

# Room-Temperature C–H Arylation: Merger of Pd-Catalyzed C–H Functionalization and Visible-Light Photocatalysis

Dipannita Kalyani, Kate B. McMurtrey, Sharon R. Neufeldt, and Melanie S. Sanford\*

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109, United States

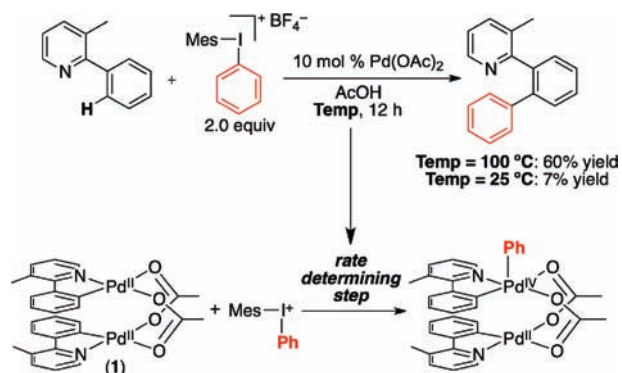
Supporting Information

**ABSTRACT:** This communication describes the development of a room-temperature ligand-directed C–H arylation reaction using aryldiazonium salts. This was achieved by the successful merger of palladium-catalyzed C–H functionalization and visible-light photoredox catalysis. The new method is general for a variety of directing groups and tolerates many common functional groups.

The biaryl motif is an important structural component of numerous natural products, pharmaceutical agents, and organic materials.<sup>1</sup> As a result, the design of mild, general, and efficient methods for aryl–aryl bond construction continues to be an area of tremendous research effort.<sup>2</sup> Over the past decade, transition-metal-catalyzed C–H arylation reactions have been particularly well studied, and there have been numerous advances in the substrate scope, functional group tolerance, and range of different catalysts for promoting these transformations.<sup>2</sup> However, despite this progress, the vast majority of C–H arylation methods still require elevated temperatures (>80 °C).<sup>3</sup> The development of general room-temperature C–H arylation reactions (particularly in nonacidic solvents) remains an important challenge for the field.<sup>3,4</sup>

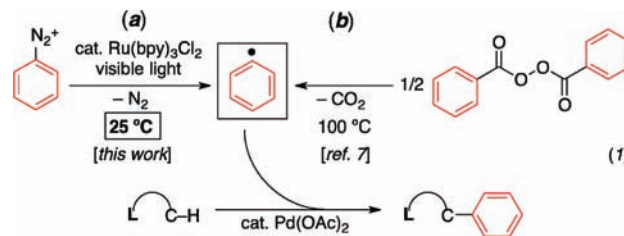
In 2005, our group reported the Pd-catalyzed, ligand-directed C–H arylation of amide and arylpyridine substrates with diaryliodonium salts.<sup>5</sup> This transformation proceeds in high yield at 100 °C; however, as shown in Scheme 1, very little product is obtained at room temperature. A detailed mechanistic study revealed that the rate-determining step of the catalytic cycle involves oxidation of dimeric intermediate **1** by [Mes–I–Ph]BF<sub>4</sub> (Scheme 1).<sup>6</sup> This

**Scheme 1.** Pd-Catalyzed C–H Arylation with Diaryliodonium Salts



result led us to hypothesize that the rate of the reaction could be accelerated (and therefore the temperature lowered) by substituting diaryliodonium salts with more kinetically reactive arylating reagents. We report herein the use of this strategy for the rational design of a new room-temperature C–H arylation reaction. This achievement was made possible by merging Pd-catalyzed C–H functionalization with visible-light photoredox catalysis.

We reasoned that room-temperature C–H arylation could be achieved by using Ph· as a highly kinetically reactive alternative to the diaryliodonium oxidant in Scheme 1. A recent report by Yu suggested that phenyl radicals can participate in Pd-catalyzed C–H arylation reactions.<sup>7</sup> However, high temperatures were required in that system in order to generate Ph· from dibenzoylperoxide via decarboxylation (eq 1b).<sup>7</sup> We sought to identify reagents that could form aryl radicals at room temperature, and a literature survey uncovered Deronzier's Ru(bpy)<sub>3</sub>Cl<sub>2</sub>-photocatalyzed generation of aryl radicals at 25 °C from aryldiazonium salts.<sup>8a–c</sup> Inspired by this transformation, we envisioned that C–H activation intermediates could potentially be intercepted by aryl radicals formed at room temperature via visible-light photocatalysis (eq 1a).<sup>9</sup>

