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Ruthenium-catalyzed direct arylation of C–H bonds in aromatic amides containing a bidentate directing group: significant electronic effects on arylation†

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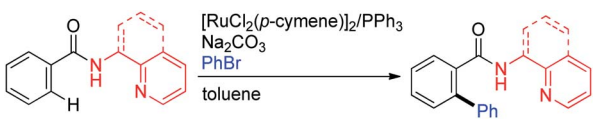
Arylation of *ortho* C–H bonds is achieved by a ruthenium-catalyzed reaction of aromatic amides having an 8-aminoquinoline moiety with aryl bromides. The reaction shows high functional group compatibility. The reaction proceeds in a highly selective manner at the less hindered C–H bonds of *meta*-substituted aromatic amides. Significant electronic effects are observed in Hammett plots. Electron-withdrawing groups on the aromatic amides facilitate the reaction. In contrast, both electron-donating groups and electron-withdrawing groups on aryl bromides accelerate the reaction.

Introduction

The formation of aryl–aryl bonds is a useful synthetic reaction, considering the fact that biaryl derivatives are important synthetic targets, such as natural products, pharmaceuticals, agrochemicals, and conjugated materials.[1] The most commonly used method for aryl–aryl bond formation involves the transition metal-catalyzed cross coupling of aryl halides with aryl metal reagents, especially organoboron reagents, a reaction that is referred to as Suzuki–Miyaura cross-coupling.[2] The direct introduction of aryl groups in conjunction with the cleavage of C–H bonds has been extensively studied as an alternative strategy for the construction of biaryl derivatives.[3] While a variety of transition metal complexes can be used in the arylation of C–H bonds, palladium or nickel catalysts are the most reliable species. Oi *et al*. reported the first example of the Ru(II)-catalyzed arylation of C–H bonds, in which 2-phenylpyridine derivatives reacted with aryl bromides to result in arylation at the *ortho* position.[4a] Later, Ackermann, Dixneuf, Bruneau, and others made some significant contributions to this field.[5,6] Various nitrogen-containing directing groups such as *N*-heterocycles and imines are applicable to the Ru(II)-catalyzed arylation reactions.[4–6] However, the Ru(II)-catalyzed arylation of C–H bonds still remains at an early stage compared with the extensively studied Pd-catalyzed C–H bond arylation reactions.[7] Expanding the scope to include other types of substrates continues to remain a critical challenge. Furthermore, the reaction mechanism for Ru(II)-catalyzed arylation has not been elucidated and even the electronic effects of substituents on the efficiency of the reactions have not been examined in detail.[5e,g,6a,i]

Chelation-assisted transformation is now one of the viable methods for transforming *ortho* C–H bonds. A wide variety of directing groups has been evaluated to date, but in most cases, structurally simple monodentate directing groups have been used. If a bidentate directing group could be used in the transformation of C–H bonds, it would open new avenues for applications and for the development of new reactions, which cannot currently be achieved using the conventional simple directing groups. The use of 8-aminoquinoline or picolinamides as an *N*,*N*-bidentate directing group was reported in a pioneering study by Daugulis *et al*. who discovered the Pd(II)-catalyzed arylation of C–H bonds.[8] Since this pioneering example appeared in the literature, a number of reactions utilizing an *N*,*N*-bidentate directing-assisted transformation of C–H bonds have been developed, especially in the case of Pd(II)-catalyzed reactions.[9] In sharp contrast, bidentate directing systems of other transition metal-catalyzed transformations of C–H bonds are quite rare. We recently reported the Ru(0)-catalyzed C–H bond carbonylation of aromatic and aliphatic amides with a 2-pyridinylmethylamine moiety as the bidentate directing group[10] and the Ni(0)-catalyzed oxidative annulation of aromatic amides with alkynes leading to isoquinolones.[11] We wish to report on the Ru(II)-catalyzed *ortho*-arylation of aromatic amides with a bidentate directing group and some interesting electronic effects on the efficiency of the arylation (eqn (1)).



