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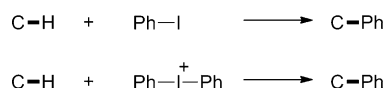
# Ruthenium(II)-Catalyzed Chelation-Assisted Arylation of C–H Bonds with Diaryliodonium Salts

Jordan Sun Ho,<sup>[a]</sup> Luis C. Misal Castro,<sup>[a]</sup> Yoshinori Aihara,<sup>[a]</sup> Mamoru Tobisu,<sup>[a, b]</sup> and Naoto Chatani<sup>\*[a]</sup>

**Abstract:** Chelation-assisted arylation of the *ortho* C–H bonds in 2-arylpyridine derivatives was achieved by using [Ru(OAc)<sub>2</sub>(*p*-cymene)] as the catalyst and diaryliodonium salts as the arylation reagent. The reaction can tolerate a broad range of functional groups and, in contrast to other Ru-catalyzed C–H arylation reactions with diaryliodonium salts, appears to proceed by a mechanism similar to Pd-catalyzed C–H arylation.

The arylation of C–H bonds has now emerged as a common and powerful method for the construction of biaryl derivatives, which are important synthetic targets, for preparing pharmaceuticals, agrochemicals, and conjugated materials, as an alternative method for cross-coupling reactions.<sup>[1]</sup> Various electrophiles and nucleophiles have been used in the arylation of C–H bonds for the construction of biaryl derivatives. In most cases, aryl halides, and more recently, phenol derivatives<sup>[2]</sup> have found broad utility as electrophilic arylation reagents. In 1982, Uchiyama et al. reported that diaryliodonium halides can be used as electrophiles instead of aryl halides in Pd-catalyzed alkoxy carbonylation reactions, and that the reaction proceeded under relatively mild reaction conditions.<sup>[3]</sup> Hypervalent iodine reagents have subsequently been used as electrophiles in various types of Pd-catalyzed cross-coupling reactions, such as the Suzuki–Miyaura, the Mizoroki–Heck, and the Sonogashira reactions.<sup>[4]</sup> In 2005, Sanford and co-workers reported the first successful Pd<sup>2+</sup>-catalyzed arylation of C–H bonds in 2-arylpyridine derivatives with diaryliodonium salts.<sup>[5]</sup> At the same time, Daugulis and Zaitsev also reported the Pd<sup>2+</sup>

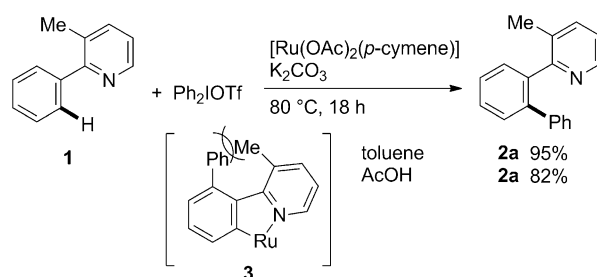
-catalyzed *ortho* phenylation of C–H bonds in anilides with Ph<sub>2</sub>IPF<sub>6</sub>.<sup>[6]</sup> Since the time when these studies appeared in the literature, the catalytic arylation of C–H bonds with diaryliodonium salts has attracted considerable attention (Scheme 1).<sup>[7–10]</sup> The most extensively used catalysts in the



Scheme 1. Phenylation of C–H bonds.

transformation of C–H bonds with diaryliodonium salts are palladium and copper complexes.<sup>[7,8]</sup> However, it is well known that other transition-metal complexes, such as those of ruthenium, rhodium, iridium, and nickel are also highly active catalysts in the catalytic functionalization of C–H bonds.<sup>[11]</sup> Herein, we report on the Ru<sup>2+</sup>-catalyzed arylation of C–H bonds in 2-arylpyridine derivatives with diaryliodonium salts.<sup>[9]</sup>

The reaction of 3-methyl-2-phenylpyridine (**1**, 0.5 mmol) with Ph<sub>2</sub>IOTf (0.6 mmol) in the presence of [Ru(OAc)<sub>2</sub>(*p*-cymene)] (0.025 mmol) as a catalyst and K<sub>2</sub>CO<sub>3</sub> (0.6 mmol) as a base in toluene at 80 °C for 18 h gave the *ortho*-phenylation product **2a** in 95% isolated yield (Scheme 2). No