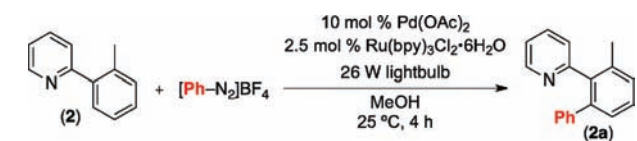


Initial investigations focused on the Pd-catalyzed C–H arylation of **2** with phenyldiazonium tetrafluoroborate. Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O was employed as the photocatalyst, and a 26 W household fluorescent compact bulb was utilized as the source of visible light. We were pleased to find that the desired C–H arylation product **2a** was formed in 31% yield at room temperature with 10 mol % Pd(OAc)<sub>2</sub>, 2.5 mol % Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O, and 2 equiv of PhN<sub>2</sub>BF<sub>4</sub> in MeOH (Table 1, entry 1). The yield was improved to 84% by using 4 equiv of PhN<sub>2</sub>BF<sub>4</sub> in conjunction with 10 mol % Ag<sub>2</sub>CO<sub>3</sub> as an additive (entry 3). Importantly, [Pd], [Ru], and visible light were all critical for this transformation. In the absence of any of these components, significantly reduced yields of **2a** (≤8%) were observed (Table 1, entries 4–6). This transformation has several attractive features in comparison with most current C–H arylation methods,<sup>2</sup>

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**Table 1. Optimization of the Reaction between 2 and PhN<sub>2</sub>BF<sub>4</sub><sup>a</sup>**



Entry	PhN <sub>2</sub> BF <sub>4</sub> (equiv)	Additive (equiv)	Yield <sup>b</sup>
1	2	none	31%
2	4	none	49%
3	4	Ag <sub>2</sub> CO <sub>3</sub> (0.10)	84%
4 <sup>c</sup>	4	Ag <sub>2</sub> CO <sub>3</sub> (0.10)	0%
5 <sup>d</sup>	4	Ag <sub>2</sub> CO <sub>3</sub> (0.10)	8%
6 <sup>e</sup>	4	Ag <sub>2</sub> CO <sub>3</sub> (0.10)	5%

<sup>a</sup> General conditions: Pd(OAc)<sub>2</sub> (0.1 equiv), Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O (0.025 equiv), MeOH (0.1 M in substrate), rt, 4 h, 26 W compact fluorescent light bulb. <sup>b</sup> Calibrated yields determined by gas chromatographic analysis of the crude reaction mixtures. <sup>c</sup> General conditions, but with no Pd(OAc)<sub>2</sub>. <sup>d</sup> General conditions, but with no Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O. <sup>e</sup> General conditions, but with no light.

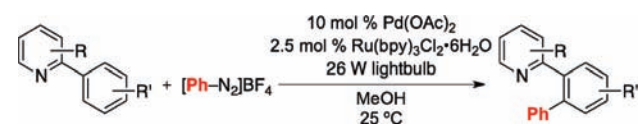
including a low operating temperature (25 °C),<sup>10</sup> a nonacidic solvent (MeOH), and the generation of innocuous nitrogen and easily removable HBF<sub>4</sub> as the only stoichiometric by-products. In addition, this is the first example of palladium-catalyzed C–H functionalization using visible-light photoredox catalysis.

With the optimal conditions in hand, we next explored the functional group compatibility of this transformation using a series of 2-arylpyridine derivatives. As shown in Table 2, C–H arylation proceeded at room temperature in modest to good yields with a variety of electronically diverse pyridine substrates. In all cases, Pd(OAc)<sub>2</sub>, Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O, and visible light were required to achieve >9% yield [see the Supporting Information (SI) for control reactions]. Electron-donating and electron-withdrawing substituents were well-tolerated on both the pyridine (entries 1–6) and the aryl ring undergoing functionalization (entries 7 and 8). Additionally, chloride and bromide substituents on the pyridine ring were compatible with the reaction conditions (entries 3 and 4), suggesting against the intermediacy of Pd<sup>0</sup> in this transformation.

This room-temperature C–H arylation reaction was also effective for substrates containing different directing groups, including amides, pyrazoles, pyrimidines, and oxime ethers (Table 3, entries 1–5). In addition, the mild reaction conditions enabled the first example of Pd-catalyzed C–H functionalization directed by a free oxime (entry 6). This functional group typically undergoes rapid hydrolysis in the acidic solvents and at the elevated temperatures required for most related reactions.<sup>11</sup> The oxime serves as a versatile functional handle for elaboration of the products, as it can be readily transformed into a ketone, alcohol, amine, or amide.<sup>11b</sup> Again, for the examples in Table 3, Pd(OAc)<sub>2</sub>, Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O, and visible light were all critical for achieving good yields of the products (see the SI for details).

