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Nitrogen-directed *ortho*-arylation and -heteroarylation of aromatic rings catalyzed by ruthenium complexes

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Abstract

The ruthenium-catalyzed direct *ortho*-arylation reactions of 2-phenylpyridine and 2-aryloxazolines have been successfully expanded to the direct aryl–heteroaryl coupling reactions using heteroaryl bromides. The reaction mechanism involving the Ru^{II}/Ru^{IV} intermediates is proposed from the results of the stoichiometric reaction of a divalent ruthenacycle complex of 2-phenylpyridine with bromobenzene.

1. Introduction

Transition metal-catalyzed cross-coupling reaction is now recognized to be one of the most useful C–C bond forming reactions.[1] Biaryl skeletons are found in a wide range of important compounds including natural products, pharmaceuticals, agrochemicals, and functional materials.[2] Many chiral ligands are also constructed with axially dissymmetric biaryl skeletons. Reactions of various arylmetal reagents, such as Mg, Zn, B, Si, and Sn, with aryl halides or pseudo aryl halides catalyzed by nickel or palladium complexes are widely employed for preparations of unsymmetrical biaryls.[3] However, these reactions require the use of two functionalized starting materials, which are often expensive and/or difficult to synthesize using conventional methods. Recently, there has been much interest in transition metal-catalyzed direct C–C bond formation of aromatic compounds involving the cleavage of a normally unreactive aromatic C–H bond, in terms of atom economy as well as synthetic efficiency.[4] The utilization of a C–H bond as a functional group allows one to use cheap and readily available starting materials, shorten reaction sequences, and obtain compounds that are difficult to synthesize. In such direct coupling process, the critical step is the C–H bond cleavage and metalation of the aromatic ring with the transition metal complex.

Regioselectivity of the cleavage and metalation of aromatic C–H bond is also very important because C–C bond formation occurs at this position. The lack of regioselectivity causes the formation of a mixture of regioisomers, which are difficult to separate. Steric and electronic properties of the substituent of the aromatic rings are often effective for the regioselectivity. On the other hand, the functional group directed metalation provides only *ortho*-selectivity. The coordination of the functional group to the metal center forces the metal complex close to the aromatic C–H bond and boosts the rate of metalation. The functional group directed *ortho*-arylation reactions of aromatic rings are briefly reviewed below.

Satoh, Miura, and co-workers reported the *ortho*-arylation of biphenyl-2-ols with aryl iodides catalyzed by palladium complexes (Scheme 1).[5] Formation of an aryl(aryloxido)palladium followed by palladium transformation to the *ortho*-position of another benzene ring was proposed as the reaction pathway. They also reported palladium-catalyzed multiple arylation of phenylketones with aryl bromides (Scheme 2),[6] *ortho*-selective arylation of benzanilides with aryl bromides or triflates (Scheme 3),[7] and *ortho*-selective arylation of tertiary arylmethanols with aryl bromides (Scheme 4).[8] These

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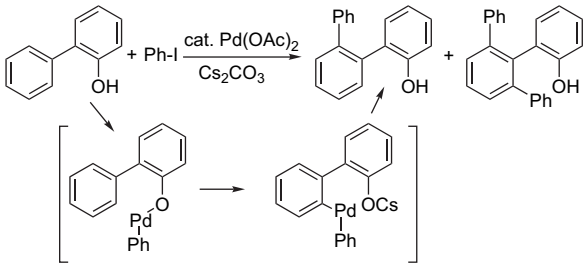
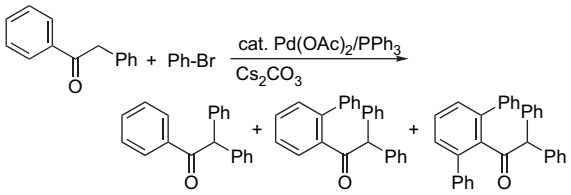
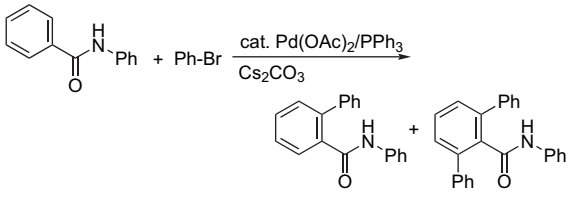
reactions are considered to involve the coordination of an enolate anion, amide anion, and alkoxide anion, respectively, to intermediary arylpalladium species.



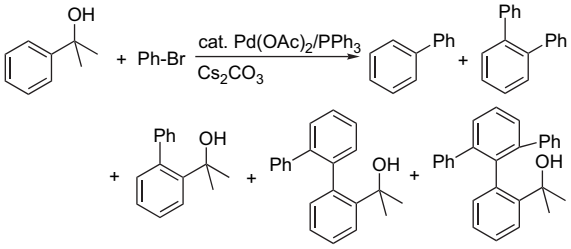
Scheme 1.



Scheme 2.

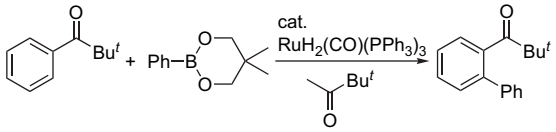


Scheme 3.



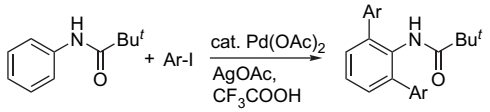
Scheme 4.

