1g**	**2a**	95 (**6ga**)	-

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ (0.0125 mmol), PPh_3 (0.05 mmol), NMP (1 mL), 120 °C, 20 h, N_2 atmosphere. [b] Arrows indicate the reacting point(s). [c] Isolated yields.

reactions of meta Me- or CF_3-substituted substrates **1c**, **1d**, or 2-(2-naphthyl)pyridine (**1e**) with bromobenzene (**2a**) gave the monophenylated products **6ca-ea** exclusively in excellent yields (entries 7−9). 2-(1-Naphthyl)pyridine (**1f**), having only one ortho C−H bond on the aromatic ring, gave the monophenylated product **6fa** in 76% yield (entry 10). 7,8-Benzoquinoline (**1g**), which has the nitrogen atom fixed in the same plane of the reacting point, reacted favorably with **2a** to afford the monophenylated product **6ga** in an excellent yield of 95% (entry 11).

In the present arylation reaction, tetravalent aryl- or alkenylruthenium species is considered to be a key intermediate, which is generated by the oxidative addition of bromide **2** to ruthenium(II) complex. A presumed reaction mechanism is shown in Scheme 2. The tetravalent arylruthenium

Scheme 2



complex **8** reacts electrophilically with reactant **1** by the aid of the chelation of the pyridyl group, to yield the zwitterionic intermediate **9**. Elimination of HBr yields the arylated ruthenacycle **10,** and the reductive elimination of ruthenium affords the product **6**.

In conclusion, the reaction reported herein provides a new method of direct arylation and alkenylation of the ortho position of pyridyl group-substituted aromatic compounds with the corresponding organic halides. The pyridyl group acts as a directing group of the ortho metalation. Further investigations to extend the scope of these reactions are currently in progress.

Acknowledgment. This work was partly supported by Grant-in-Aid for Scientific Research (No. 13555250) from JSPS (Japan Society for the Promotion of Science), JSPS Research for the Future Program, and Konica Award in Synthetic Organic Chemistry, Japan.

Supporting Information Available: Characterization data for **6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016257Z