(1)

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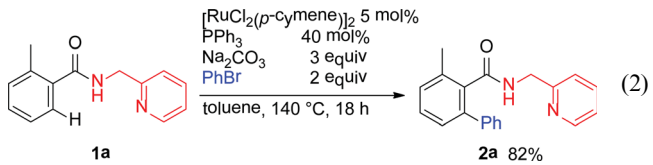
Results and discussion

Initial studies

The reaction of amide **1a** (0.3 mmol) with PhBr (0.4 mmol) in the presence of $[RuCl_2(p\text{-cymene})]_2/PPh_3$ as the catalyst and Na_2CO_3 as a base in toluene at 140 °C for 18 h gave the *ortho*-phenylation product **2a** in 46% NMR yield, along with 33% of recovered **1a** (eqn (2)). The use of 2 equivalents of PhBr improved the product yield to 86% NMR yield (82% isolated yield), with **1a** being recovered in 3%. Product yield was significantly affected by the nature of base used: Li_2CO_3 0%, K_2CO_3 75%, Cs_2CO_3 19%, NaOAc 38%, KOAc 16%, CsOAc 7%, 2,6-lutidine 0%. In most Ru-catalyzed arylation reactions of C–H bonds reported to date,[4–6] *N*-methylpyrrolidinone (NMP) was the solvent of choice. Contrary to these previous examples, when NMP was used in place of toluene, **2a** was produced in only 25% yield. Although carboxylic acids were well used as a co-catalyst in the Ru(II)-catalyzed arylation reaction,[2–6] the addition of a carboxylic acid, such as 1-adamantancarboxylic acid or $MesCO_2H$ did not result in the formation of **2a**. The addition of PPh_3 was significantly important. No reaction took place when the reaction was carried out in the absence of PPh_3. The use of PCy_3 gave **2a** only in 38% yield. The efficiency of the reaction was not affected by the nature of the catalyst. Among the Ru(II) catalysts examined, $RuCl_2(PPh_3)_3$ (81%) and $Ru(OAc)_2(p\text{-cymene})$ (85%) were found to be as equally effective as $[RuCl_2(p\text{-cymene})]_2$.



(2)

We next examined the effect of a directing group. No reaction occurred when the corresponding *N*-benzyl benzamide (**3**, Fig. 1) and 2-pyridynylmethyl ester **4** were used as the substrate in place of **1a**, indicating that coordination in an *N*,*N*′-fashion by the 2-pyridinylmethylamine moiety is essential for the reaction to proceed. Furthermore, the use of *N*-methyl amide **5** did not provide the phenylation product, indicating that the presence of a proton on the amide nitrogen is important for the reaction to proceed, although NH is not included in the product formation at first sight. Amides having longer carbon chains, such as **6**, did not give the corresponding coupling product. However, it was found that 2-methyl-*N*-(quinolin-8-yl)benzamide (**7a**) was also a good substrate and that **7a** was more reactive than **1a**. A