Kakiuchi and co-workers reported the *ortho*-arylation of arylketones with arylboronic esters catalyzed by a ruthenium complex (Scheme 5).[9] In this reaction, ketones, such as pinacolone, have been proved to act as an oxidant. The reaction was proposed to involve the coordination of the ketone carbonyl to the ruthenium center, followed by oxidative addition of *ortho*-C–H bond to the ruthenium(0) complex.

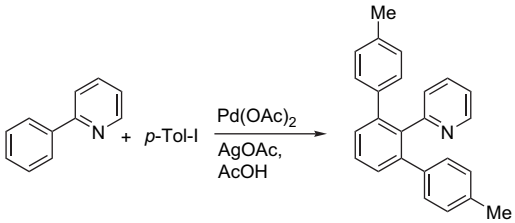


Scheme 5.

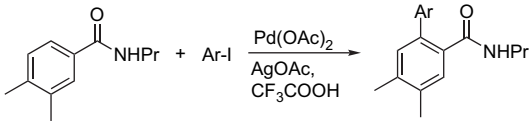
Daugulis and co-workers reported the palladium-catalyzed *ortho*-arylation of acyl anilides,[10] 2-arylpyridines,[11] benzamides,[12] benzylamines,[13] and benzoic acids[14] with aryl halides in the presence of silver acetate (Schemes 6–10, respectively). The reaction pathway has been proposed to involve the functional group directed *ortho*-palladation followed by oxidative addition of aryl halides to give diarylpalladium(IV) species.



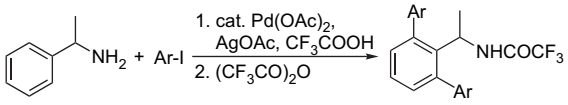
Scheme 6.



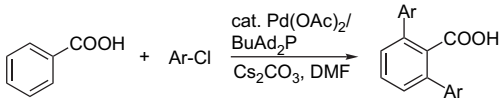
Scheme 7.



Scheme 8.

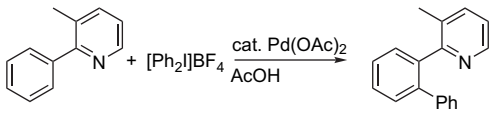


Scheme 9.

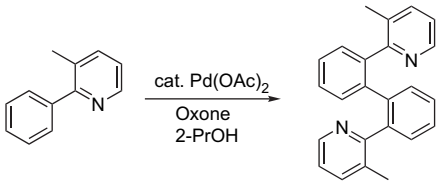


Scheme 10.

Sanford and co-workers reported the oxidative coupling of 2-arylpyridines and acyl anilides with diaryliodonium salts catalyzed by palladium complexes (Scheme 11).[15] The reaction has been proposed to proceed via the formation of *ortho*-palladacycle complexes, which then react with diaryliodonium salts to give a diarylpalladium(IV) intermediate. They also reported the *ortho*-selective direct oxidative coupling of 2-arylpyridines to give 1,1′-bis(2-pyridyl)-2,2′-biphenyls catalyzed by palladium complexes using Oxone as the oxidant (Scheme 12).[16]

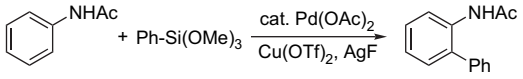


Scheme 11.

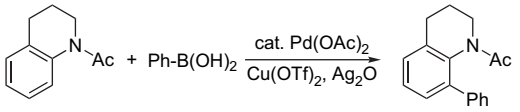


Scheme 12.

Shi and co-workers reported that acyl anilides have also been arylated at *ortho*-positions, in the presence of palladium catalyst, copper triflate, and silver fluoride or oxide, with aryltrialkoxy silanes (Scheme 13)[17] and arylboronic acids (Scheme 14).[18] Copper and silver salts were considered to be the oxidants for Pd^0 to Pd^{II}.

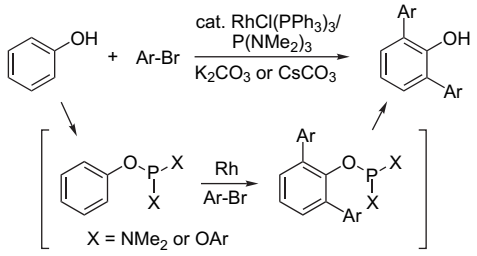


Scheme 13.



Scheme 14.

Bedford and co-workers and we independently reported the *ortho*-arylation of phenols with aryl halides catalyzed by rhodium complexes (Scheme 15).[19] The reaction involves in situ formation of phosphoroamidites $(P(OAr)_n(NMe_2)_{3-n}$, $n=1$ or 2), which are then arylated at their *ortho*-positions. Transesterification between the arylated phosphoroamidites with the substrate phenols gives the *ortho*-arylated phenols.



Scheme 15.

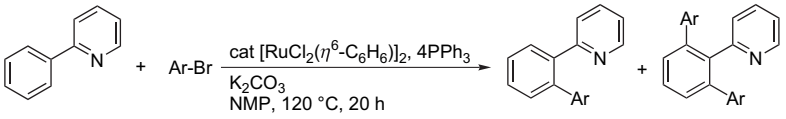
We have focused our research on nitrogen-directed *ortho*-arylation reactions catalyzed by ruthenium complexes.[20,21] Herein, we report on the regioselective arylation and heteroarylation of 2-arylpyridines and 2-aryloxazolines catalyzed by ruthenium complexes. Furthermore, synthesis and reactions of ruthenacycle complexes from 2-phenylpyridine and insights into the reaction mechanism involving a ruthenium(IV) intermediate are also presented.

