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Ruthenium Complex Catalyzed Direct Ortho Arylation and Alkenylation of Aromatic Imines with Organic Halides

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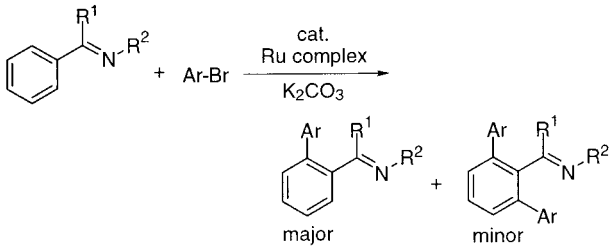
ABSTRACT



The ortho position of the aromatic ring of imino group substituted aromatic compounds is directly arylated and 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 greatly useful 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] Recently, there has been much interest in transition metal catalyzed direct C−C bond formation of aromatic compounds involving the activation of a normally unreactive aromatic C−H bond, in terms of synthesis efficiency and minimization of atomic waste.[2] For the direct arylation of aromatic compounds that gives the unsymmetrical biaryls, Miura and co-workers reported that phenolic compounds such as 1-naphthols and 2-phenylphenols,[3] benzyl phenyl ketones,[4] and benzanilides[5] were arylated with aryl halides in the presence of palladium catalysts. 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. 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.[6] The protocol was then developed for the arylation and alkenylation reaction of the pyridylbenzenes with organic halides instead of the organostannanes by use of ruthenium(II)−phosphine complexes.[7] In these

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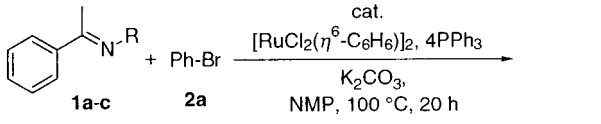
reactions, coordination by the pyridyl group is presumed to direct the aryl-rhodium or -ruthenium intermediate to the ortho position of the aromatic ring and promote the metalation. Such an idea leads us to expect that the imino group also acts as the directing group in our reaction system. The imino groups are synthetically very useful because they can be converted to many other functional groups such as ketones, alcohols, carboxylic acids, and amines and are sometimes utilized as the directing group in transition metal catalyzed direct functionalization of aromatic rings with alkenes or alkynes.[8] Herein we report that, in the presence of a catalytic amount of a ruthenium(II)−phosphine complex, the aromatic rings of imino group substituted aromatic compounds were directly arylated and alkenylated, in the ortho position, with the corresponding organic halides.

Initially, reactivity of 1-phenylethylimines (**1a**−**c**) bearing different substituents on nitrogen was examined. When *N*-(4-methoxyphenyl)-1-phenylethylimine (**1a**, 0.5 mmol) was treated with a slightly excess amount of bromobenzene (**2a**, 0.6 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 100 °C for 20 h, 90% total yield of monophenylated product **3aa** and diphenylated product **4aa** was obtained with a **3aa**:**4aa** ratio of 81:19 (Scheme 1). Changing the substituent to either a

Scheme 1

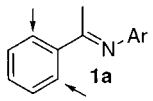
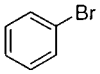
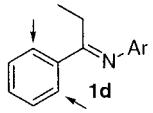
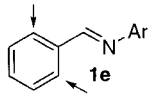
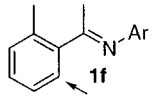
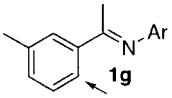
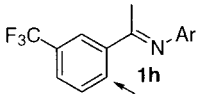
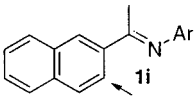
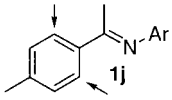
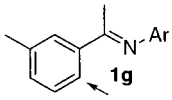
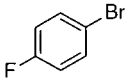
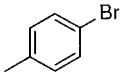
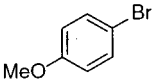
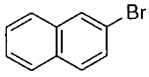


R	yield (%)	ratio (**3**:**4**)
4-MeO-C_6H_4 (**1a**)	90 (**3,4aa**)	81:19
Ph (**1b**)	78 (**3,4ba**)	85:15
$PhCH_2$ (**1c**)	74 (**3,4ca**)	82:18

phenyl group (**1b**) or benzyl group (**1c**) decreased the total yield to 78% and 74%, respectively. The electron-donating 4-methoxyphenyl group would be favorable for the nitrogen atom to coordinate to the metal center. Besides, 4-methoxyphenyl group is advantageous for deprotection because it easily undergo oxidative cleavage with CAN.[9]

$RuCl_2(PPh_3)_3$ or $[RuCl_2(cod)]_2$−$4PPh_3$ catalytic systems also showed good activities in affording the products in similar yields. However, various phosphine ligands other than PPh_3, such as alkyl phosphines, phosphites, and bidentate diphosphines, examined in combination with $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ did not exhibit comparably favorable results. Aprotic polar solvents were suitable for the reaction, of which NMP exhibited the best results.