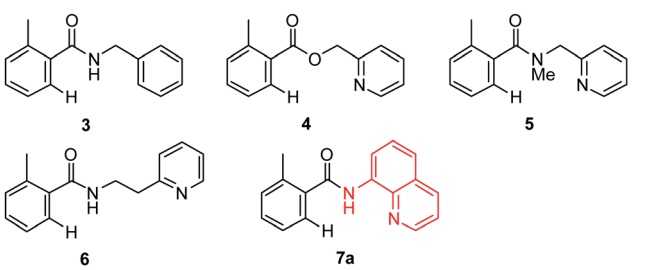
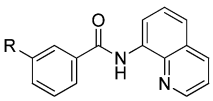
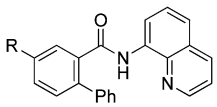
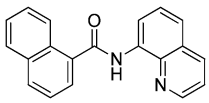
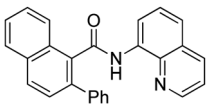
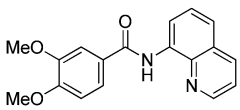
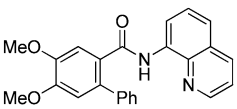
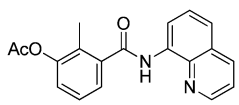
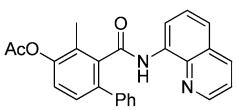
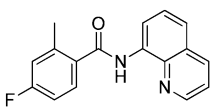
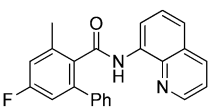
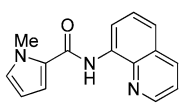
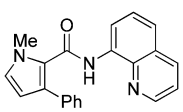
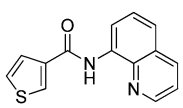
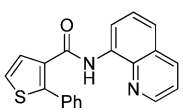
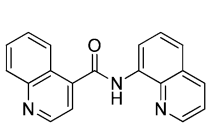
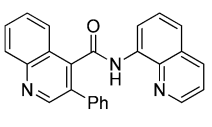


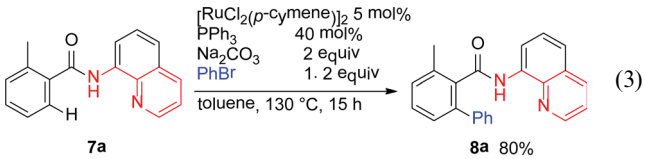
Fig. 1 Directing groups for phenylation of C–H bonds.

Table 1 Substrate scope with phenyl bromide[a]

Amide	Product[b]
 R = NMe_2 (**7b**), $OSiMe_2Bu^t$ (**7c**), Me (**7d**), Ph (**7e**), CF_3 (**7f**)	 **8b** 65%[c,d] **8c** 75%[c] **8d** 74% **8e** 88% **8f** 76%
	 **9** 80%
	 **10** 75%
	 **11** 88%[c,e]
	 **12** 84%
	 **13** 43%[c,f]
	 **14** 63%[c,f,g]
	 **15** 86%[c,e]

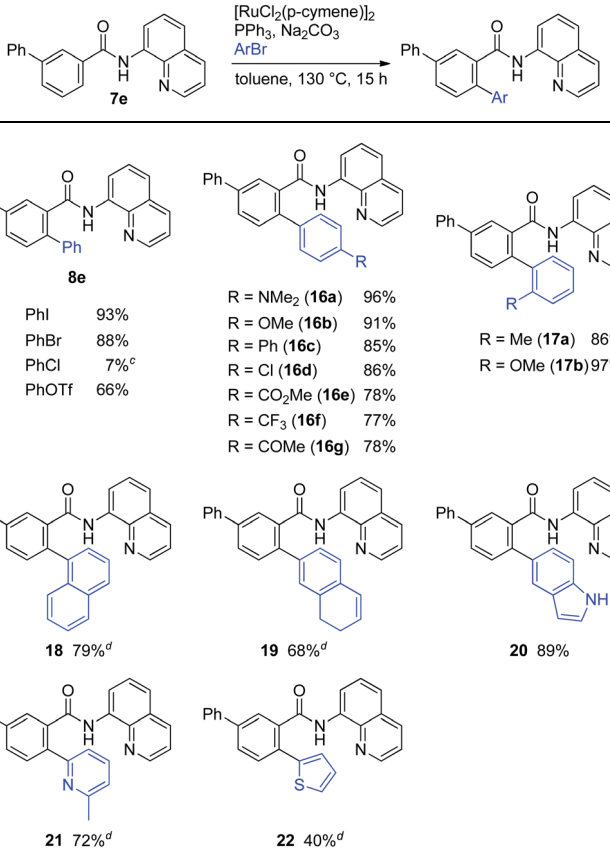
[a] Reaction conditions: amide (0.3 mmol), PhBr (0.36 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.015 mmol), PPh_3 (0.12 mmol), Na_2CO_3 (0.6 mmol) in toluene (2 mL) at 130 °C for 15 h. [b] Isolated yields. [c] $Ru(OAc)_2(p\text{-cymene})$ (0.03 mmol) as the catalyst. [d] Run at 140 °C for 36 h. [e] Run at 140 °C for 24 h. [f] For 24 h. [g] The bisphenylation product was formed in 12% yield.