2. Results and discussion

The reaction of 2-phenylpyridine (**1a**) with an equimolar amount of bromobenzene (**2a**, 1.0 equiv) in the presence of 2.5 mol % of $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$, 10 mol % of PPh_3, and K_2CO_3 (2.0 equiv) in NMP at 120 °C for 20 h afforded the *ortho*-phenylated product **3aa** and diphenylated product **4aa** in 82% total yield with a ratio of 87:13 (Table 1, entry 1).[20a] When the reaction was carried out using 2.2 equiv of **2a**, 1:2 coupling product **4aa** was obtained predominantly (entry 2). We next examined the heteroarylation of **1a** with heteroaryl bromides because the aryl–heteroaryl bonds are found in many important compounds, such as organic semiconductors, organic electroluminescent materials, natural products, and pharmaceuticals. Using the same reaction conditions, coupling of **1a** with 2-bromothiophene (**2b**) proceeded well affording the corresponding 1:1 and 1:2 coupling products (**3ab** and **4ab**, respectively) in 63% total yield with a ratio of 71:29 (entry 3). The lower selectivity of the 1:1 coupling product would be attributed to the lower steric hindrance for the five-membered thiophene ring compared to that for the benzene ring. Thus, the use of 2.2 equiv of **2b** resulted in the exclusive formation of **4ab** in a good yield of 90% (entry 4). Similarly, the reaction of **1a** with 2.2 equiv of 3-bromothiophene (**2c**) and 2-bromofuran (**2d**) gave the corresponding 1:2 coupling products **4ac** and **4ad** in excellent yields of 99 and 93%, respectively (entries 5 and 6). On the contrary, the reaction of **1a** with 2-bromothiazole (**2e**) afforded the 1:1 coupling product **3ae** in a poor yield of 10% in spite of the longer reaction time (40 h). Nitrogen containing six-membered heteroaryl bromides were then examined. The reaction of **1a** with 1.0 equiv of 3-bromopyridine (**2f**) gave the 1:1 and 1:2 coupling products **3af** and **4af** in a total yield of 71% with a preferential formation of **3af** (**3af/4af**=76:24, entry 8). The use of 2.2 equiv of **2f**, however, resulted in the slightly increased formation of **4af** (entry 9). The reaction of **1a** with 2-bromopyridine afforded the products **3ag** and **4ag** in a total yield of 64% with a ratio of 59:41 (entry 10). 2-Bromopyrimidine (**2h**) merely resulted in a low yield formation of 1:1 coupling product **3ah** (entry 11), whereas 5-bromopyrimidine (**2i**) afforded the products **3ai** and **4ai** in a total yield of 68% with a preferential formation of **3ai** (**3ai/4ai**=85:15, entry 12).

We also reported the ruthenium-catalyzed direct arylation of 2-phenyl-2-oxazolines with aryl bromides.[20c] Examples of the reaction are shown in Table 2, entries 1 and 2. The reaction between 2-phenyl-2-oxazoline (**1b**, 0.5 mmol) and a slight excess of bromobenzene (**2a**, 0.6 mmol), in the presence of 2.5 mol % of $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$, PPh_3 (0.05 mmol, P/Ru ratio=2:1), and K_2CO_3 (1.0 mmol) in NMP at 120 °C for 20 h, afforded 60% yield of a mixture of 1:1 coupling product **3ba** and 1:2 coupling product **4ba** in a 25:75 ratio (entry 1). In the case of 2-phenyl-2-oxazolines, 1:2 coupling products were obtained preferentially even when equimolar amount of bromobenzene was used. The preferential formation of **4ba** was further enhanced when 2.2 equiv of bromobenzene was used, affording the 1:2 *ortho*-coupled product as the sole product in 95% yield (entry 2). The scope of the direct coupling reaction was then expanded to the heteroaryl bromides as in the case of 2-phenylpyridine. The reaction of **1b** with 2.2 equiv of 3-bromothiophene (**2c**) successfully afforded the 1:2 coupling product **4cb** in good yield together with

Table 1
Ruthenium-catalyzed *ortho*-arylation of 2-phenylpyridine (**1a**) with aryl and heteroaryl bromides **2**[a]



1a 2 3 4

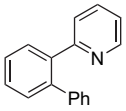
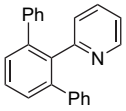
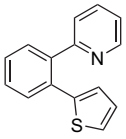
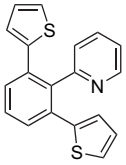
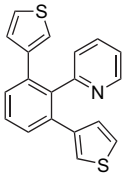
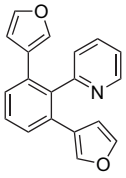
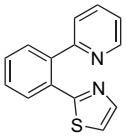
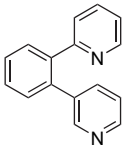
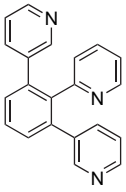
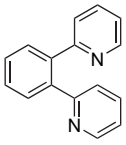
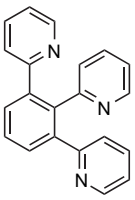
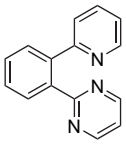
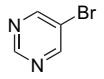
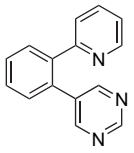
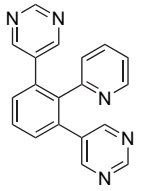
Entry	Ar–Br **2**		Equiv of **2**	Product **3**		Product **4**		Total yield (%)	Ratio (**3**/**4**)
1	Ph–Br	(**2a**)	1.0		(**3aa**)		(**4aa**)	82	87:13
2			2.2					94	0:100
3		(**2b**)	1.0		(**3ab**)		(**4ab**)	63	71:29
4			2.2					90	0:100
5		(**2c**)	2.2				(**4ac**)	99	0:100
6		(**2d**)	2.2				(**4ad**)	93	0:100
7[b]		(**2e**)	2.2		(**3ae**)			10	100:0
8		(**2f**)	1.0		(**3af**)		(**4af**)	71	76:24
9			2.2					77	70:30
10		(**2g**)	2.2		(**3ag**)		(**4ag**)	64	59:41
11[b]		(**2h**)	2.2		(**3ah**)			17	100:0