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

entry	**1**[b]	**2**	yield (%)[c]	ratio (**3**:**4**)
1	 **1a**	 **2a**	90 (**3,4aa**)[d]	81:19
2			92 (**3,4aa**)[e]	61:39
3	 **1d**	**2a**	91 (**3,4da**)	78:22
4	 **1e**	**2a**	52 (**3,4ea**)[f]	10:90
5			92 (**4ea**)[e,f]	0:100
6	 **1f**	**2a**	17 (**3fa**)	-
7	 **1g**	**2a**	83 (**3ga**)	100:0
8	 **1h**	**2a**	93 (**3ha**)	100:0
9	 **1i**	**2a**	90 (**3ia**)	100:0
10	 **1j**	**2a**	81 (**3,4ja**)	67:33
11	 **1g**	 **2b**	85 (**3gb**)	100:0
12	**1g**	 **2c**	74 (**3gc**)	100:0
13	**1g**	 **2d**	88 (**3gd**)	100:0
14	**1g**	 **2e**	95 (**3ge**)[g]	100:0
15	**1g**	 **2f**	73 (**3gf**)[f]	100:0

[a] Common reaction conditions: Ar = 4-MeO-C_6H_4, **1** (0.5 mmol), **2** (0.6 mmol), $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ (0.0125 mmol), PPh_3 (0.05 mmol), K_2CO_3 (1.0 mmol), NMP (1 mL), 120 °C, 20 h, N_2 atmosphere. [b] Arrows indicate the reacting point(s). [c] Isolated yields. [d] Reaction at 100 °C. [e] 1.5 mmol of **2** and 2.0 mmol of K_2CO_3 were used. [f] Isolated as aldehydes or ketones after hydrolysis. [g] Reaction for 40 h.

Table 1 summarizes the representative results for the reactions of aromatic imines **1** with organic bromides **2**.[10] When imine **1a** (0.5 mmol) was treated with an excess

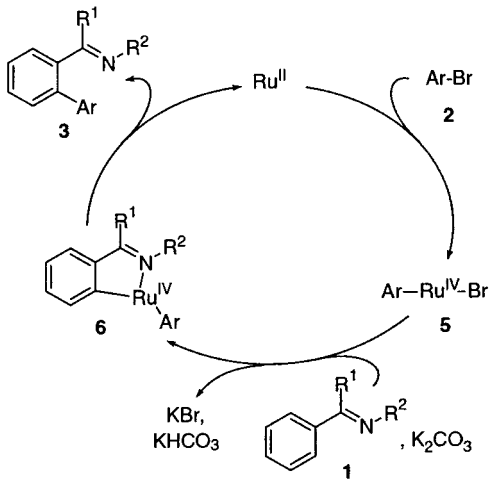
amount of bromobenzene (**2a**, 1.5 mmol) under similar reaction conditions, except for the increased amount of K_2CO_3 (2.0 mmol), the ratio of diphenylated product **4aa** was increased to 61:39 with a good yield of 92%; however, the formation of monophenylated product **3aa** was still predominant (entry 2). Steric interaction between the first introduced phenyl group and the methyl group on the imino moiety would prevent the second phenylation. Although introduction of an ethyl group on the imino moiety (**1d**) was expected to increase the ratio of monophenylated product **3da**, the ratio was similar to that from **1a** (entry 3). On the other hand, the imine from benzaldehyde (**1e**) bearing a hydrogen on the imino group underwent diphenylation predominantly (**3ea**:**4ea** = 10:90) even when 1.2 equiv of bromobenzene was used (entry 4). Thus the use of an excess amount of bromobenzene (3 equiv) gave only diphenylated product **4ea** in a good yield of 92% (entry 5).

The reaction of imine **1f** bearing a methyl group at the ortho position of the benzene ring with bromobenzene gave only 17% yield of product **3fa** (entry 6). The low yield can be also explained by steric interaction between the *o*-methyl group and the methyl group on the imino moiety. *m*-Methyl substituted imine **1g** underwent the arylation only at the less hindered ortho position where monophenylated product **3ga** was formed exclusively in 83% yield (entry 7). Similarly, imines having substituents at the meta position of the benzene rings (**1h** and **1i**) gave only monophenylated products, **3ha** and **3ia**, selectively in very good yield (entries 8 and 9). These results also indicate that the reaction is compatible to either an electron-withdrawing or -donating substituent on the reacting aromatic ring. The reaction of imine **1j** bearing a methyl group at the para position gave both mono- and diphenylated products (**3ja** and **4ja**) in 81% total yield with a **3ja**:**4ja** ratio of 67:33 (entry 10).

The arylation of *m*-methyl-substituted imine **1g** with substituted bromobenzenes were then examined. The present arylation reaction also showed good compatibility with the substituents on the arylbromides. As shown in entries 11−14, all of the reactions proceeded smoothly, affording only the monoarylated products selectively in good yield. Alkenylation was also observed when **1g** was treated with 1-bromo-2-methylbutene (**2f**) to afford monoalkenylated product **3gf** in 73% yield (entry 15).

As was proposed in our previous paper for arylation of pyridylbenzenes,[7] 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 complex **5** reacts

Scheme 2



electrophilically with reactant **1** by the aid of the chelation of the imino group to yield the arylated ruthenacycle **6**, and the reductive elimination of ruthenium affords the product **3**.

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

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Supporting Information Available: Characterization data for **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) **Representative Procedure.** (Table 1, entry 3) A mixture of **1d** (119.7 mg, 0.5 mmol), **2a** (94.2 mg, 0.6 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 20 mL of Et_2O, washed with water (20 mL × 3), and dried over $MgSO_4$. After the solvent was evaporated in vacuo, the residue was purified by silica gel column chromatography (hexanes−EtOAc, 5:1) to give the phenylated products **3da** (112.0 mg, 71%) and **4da** (39.2 mg, 20%). Spherical, neutral silica gel (Silica Gel 60 N, 100−210 μm, Kanto Chemical) was used for column chromatography.