Scheme 2. Ru<sup>2+</sup>-catalyzed phenylation of **1** with Ph<sub>2</sub>IOTf. Tf = trifluoromethanesulfonyl.

product was formed when the reaction was carried out at 60 °C and no double phenylation product was formed. For **2a** to be converted into the double phenylation product, it would be required to adopt a conformation in which the planes of phenyl ring and the pyridine ring are coplanar when the second C–H bond undergoes cleavage. However,

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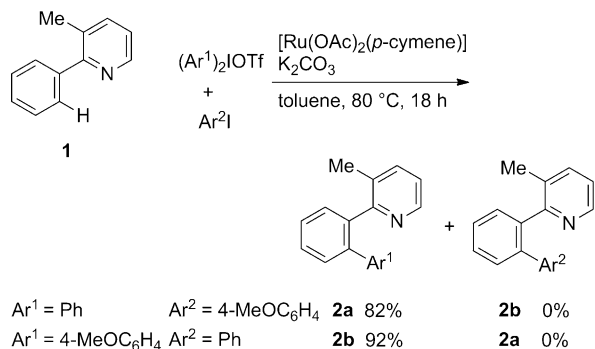
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the presence of the methyl and phenyl groups as substituents prevents the two rings from achieving such a coplanar arrangement, which would lead to **3**, because of steric congestion.<sup>[12]</sup> Other bases, such as Na<sub>2</sub>CO<sub>3</sub>, NaOAc, and KOAc also are effective. The use of AcOH as the solvent also gave **2a** in 82 % isolated yield.

[RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> is also catalytically active in this reaction to give **2a** in 74 % NMR yield; however, 13 % of **1** was recovered when toluene was used as the solvent. In contrast, use of AcOH as the solvent resulted in complete conversion to give **2a** in 83 % NMR yield, which suggests that “Ru(OAc)<sub>2</sub>” is a key catalytic species. When Pd(OAc)<sub>2</sub> was used as the catalyst under our reaction conditions in toluene, the yield dramatically decreased to 16 %, and 77 % of **1** was recovered. This result is in sharp contrast to the results reported by Sanford and co-workers, who used AcOH as the solvent in the Pd-catalyzed reaction.<sup>[5]</sup>

Oi et al. reported on the reaction of 2-arylpyridines with PhX (X = Br, I, Cl, OTf) in the presence of Ru<sup>2+</sup> complexes at 120 °C.<sup>[13]</sup> We anticipated that PhI would function as the actual phenylation reagent, which would be produced as a byproduct or as the result of the degradation of the Ph<sub>2</sub>I<sup>+</sup> salt under the reaction conditions used.<sup>[14]</sup> Actually, it was found that the reaction of **1** with PhI proceeds in toluene, even at a temperature of 80 °C to give **2a** in 61 %, which suggests the possibility that PhI also functions as the electrophile. However, the reaction with PhI in AcOH as the solvent gave no phenylation product. In sharp contrast, Ph<sub>2</sub>IOTf worked even in AcOH and **2a** was obtained in 82 % isolated yield. Furthermore, the results obtained from competition experiments between **1** and a 1:1 mixture of (Ar<sup>1</sup>)<sub>2</sub>IOTf and Ar<sup>2</sup>I indicate that aryl iodides are not the actual phenylation reagent in this reaction (Scheme 3).



Scheme 3. Competition experiments between **1** and a 1:1 mixture of (Ar<sup>1</sup>)<sub>2</sub>IOTf and Ar<sup>2</sup>I.

With the optimized reaction conditions in hand, we examined the scope of the reaction. Table 1 shows the results for reactions of some 2-arylpyridine derivatives with Ph<sub>2</sub>IOTf. The reaction of *o*-tolyl substrate **4** gave the corresponding product **5** only in 28 % yield. Some other functional groups, however, are tolerated in the reaction. In some cases, the use of AcOH resulted in a better yield in

Table 1. Ru<sup>2+</sup>-catalyzed phenylation of C–H bonds.<sup>[a]</sup>

Entry	Substrate	Product <sup>[b]</sup>
1		 <b>5</b> 28%
2		 <b>7</b> 42% (7%)
3		 <b>9</b> 69% (28%)
4		 <b>11</b> 65% (nd)
5		 <b>13</b> 36% (76%) 76% <sup>[c]</sup>