Table 1 (*continued*)

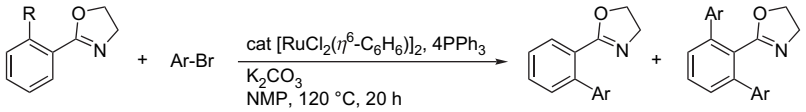
Entry	Ar–Br **2**	Equiv of **2**	Product **3**	Product **4**	Total yield (%)	Ratio (**3**/**4**)
12	 (**2i**)	2.2	 (**3ai**)	 (**4ai**)	68	85:15

[a] Reactions were carried out using 0.5 mmol of **1a**, 0.6–1.1 mmol of **2**, 0.0125 mmol of $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$, 0.05 mmol of PPh_3, and 2.0 mmol of K_2CO_3 in 1 mL of NMP at 120 °C for 20 h under N_2.
[b] Reaction for 40 h.

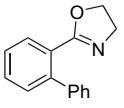
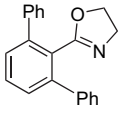
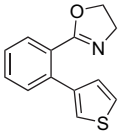
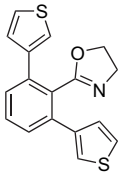
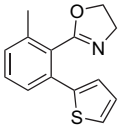
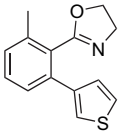
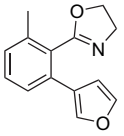
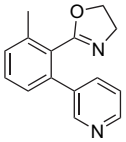
a small amount of 1:1 coupling product (entry 3). The reaction of 2-phenyl-2-oxazoline bearing a methyl group at the *ortho*-position **1c** with 2-bromothiophene (**2b**) gave the expected *ortho*-coupling product **3cb**, though the yield was moderate (31%, entry 4). On the other hand, reactions of **1c** with **2c**, **2d**, and **2f** successfully gave the corresponding 1:1 coupling products **3cc**, **3cd**, and **3cf**, respectively, in good yields (entries 5–7).

We next examined the microwave assisted reaction to shorten the reaction time. As shown in Scheme 16, the reaction

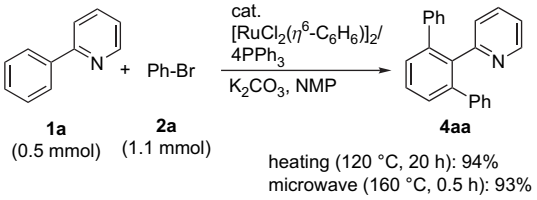
Table 2
Ruthenium-catalyzed *ortho*-arylation of 2-phenyl-2-oxazoline (**1b**) with aryl and heteroaryl bromides **2**[a]



1b (R = H) **1c** (R = Me) **2** **3** **4**

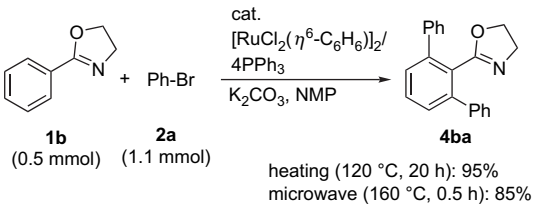
Entry	**1**	Ar–Br **2**	Equiv of **2**	Product **3**	Product **4**	Total yield (%)	Ratio (**3**/**4**)
1	**1b**	Ph–Br (**2a**)	1.2	 (**3ba**)	 (**4ba**)	60	25:75
2			2.2			95	0:100
3	**1b**	 (**2c**)	2.2	 (**3bc**)	 (**4bc**)	81	5:95
4	**1c**	 (**2b**)	2.2	 (**3cb**)	—	31	—
5	**1c**	(**2c**)	2.2	 (**3cc**)	—	88	—
6	**1c**	 (**2d**)	2.2	 (**3cd**)	—	75	—
7	**1c**	 (**2f**)	2.2	 (**3cf**)	—	83	—

[a] Reactions were carried out using 0.5 mmol of **1**, 0.6–1.1 mmol of **2**, 0.0125 mmol of $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$, 0.05 mmol of PPh_3, and 2.0 mmol of K_2CO_3 in 1 mL of NMP at 120 °C for 20 h under N_2.



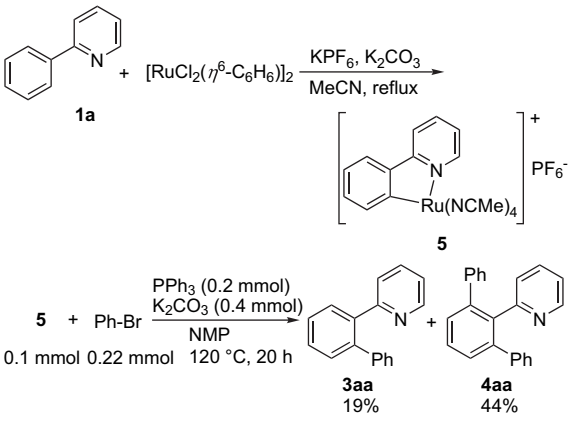
Scheme 16.

of **1a** with **2a**, under microwave irradiation at 160 °C for 30 min and otherwise identical reaction conditions, afforded **4aa** in 93% yield, which was a comparable result with the thermal reaction conditions (Table 1, entry 2). Similarly, the reaction of **1b** with **2a** under microwave irradiation at 160 °C for 30 min gave **4ba** in 85% yield (Scheme 17).