considerably higher yield of the phenylation product **8a** was obtained when less PhBr (1.2 equivalents) was used at a lower reaction temperature of 130 °C for shorter reaction time (15 h). Similar to the reaction of **1a**, the choice of base was important: $Na_2CO_3 > K_2CO_3 \gg Cs_2CO_3$. The addition of PPh_3 was again significantly important. No reaction took place when the reaction was carried out in the absence of PPh_3. The following conditions were finally selected as standard reaction conditions: the reaction of amide **7a** (0.3 mmol) with PhBr (0.36 mmol) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (0.015 mmol), PPh_3 (0.12 mmol), Na_2CO_3 (0.6 mmol) in toluene (2 mL) at 130 °C for 15 h gave **8a** in 80% isolated yield (eqn (3)).



(3)

Table 2 Scope of aryl halides[a,b]



[a] Reaction conditions: amide **7e** (0.3 mmol), ArBr (0.36 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.015 mmol), PPh_3 (0.12 mmol), Na_2CO_3 (0.6 mmol) in toluene (2 mL) at 130 °C for 15 h. [b] Yields are isolated yields based on **7e**. [c] NMR yield. [d] $Ru(OAc)_2(p\text{-cymene})$ (0.03 mmol) as the catalyst at 140 °C for 24 h.

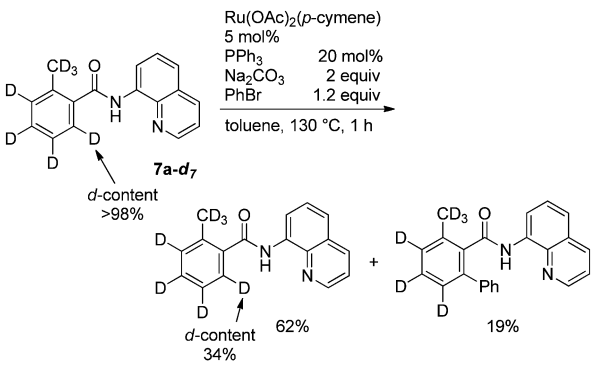
Synthetic scope

With the optimized reaction conditions in hand, we examined the scope of the reaction. Table 1 shows the results for the reaction of aromatic amides with an 8-quinolinyl group under standard reaction conditions. A variety of functional groups were tolerated in the reaction and the reaction proceeded in a highly regioselective manner. The reaction of *meta*-substituted substrates resulted in the selective phenylation at the less hindered C–H bonds, irrespective of the electronic nature of the substituent, indicating that the regioselectivity was controlled by the steric nature of the substituent groups.

A variety of aryl bromides or iodides were applicable to the arylation reaction, as shown in Table 2, however when phenyl chloride was used, **8e** was produced in only a low yield. Various functional groups, such as dimethylamino, methoxy, chloro, ester, trifluoromethyl, and ketone groups, were tolerated in the reaction. Electron-rich aryl bromides gave higher yields than electron-poor aryl bromides. Various heteroaromatic bromides also participated in the present arylation reaction of C–H bonds as coupling partners.

Mechanistic aspects

To investigate the mechanism for the reaction, the deuterated amide **7a-*d*$_7$** was reacted for 1 h under otherwise standard reaction conditions (eqn (4)). We observed a significant amount of H/D exchange between at the *ortho* position (the *d*-content dropped from >98% to 34%) and on the nitrogen in the recovered amide. Even for a shorter reaction time of 0.5 h in the absence of PhBr, a significant amount of H/D exchange again occurred at the *ortho* position (the *d*-content dropped from >98% to 30%) and on the nitrogen (eqn (5)), indicating that the cleavage of C–H bonds is reversible and very rapid. This result indicates that the cleavage of C–H bonds is likely not the rate determining step. It was also found that PPh_3 accelerates the cleavage of C–H bonds. When the reaction was run in the absence of PPh_3 (eqn (5)), H/D exchange occurred at only 11% (89% *d*-content) at the *ortho* position.