We next examined the use of diverse aryldiazonium salts in these transformations. As depicted in Table 4, C–H arylation proceeded in good to excellent yields with electron-deficient, electron-rich, and relatively sterically hindered arylating reagents. Interestingly, the electron-deficient derivatives 17–19 showed modest to high photoreactivities with 1-phenylpyrrolidin-2-one (10) in

**Table 2. Substrate Scope of the Room-Temperature Pd/Ru-Catalyzed C–H Arylation of 2-Arylpyridine Derivatives<sup>a</sup>**



Entry	Substrate	Product	Isolated Yield
1 <sup>b</sup>			76%
2 <sup>c,d</sup>			66%
3 <sup>b,d,e,f</sup>			62%
4 <sup>b,c,d,e,f</sup>			63%
5 <sup>d,g</sup>			59%
6 <sup>c,d,e,h</sup>			47%
7 <sup>d,f</sup>			69%
8 <sup>c,d,e,g</sup>			60%

<sup>a</sup> General procedure: Substrate (1.0 equiv), Pd(OAc)<sub>2</sub> (0.1 equiv), Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O (0.025 equiv), PhN<sub>2</sub>BF<sub>4</sub> (4.0 equiv), MeOH (0.1 M in substrate), rt, 4 h, 26 W compact fluorescent light bulb. <sup>b</sup> Ag<sub>2</sub>CO<sub>3</sub> (0.1 equiv) was used as an additive. <sup>c</sup> General conditions, but with 0.15 equiv of Pd(OAc)<sub>2</sub>. <sup>d</sup> MeOH (0.05 M in substrate). <sup>e</sup> 5.0 equiv of PhN<sub>2</sub>BF<sub>4</sub>. <sup>f</sup> Reaction was run for 10 h. <sup>g</sup> Reaction was run for 8 h. <sup>h</sup> Reaction was run for 9.5 h.

the absence of Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O. In one of the most pronounced cases, 10 underwent Pd-catalyzed photoreaction with [4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>N<sub>2</sub>]BF<sub>4</sub> to afford 23 in 97% calibrated GC yield without [Ru] (Scheme 2). This yield was comparable to that obtained using 2.5 mol % Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O under otherwise analogous conditions (92% by GC). Interestingly, this uncatalyzed photoreaction was highly substrate-dependent; for example, relatively little reaction was observed between [4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>N<sub>2</sub>]BF<sub>4</sub> and oxime ether 14 in the absence of [Ru] (Scheme 2).<sup>12</sup>

Although the mechanistic details of this Pd/Ru photocatalyzed C–H arylation remain to be elucidated, a possible catalytic

Table 3. Scope of Directing Groups for the Pd/Ru-Catalyzed C–H Arylation<sup>a</sup>

$$\text{L-C-H} + [\text{Ph-N}_2]\text{BF}_4 \xrightarrow[\text{MeOH, 25 }^\circ\text{C}]{\text{10 mol \% Pd(OAc)}_2, \text{2.5 mol \% Ru(bpy)}_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}, \text{26 W lightbulb}} \text{L-C-Ph}$$

Entry	Substrate	Product	Isolated Yield
1			72%
2 <sup>b</sup>			79%
3 <sup>c,d</sup>			53%
4 <sup>d</sup>			44%
5 <sup>e</sup>			49%
6 <sup>f,g,h</sup>			50%

<sup>a</sup> General procedure: Substrate (1.0 equiv), Pd(OAc)<sub>2</sub> (0.1 equiv), Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O (0.025 equiv), PhN<sub>2</sub>BF<sub>4</sub> (4.0 equiv), MeOH (0.1 M in substrate), rt, 4 h, 26 W compact fluorescent light bulb. <sup>b</sup> General conditions, but with 0.05 equiv of Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O. <sup>c</sup> Ag<sub>2</sub>CO<sub>3</sub> (1.0 equiv) was used as an additive. <sup>d</sup> Reaction was run for 5 h. <sup>e</sup> 3.5 equiv of PhN<sub>2</sub>BF<sub>4</sub>. <sup>f</sup> General conditions, but with 0.20 equiv of Pd(OAc)<sub>2</sub>. <sup>g</sup> Reaction was run for 5.5 h. <sup>h</sup> MeOH (0.2 M in substrate).

cycle is shown in Figure 1. The key steps include (i) photoexcitation of the Ru catalyst to generate Ru(bpy)<sub>3</sub><sup>2+\*</sup>, (ii) reduction of the aryldiazonium salt to Ar· and concomitant oxidation of the Ru center to Ru(bpy)<sub>3</sub><sup>3+</sup>,<sup>8</sup> (iii) reaction of Ar· with palladacycle **29** (generated by C–H activation of the substrate) to afford the Pd<sup>III</sup> intermediate **30**, (iv) one-electron oxidation of **30** by Ru(bpy)<sub>3</sub><sup>3+</sup> to regenerate the photocatalyst and form Pd<sup>IV</sup> intermediate **31**, and finally (v) C–C bond-forming reductive elimination to release the arylated product and regenerate the Pd<sup>II</sup> catalyst. Efforts to obtain a detailed mechanistic understanding of this transformation are currently underway.