[a] Reaction conditions: arylpyridine (0.5 mmol), Ph<sub>2</sub>IOTf (0.6 mmol), toluene (2 mL), at 80 °C for 18 h. [b] Yield of isolated product. Numbers in a parenthesis are the yield of recovered starting arylpyridine. [c] AcOH was used as the solvent. nd = not determined.

the reaction of substituted 2-arylpyridines. When AcOH was used as the solvent in the reaction of **12**, the yield of **13** improved to 76 %

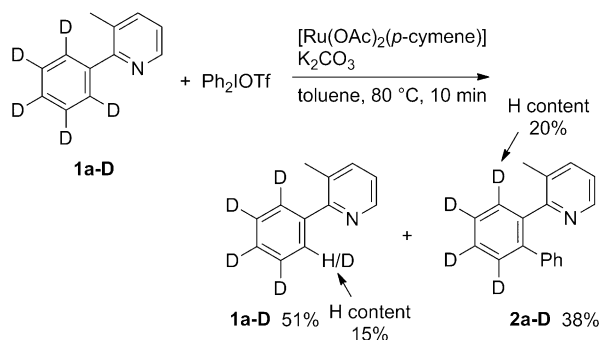
We next expanded the transformation to the transfer of a variety of aryl groups, as shown in Table 2. When mixed diaryliodonium salts were used, an electron-rich aryl group was selectively transferred to give **2a**, as in the case of (4-ClC<sub>6</sub>H<sub>4</sub>-I-Ph)OTf. However, as we anticipated, a mixture of two possible isomers was obtained when the electronic bias is small, as in the case of (4-MeC<sub>6</sub>H<sub>4</sub>-I-Ph)OTf. A sterically less demanding aryl group was transferred exclusively to give **2c** in the case of (4-MeC<sub>6</sub>H<sub>4</sub>-I-2-MeC<sub>6</sub>H<sub>4</sub>)OTf. To achieve the selective transfer, some (Ar-I-mesityl)OTf derivatives were examined.<sup>[5]</sup> As we expected, these transformations proceeded cleanly to provide a single arylated product in reasonably good to excellent isolated yield.

A deuterium labeling experiment was carried out to investigate the mechanism for the reaction, (Scheme 4). Even when the reaction was stopped after ten minutes, a proton was incorporated into the recovered substrate **1a-D**, which indicates that C–H bond cleavage is reversible and very fast.<sup>[15]</sup>

Table 2. Ruthenium-catalyzed reaction of **1a** with Ar<sup>1</sup>Ar<sup>2</sup>IOTf.<sup>[a]</sup>

Ar <sup>1</sup>	Ar <sup>2</sup>	Yield [%] <sup>[b,c]</sup>
Ph	4-ClC <sub>6</sub> H <sub>4</sub>	<b>2a</b> 64
Ph	4-MeC <sub>6</sub> H <sub>4</sub>	<b>2a</b> 27, <b>2c</b> 55
2-MeC <sub>6</sub> H <sub>4</sub>	4-MeC <sub>6</sub> H <sub>4</sub>	<b>2d</b> 0, <b>2c</b> 59
Ph	mesityl	<b>2a</b> 74
4-MeC <sub>6</sub> H <sub>4</sub>	mesityl	<b>2c</b> 95 (90)
4-EtO(O)CC <sub>6</sub> H <sub>4</sub>	mesityl	<b>2e</b> 79 (73)
4-EtO(O)CC <sub>6</sub> H <sub>4</sub>	mesityl	<b>2e</b> (71) <sup>[d]</sup>
3-EtO(O)CC <sub>6</sub> H <sub>4</sub>	mesityl	<b>2f</b> 74 (60)
4-BrC <sub>6</sub> H <sub>4</sub>	mesityl	<b>2g</b> 42 (40)