(4)

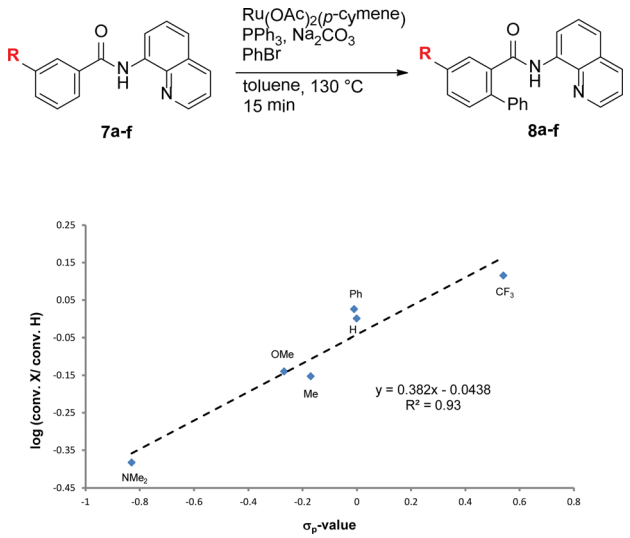
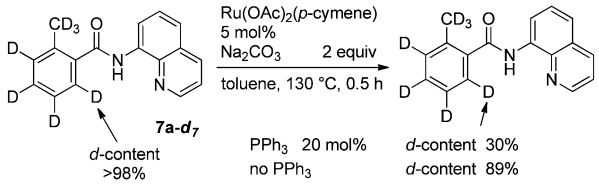


Fig. 2 Hammett plot of *m*-R-C_6H_4CONHQ (Q = 8-quinolinyl) **7a–f** with PhBr.



(5)

To probe the electronic effects on the arylation, the reaction of an electronically different set of *meta*-substituted aromatic amides **7a–f** with PhBr was carried out (see Table S1 in ESI†). A Hammett plot was constructed from the correlation for the conversion of **7a–f** with σ_p for *meta*-substituted aromatic amides (Fig. 2). The plot resulted in a linear fit with a positive slope of $\rho = 0.38$, indicating that electron-withdrawing groups clearly facilitate the reaction.

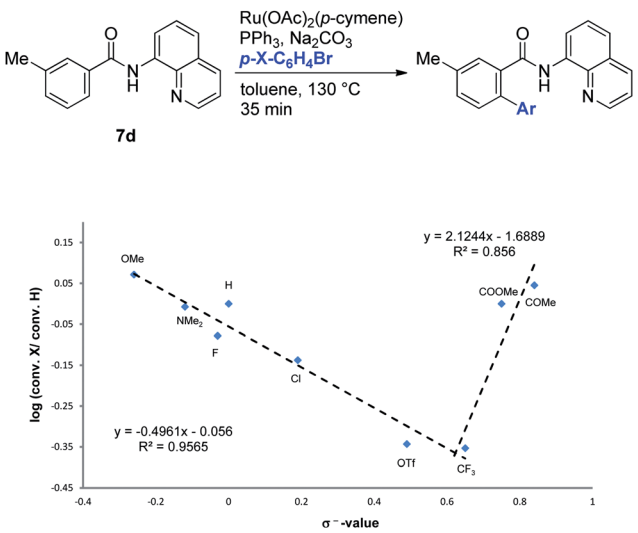
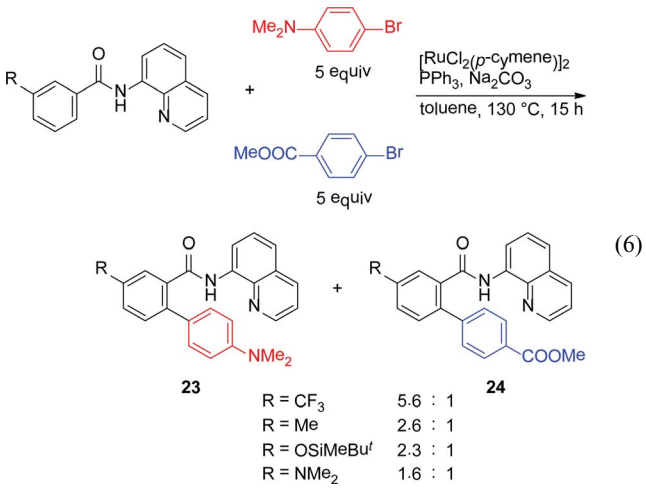