Scheme 17.

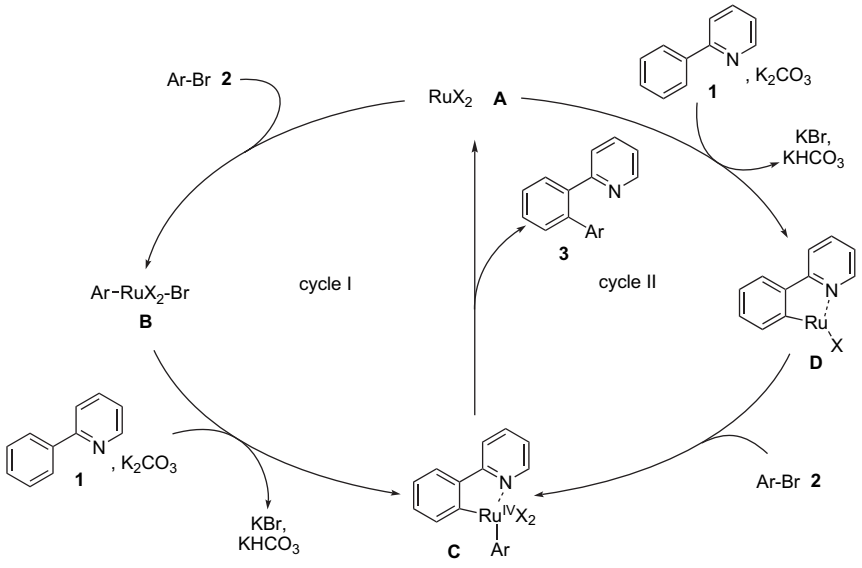
For the reaction mechanism of the present direct arylation, the following two steps are believed to play some part in the catalytic pathway: (i) oxidative addition of the aryl halide to the ruthenium complex to afford an arylruthenium intermediate; and (ii) *ortho*-ruthenation of the aromatic ring directed by coordination of the pyridine or oxazoline nitrogen to the ruthenium atom. Of the several possible reaction mechanisms, the two likely pathways are shown in Scheme 18. In cycle I, the oxidative addition of the aryl halide **2** to a suitable ruthenium(II) complex **A** generates an arylruthenium intermediate **B**. *ortho*-Ruthenation of the arylpyridine or aryloxazoline **1** with **B** gives



Scheme 19.

the corresponding ruthenacycle **C**. The coupled product **3** is then formed through reductive elimination from **C**, with the simultaneous regeneration of **A**. In cycle II, the arylpyridine or aryloxazoline **1** reacts with ruthenium(II) complex **A** to generate a ruthenacycle **D**. Subsequently, the oxidative addition of the aryl halide **2** to **D** affords ruthenacycle **C**, from which the coupled product **3** is formed through reductive elimination. To gain insight into the reaction mechanism, we prepared the ruthenacycle complex **5** by the reaction between **1a** and $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$,[22] which was then utilized as an intermediate in the stoichiometric coupling reaction with **2a** (Scheme 19). The reaction of **5** (0.1 mmol) and 2.2 equiv of **2a** in the presence of 0.2 mmol of PPh_3 and 0.4 mmol of K_2CO_3 afforded the coupling products **3aa** and **4aa** in 19 and 44% yields, respectively. These results suggest that the cycle II in Scheme 18 is the most likely mechanism in the present direct arylation reaction.

In conclusion, the ruthenium-catalyzed direct *ortho*-arylation reactions of 2-phenylpyridine and 2-aryloxazolines have been successfully expanded to the heteroarylation reactions using the heteroaryl bromides to obtain the multi-heteroaryl substituted benzenes. We also demonstrated that microwave



Scheme 18. Possible reaction mechanisms. Neutral ligands are omitted for clarity.

assisted reactions, which dramatically shorten the reaction time, gave comparable results to the thermal reactions. Finally, we proposed the reaction mechanism involving Ru^{II}/Ru^{IV} intermediates from the results of the stoichiometric reaction of the divalent ruthenacycle complex **5** with bromobenzene.

3. Experimental section

3.1. General comments

All reactions were performed in Schlenk tubes under a N_2 atmosphere. Anhydrous NMP was purchased and used as received. K_2CO_3 was dried at 250 °C under reduced pressure and stored under N_2. Flash chromatography was performed using spherical silica gel (40–100 μm, Kanto Chemical). Microwave reactions were performed on a Biotage Initiator. Infrared (IR) spectra were recorded on a JASCO FT/IR-350 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a Bruker DRX-500, DPX-400, or AC-250 spectrometer. High resolution mass spectra (HRMS) were obtained on a Bruker Apex III.

3.2. General procedure for the direct coupling reaction

A mixture of **1** (0.5 mmol), **2** (1.1 mmol), K_2CO_3 (277.2 mg, 2.0 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) in 1 mL of dried NMP was stirred at 120 °C for 20 h. The reaction mixture was diluted with 30 mL of AcOEt and precipitate was filtered off. After the solvent was removed under reduced pressure, the residue was purified by silica gel flash chromatography (CH_2Cl_2/AcOEt) to give the products **3** and **4**. Analytical and spectral data for **3aa**, **4aa**, **3ag**, **4ag**,[20a] **3ba**, and **4ba**[20c] have been previously reported.