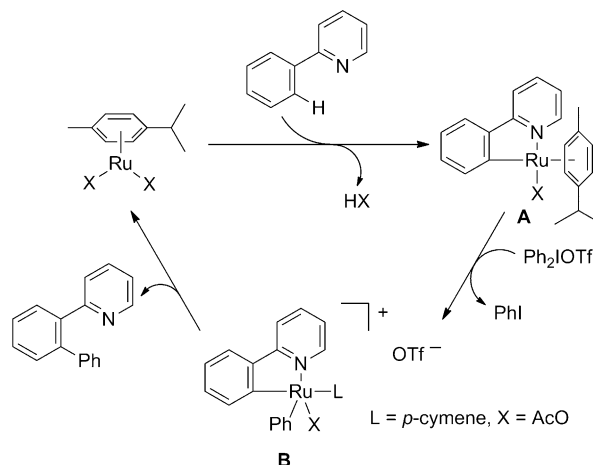
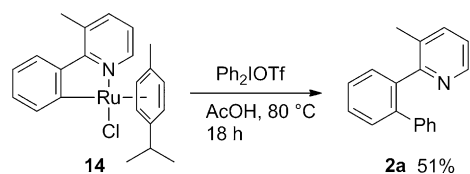
[a] Reaction conditions: arylpyridine (0.5 mmol), Ar<sup>1</sup>Ar<sup>2</sup>IOTf (0.6 mmol), AcOH (2 mL), at 80 °C for 18 h. [b] Yield determined by <sup>1</sup>H NMR spectroscopy. [c] Numbers in parentheses are yields of isolated product. [d] Toluene was used as a solvent.



Scheme 4. Deuterium labeling experiment.

While details of the mechanism have not been elucidated yet, we propose that the reaction proceeds by a mechanism similar to that established for well-known Pd<sup>2+</sup>-catalyzed C–H bond arylation reactions, such as a Pd<sup>2+</sup>/Pd<sup>4+</sup> cycle (Scheme 5).<sup>16</sup> The reaction of 2-phenylpyridine with Ru<sup>2+</sup> gives the cyclometalated ruthenium complex **A**. The oxidative addition of Ph<sub>2</sub>IOTf to **A** gives the Ru<sup>4+</sup> complex **B**, which undergoes reductive elimination to afford the phenylated product with the regeneration of Ru<sup>2+</sup>. Ackermann et al. isolated a similar ruthenium complex to **A** from 2-phenylpyridine and [Ru(O<sub>2</sub>CMes)<sub>2</sub>(*p*-cymene)].<sup>[15b]</sup> Dixneuf and co-workers also recorded the formation of a cyclometalated ruthenium complex similar to **A** from 2-phenylpyridine and [Ru(OAc)<sub>2</sub>(*p*-cymene)].<sup>[15c]</sup> In fact, a stoichiometric reaction of the complex **14** with Ph<sub>2</sub>IOTf in AcOH gave monophenylation product **2a** in 51 % NMR yield (Scheme 6).

In summary, we have reported the chelation-assisted arylation of the *ortho* C–H bonds in 2-arylpyridine derivatives by using [Ru(OAc)<sub>2</sub>(*p*-cymene)] as the catalyst and diaryliodonium salts as arylation reagents. The reaction is compatible with a wide range of functional groups. Although diaryliodonium salts have been commonly used as arylation


 Scheme 5. Proposed mechanism of *ortho* phenylation of C–H bonds.


Scheme 6. A stoichiometric reaction.

reagent in Pd- and Cu-catalyzed arylation of C–H bonds,<sup>[7,8]</sup> only two examples of the Ru-catalyzed arylation of C–H bonds have appeared in the literature.<sup>[9]</sup> However, these reactions proceed by a radical mechanism because irradiation is required.

## Experimental Section

### Experimental Details

3-Methyl-2-phenylpyridine (85 mg, 0.5 mmol), diphenyliodonium trifluoromethane sulfonate (263 mg, 0.6 mmol), [Ru(OAc)<sub>2</sub>(*p*-cymene)] (9 mg, 0.025 mmol), K<sub>2</sub>CO<sub>3</sub> (83 mg, 0.6 mmol), and toluene (2 mL) were added to an oven-dried 5 mL screw-capped vial under a gentle stream of nitrogen. The mixture was stirred for 18 h at 80 °C then cooled. The mixture was filtered through a celite pad and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane /EtOAc=20:1) to afford the desired arylated product in 95% yield.

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**Keywords:** aryl pyridines • C–H activation • chelation • diaryliodonium salts • ruthenium

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