Fig. 3 Hammett plot of **7d** with *p*-X-C_6H_4Br.

We next carried out the reaction of **7d** with an electronically different set of *para*-substituted aryl bromides (see Table S2 in ESI†). We observed a V-shaped Hammett plot,[12] as shown in Fig. 3. The Hammett plot shows two segments and the two ρ values for the two segments are −0.5 and +2.1, respectively. This result suggests that the mechanism or rate-determining step for the reaction changes, depending on the nature of the substituents on the aryl bromides.

To collect additional information on the reaction mechanism, competition experiments using 4-dimethylaminophenyl bromide and methyl 4-bromobenzoate, both of which are highly active substrates, as shown in Fig. 3, were carried out. It was observed that **23** gave higher yields than **24**, irrespective of the electronic nature of the substituent at the *meta* position of the aromatic amide (eqn (6), Fig. 4). However, the ratio of **23** and **24** decreased to close to 1 : 1 when the electron-donating nature of the substituents became stronger. These results suggest that the electronic nature of a substituent in the aromatic amide is a dominant factor.



(6)

We next performed competition experiments of a mixture of **7f** and **7c** with three different aryl bromides (eqn (7)). As shown in Fig. 3, Me_2N- and MeO_2C-substituted aryl bromides are highly reactive, but CF_3-substituted aryl bromide is less reactive.[13] However, only **7f** reacted to give **25**, **27**, or **29** in the competition experiments, irrespective of electronic nature of

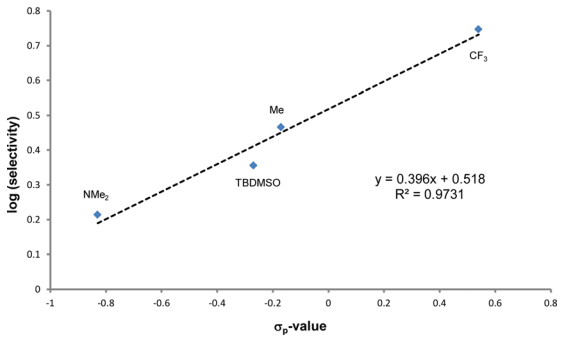
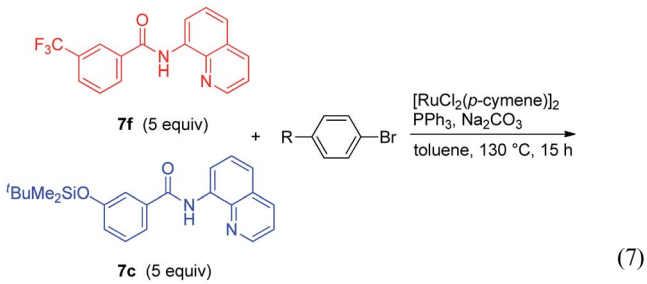


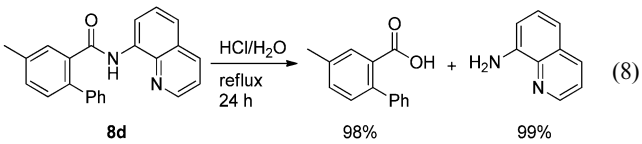
Fig. 4 Hammett plot for eqn (6).

the substituent on the aryl bromide. These results again suggest that the electronic nature of the substituent in the aromatic amide is a dominant factor.