3.2.1. Compound *3ab*

Colorless oil. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 8.68–8.64 (m, 1H), 7.62–7.47 (m, 3H), 7.45–7.40 (m, 2H), 7.22–7.15 (m, 2H), 7.11(d, *J*=7.8 Hz, 1H), 6.89–6.85 (m, 1H), 6.69 (d, *J*=3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 159.02, 149.25, 142.71, 139.571, 135.57, 132.97, 130.63, 130.45, 128.48, 127.96, 127.02, 126.93, 125.63, 127.93, 121.77. IR (neat): 3062, 1585, 1464, 1425, 1260, 1022, 848, 755, 700 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{11}NSNa$ ($M+Na^+$) 260.0504; found 260.0504.

3.2.2. Compound *4ab*

White solid. Mp 189.6–192.0 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.56 (ddd, *J*=5.0, 1.8, 1.0 Hz, 1H), 7.58 (dd, *J*=7.9, 0.8 Hz, 2H), 7.50 (td, *J*=7.7, 1.8 Hz, 1H), 7.46 (dd, *J*=7.7, 5.0 Hz, 1H) 7.13–7.18 (m, 3H), 7.09 (dt, *J*=7.7, 1.0 Hz, 1H), 6.83 (dd, *J*=5.0, 3.5 Hz, 2H), 6.60 (dd, *J*=3.5, 1.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 158.5, 148.9, 142.6, 138.4, 135.8, 134.6, 130.0, 128.4, 127.2, 126.7, 126.2, 125.8, 122.2. IR (KBr): 3057, 1581, 1415, 1252, 1145, 1019, 850, 800, 753, 709 cm^{-1}. HRMS (ESI): calcd for $C_{19}H_{14}NS_2$ ($M+H^+$) 320.0562; found 320.0561.

3.2.3. Compound *4ac*

White solid. Mp 160.7–162.1 °C. ^1H NMR ($CDCl_3$, 250 MHz): δ (ppm) 8.46 (d, *J*=4.8 Hz, 1H), 7.45–7.50 (m, 3H), 7.42 (td, *J*=7.7, 1.5 Hz, 1H), 7.01–7.10 (m, 3H), 6.96 (d, *J*=7.7 Hz, 1H), 6.90 (dd, *J*=2.9, 1.2 Hz, 2H), 6.69 (dd, *J*=5.0, 1.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) 159.2, 148.7, 141.6, 138.2, 136.5, 135.4, 129.0, 128.9, 128.3, 126.0, 124.3, 123.1, 121.5. IR (KBr): 3057, 1582, 1418, 1144, 1084, 870, 835, 779, 696, 650 cm^{-1}. HRMS (ESI): calcd for $C_{19}H_{14}NS_2$ ($M+H^+$) 320.0562; found 320.0562.

3.2.4. Compound *4ad*

Pale yellow solid. Mp 165.1–166.8 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.63 (ddd, *J*=4.9, 1.8, 0.9 Hz, 1H), 7.55 (td, *J*=7.5, 1.8 Hz, 1H), 7.42–7.43 (m, 3H), 7.20 (ddd, *J*=7.5, 4.9, 1.8 Hz, 1H), 7.19 (t, *J*=1.7 Hz, 2H), 7.09 (dt, *J*=7.5, 0.9 Hz, 1H), 6.92 (dd, *J*=1.5, 0.9 Hz, 2H), 6.07 (dd, *J*=1.8, 0.9 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 159.43, 148.89, 142.05, 140.08, 137.78, 136.08, 132.40, 128.47, 128.04, 125.67, 125.27, 122.23. IR (KBr): 3122, 1583, 1505, 1417, 1353, 1228, 1159, 1067, 1019, 967, 872, 784, 727, 596 cm^{-1}. HRMS (ESI): calcd for $C_{19}H_{14}NO_2$ ($M+H^+$) 288.1019; found 288.1018.

3.2.5. Compound *3ae*

Colorless oil. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 8.64 (ddd, *J*=4.9, 1.8, 0.9 Hz, 1H), 7.88 (ddd, *J*=7.0, 1.6, 0.7 Hz, 1H), 7.75 (d, *J*=3.2 Hz, 1H), 7.61 (td, *J*=7.5, 1.8 Hz, 1H), 7.59 (ddd, *J*=7.0, 1.6, 0.7 Hz, 1H), 7.54 (td, *J*=7.0, 1.6 Hz, 1H), 7.51 (td, *J*=7.0, 1.6 Hz, 1H), 7.26 (d, *J*=3.2 Hz, 1H), 7.25–7.21 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 167.15, 158.63, 149.49, 142.65, 140.16, 135.96, 132.45, 130.47, 130.23, 129.59, 128.63, 124.92, 122.19, 120.43. IR (neat): 3071, 1585, 1466, 1426, 1263, 1147, 1058, 972, 876, 763 cm^{-1}. HRMS (ESI): calcd for $C_{14}H_{11}N_2S$ ($M+H^+$) 239.0637; found 239.0636.