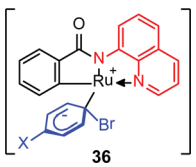
(7)

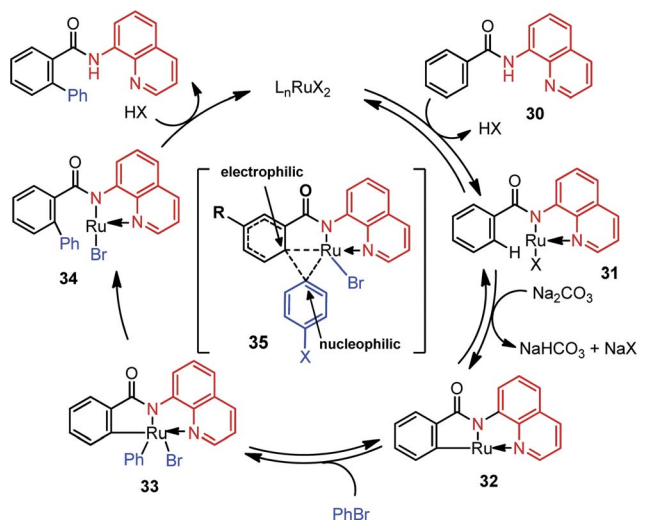
The directing group could be easily removed and recovered by hydrolysis under acidic conditions (eqn (8)).



(8)

A proposed mechanism is shown in Scheme 1. Coordination of the amide **30** to the ruthenium center followed by ligand exchange with the concomitant generation of HX gives the ruthenium complex **31**, which undergoes reversible cyclometalation to give the complex **32** probably *via* a concerted metalation–deprotonation (CMD) mechanism.[14] The oxidative addition of PhBr followed by reductive elimination gives **34**, which undergoes protonation to afford the phenylation product with the regeneration of ruthenium(II). As shown in eqn (2), the cleavage of C–H bonds is a reversible and rapid step, and is not the rate determining step. The Hammett plots shown in Fig. 2 and the region on the left in Fig. 3 suggest that the reductive elimination is the rate-determining step and it proceeds through the transition state **35**, in which a developing negative charge is stabilized by the carbonyl group and the substituents.[15] If the oxidative addition of PhBr to **32** is the rate determining step, the Hammett ρ shown should be a straight line with a positive slope in Fig. 3 because electron-deficient aryl bromides accelerate the oxidative addition. However, a V-shaped Hammett plot was observed in Fig. 3, suggesting that the rate determining step changes depending on the substituent on the aryl bromide. These collective results suggest that the reaction is dominantly affected by the electronic nature of the substituent R in the aromatic amides. However, the reaction is also accelerated by the electron-withdrawing nature of the substituent X in the aryl bromides. This suggests that the oxidative addition proceeds through a nucleophilic substitution mechanism as in **36**. The equilibrium position can be shifted to **33** from **32** by the electron-withdrawing groups, such as an ester and a ketone functional group on the ArBr.





Scheme 1 A proposed mechanism.

Conclusions

We report on the Ru(II)-catalyzed arylation of *ortho* C(sp^2)–H bonds in aromatic amides, in which the presence of a bidentate directing group, such as 2-pyridynylmethylamino or 8-aminoquiloline is essential for the arylation to proceed. The reaction proceeds in a highly selective manner at the less hindered C–H bonds of *meta*-substituted aromatic amides. Contrary to most Ru-catalyzed *ortho*-arylations, in which NMP is a solvent of choice, a common solvent, such as toluene gave the best results in the present system. Although the mechanism is not currently completely understood, dramatically different slopes were obtained in Hammett plots. The elucidation of the mechanism for the reaction is the subject of current investigations.[16,17]

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