3.2.6. Compound *3af*

White solid. Mp 104.2–105.0 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 8.60 (ddd, *J*=4.8, 1.6, 0.9, 1H), 8.46 (dd, *J*=4.8, 0.9 Hz, 1H), 8.44 (d, *J*=1.6 Hz, 1H), 7.70 (m, 1H), 7.52 (m, 2H), 7.46 (td, *J*=7.8, 1.6, 1H), 7.44 (m, 2H), 7.16 (ddd, *J*=7.8, 4.8, 0.9, 1H), 7.13 (ddd, *J*=7.8, 4.8, 0.9 Hz, 1H), 6.96 (ddd, *J*=7.8, 1.6, 0.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 158.56, 150.12, 149.54, 147.80, 139.79, 136.94, 136.81, 136.74, 135.61, 130.59, 130.42, 128.73, 128.36, 125.10, 122.78, 121.64. IR (KBr): 3021, 1584, 1469, 1406, 1022, 994, 798, 758, 713, 622, 523 cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{12}N_2Na$ ($M+Na^+$) 255.0893; found 255.0892.

3.2.7. Compound *4af*

Pale yellow solid. Mp 175.2–177.2 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 8.40 (m, 4H), 8.36 (ddd, *J*=4.8, 1.8, 0.9 Hz, 1H), 7.61 (t, *J*=7.6 Hz, 1H), 7.50 (d, *J*=7.5 Hz, 1H), 7.41 (dt, *J*=8.3, 1.8 Hz, 2H), 7.36 (td, *J*=7.6, 1.8 Hz, 1H),

7.10 (m, 2H), 6.98 (ddd, J=7.6, 4.8, 0.9 Hz, 1H), 6.87 (d, J=7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 157.50, 149.99, 148.96, 147.72, 139.06, 138.45, 136.83, 136.66, 135.52, 130.14, 128.75, 126.73, 122.60, 121.69. IR (KBr): 3047, 1582, 1394, 1190, 1024, 795, 759, 716, 618 cm^{-1}. HRMS (ESI): calcd for $C_{21}H_{16}N_3$ ($M+H^+$) 310.1339; found 310.1338.

3.2.8. Compound ***3ah***

White solid. Mp 121.8–122.9 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 8.62 (d, J=4.8 Hz, 1H), 8.44 (ddd, J=4.8, 1.6, 0.9 Hz, 1H), 7.91 (ddd, J=6.7, 2.2, 1.3 Hz, 1H), 7.66 (ddd, J=6.7, 2.2, 1.3 Hz, 1H), 7.58 (td, J=7.8, 1.6 Hz, 1H), 7.56 (td, J=6.7, 1.2 Hz, 1H), 7.54 (td, J=6.7, 1.2 Hz, 1H), 7.25 (m, 1H), 7.12 (ddd, J=7.8, 1.6, 0.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 167.73, 159.55, 156.65, 148.93, 140.57, 138.40, 135.81, 130.70, 130.31, 129.43, 128.44, 123.73, 121.28. IR (KBr): 3049, 1558, 1470, 1413, 1161, 091, 1022, 992, 799, 992, 799, 755, 627, 540 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{12}N_3$ ($M+H^+$) 234.1026; found 234.1025.

3.2.9. Compound ***3ai***

Pale yellow solid. Mp 69–72 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 9.07 (d, J=0.8 Hz, 1H), 8.54–8.56 (m, 1H), 8.52 (d, J=0.8 Hz, 2H), 7.68–7.71 (m, 1H), 7.55–7.62 (m, 3H), 7.43–7.46 (m, 1H), 7.18 (ddd, J=7.6, 5.0, 1.0 Hz, 1H), 7.12 (ddd, J=7.6, 1.8, 1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 158.1, 156.7, 149.7, 140.0, 136.2, 135.1, 133.3, 130.8, 130.4, 129.2, 129.0, 124.8, 122.1. IR (KBr) 3023, 1586, 1549, 1406, 1188, 994, 759, 727, 630, 542 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{12}N_3$ ($M+H^+$) 234.1026; found 234.1025.

3.2.10. Compound ***4ai***

Pale yellow solid. Mp 179.5–180.4 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) 9.03 (s, 2H), 8.50 (s, 4H), 8.44 (m, 1H), 7.71 (t, J=7.6 Hz, 1H), 7.56 (d, J=7.6 Hz, 2H), 7.45 (td, J=7.6, 1.5 Hz, 1H), 7.10 (ddd, J=7.6, 4.8 Hz, 1H), 6.90 (d, J=7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) 156.9, 156.5, 156.2, 149.5, 139.4, 136.1, 135.2, 134.4, 130.7, 129.4, 126.5, 122.5. IR (KBr): 2925, 1583, 1553, 1405, 1259, 1188, 1039, 912, 797, 757, 729, 633 cm^{-1}. HRMS (ESI): calcd for $C_{19}H_{14}N_5$ ($M+H^+$) 312.1244; found 312.1245.

3.2.11. Compound ***3bc***

Pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.69 (dd, J=7.4, 1.5 Hz, 1H), 7.47 (td, J=7.4, 1.5 Hz, 1H), 7.44 (dd, J=7.4, 1.5 Hz, 1H), 7.30–7.33 (m, 2H), 7.16 (dd, J=4.7, 1.5 Hz, 2H), 4.22 (t, J=9.3 Hz, 2H), 3.97 (t, J=9.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.1, 141.6, 136.4, 130.6, 130.1, 128.3, 127.7, 127.2, 125.0, 122.2, 67.9, 55.2. IR (neat): 3020, 1584, 1469, 1406, 994, 798, 759, 715, 622, 524 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{11}NOSNa$ ($M+Na^+$) 252.0454; found 252.0453.

3.2.12. Compound ***4bc***

White solid. Mp was not clear. ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) 7.35–7.52 (m, 5H), 7.32 (dd, J=5.0, 3.2 Hz, 2H), 7.22 (dd, J=5.0, 1.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) 164.0, 140.9, 137.0, 129.6, 128.5, 128.3, 127.1, 125.0, 122.7, 67.3, 55.1. IR (KBr) 3086, 1657, 1581, 1461, 1363, 1245, 1100, 1040, 974, 935, 782 cm^{-1}. HRMS (ESI): calcd for $C_{17}H_{14}NOS_2$ ($M+H^+$) 312.0511; found 312.0510.

3.2.13. Compound ***3cb***

Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.35 (dd, J=7.3, 1.6 Hz, 1H), 7.32 (t, J=7.3 Hz, 1H), 7.30 (dd, J=5.0, 1.3 Hz, 1H), 7.20 (dd, J=7.5, 1.5 Hz, 1H), 7.15 (dd, J=3.4, 1.3 Hz, 1H), 7.03 (dd, J=5.0, 3.4 Hz, 1H), 4.28 (t, J=9.6 Hz, 2H), 3.99 (t, J=9.6 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 164.12, 142.25, 137.74, 134.22, 129.52, 129.33, 128.00, 127.43, 127.12, 125.99, 125.72, 67.33, 55.17, 19.70. IR (neat): 2964, 1661, 1445, 1342, 1239, 1049, 935, 787, 710 cm^{-1} HRMS (ESI): calcd for $C_{14}H_{14}NOS$ ($M+H^+$) 224.0791; found 224.0790.

3.2.14. Compound ***3cc***

White solid. Mp 74.3–74.8 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.34–7.29 (m, 3H), 7.28–7.24 (m, 1H), 7.21–7.17 (m, 2H), 4.22 (t, J=9.5 Hz, 2H), 3.94 (t, J=9.5 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 164.45, 141.29, 137.46, 136.38, 129.44, 128.87, 128.14, 127.92, 126.80, 124.99, 122.20, 67.24, 55.10, 19.66. IR (KBr): 3089, 1662, 1465, 1244, 1245, 1041, 974, 935, 779 cm^{-1}. HRMS (ESI): calcd for $C_{14}H_{14}NOS$ ($M+H^+$) 224.0791; found 224.0790.

3.2.15. Compound ***3cd***

Pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.57 (dd, J=1.5, 0.9 Hz, 1H), 7.42 (dd, J=1.8, 1.5 Hz, 1H), 7.31 (t, J=8.0 Hz, 1H), 7.23 (d, J=8.0 Hz, 1H), 7.16 (d, J=8.0 Hz, 1H), 6.55 (dd, J=1.8, 0.9 Hz, 1H), 4.31 (t, J=9.5 Hz, 2H), 4.02 (t, J=9.5 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 164.50, 142.66, 139.60, 137.53, 132.31, 129.56, 128.74, 127.75, 126.36, 125.08, 110.79, 67.27, 55.11, 19.56. IR (neat): 2970, 1665, 1350, 1247, 1164, 1044, 973, 874, 784 cm^{-1}. HRMS (ESI): calcd for $C_{14}H_{14}$ NO_2 ($M+H^+$): 228.1019; found 228.1018.

3.2.16. Compound ***3cf***

Pale yellow solid. Mp 89.4–90.3 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 8.66 (dd, J=2.0, 0.8 Hz, 1H), 8.56 (dd, J=4.9, 2.0 Hz, 1H), 7.73 (dt, J=7.8, 2.0 Hz, 1H), 7.39 (t, J=7.8 Hz, 1H), 7.31 (ddd, J=7.8, 4.9, 0.8 Hz, 1H), 7.28 (d, J=7.8 Hz, 1H), 7.21 (d, J=7.8 Hz, 1H), 4.17 (t, J=9.7 Hz, 2H), 3.88 (t, J=9.7 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 163.89, 149.05, 148.29, 138.21, 137.85, 136.68, 135.59, 129.74, 129.67, 128.26, 127.13, 122.81, 67.17, 55.03, 19.74. IR (KBr): 2965, 1665, 1464, 1346, 1244, 1043, 936, 788, 702, 496 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{15}N_2O$ ($M+H^+$) 239.1179; found 239.1178.

3.3. Synthesis of ruthenacycle complex 5[22]

A mixture of 2-phenylpyridine (**1a**, 327.9 mg, 2.11 mmol), $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ (535.7 mg, 1.07 mmol), KPF_6 (1.459 g, 7.93 mmol), and K_2CO_3 (528.3 mg, 3.82 mmol) in acetonitrile (4.0 mL) was refluxed for 12 h under a N_2 atmosphere. After cooling, acetonitrile (4.0 mL) was added to the reaction mixture and precipitate was filtered off. Solvent was removed in vacuo and the residue was purified by alumina column chromatography (CH_2Cl_2/acetonitrile=10:1) to give ruthenacycle complex **5** (1.138 g, 2.01 mmol, 95%) as yellow powder. ^1H NMR (CD_3CN, 500 MHz): δ (ppm) 8.91 (ddd, J=5.7, 1.6, 0.9 Hz, 1H), 7.96 (dd, J=7.5, 1.0 Hz, 1H), 7.87 (m, 1H), 7.74 (ddd, J=7.2, 5.7, 1.6 Hz, 1H), 7.71 (m, 1H), 7.15 (td, J=7.5, 1.0 Hz, 1H), 7.08 (td, J=7.5, 1.0 Hz, 1H), 6.94 (td, J=7.4, 0.9 Hz, 1H), 2.51 (s, 3H), 2.15 (s, 3H), 2.00 (s, 6H). HRMS (ESI): calcd for $C_{17}H_{17}N_4Ru$ ($[M-MeCN-PF_6^-]^+$) 379.0491; found 379.0492.

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