In summary, this communication has described a mild approach for palladium-catalyzed, ligand-directed arylation of aromatic C–H bonds. These reactions proceed at room temperature and are compatible with a range of functional groups, directing ligands, and aryldiazonium salts. This system introduces the idea of merging visible-light photoredox catalysis (which can be used to generate diverse reactive intermediates) with palladium-catalyzed C–H functionalization. We anticipate

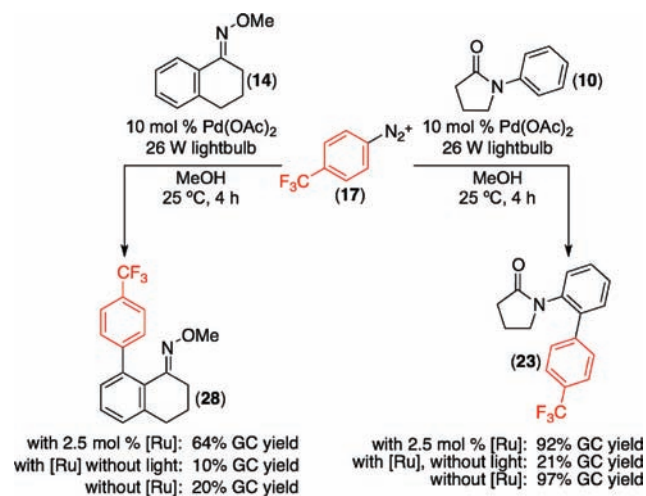
Table 4. Scope of Aryldiazonium Salts for the Pd/Ru-Catalyzed C–H Arylation<sup>a</sup>

$$\text{L-C-H} + [\text{Aryl-N}_2]\text{BF}_4 \xrightarrow[\text{MeOH, 25 }^\circ\text{C}]{\text{10 mol \% Pd(OAc)}_2, \text{2.5 mol \% Ru(bpy)}_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}, \text{26 W lightbulb}} \text{L-C-Aryl}$$

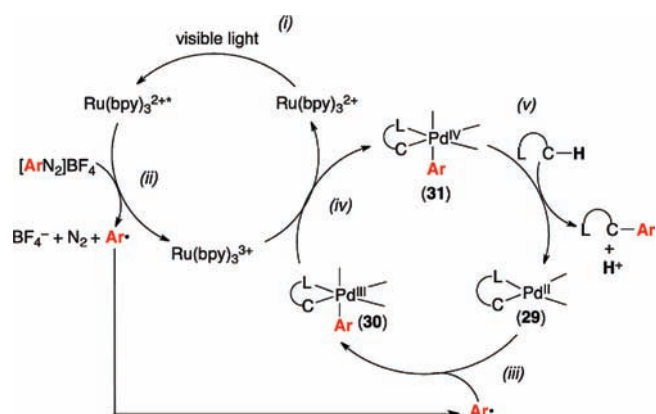
Entry	[Aryl-N <sub>2</sub> ]BF <sub>4</sub>	Product	Isolated Yield
1 <sup>b</sup>			76%
2 <sup>c</sup>			87%
3			76%
4			78%
5 <sup>d</sup>			79%
6 <sup>d,e,f</sup>			57%

<sup>a</sup> General procedure: Substrate (1.0 equiv), Pd(OAc)<sub>2</sub> (0.1 equiv), Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O (0.025 equiv), [aryl-N<sub>2</sub>]BF<sub>4</sub> (4.0 equiv), MeOH (0.1 M in substrate), rt, 4 h, 26 W compact fluorescent light bulb. <sup>b</sup> Reaction was run for 6 h. <sup>c</sup> General conditions, but with 3.4 equiv of [aryl-N<sub>2</sub>]BF<sub>4</sub>. <sup>d</sup> General conditions, but with 0.05 equiv of Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O. <sup>e</sup> Reaction was run for 10 h. <sup>f</sup> MeOH (0.2 M in substrate).

## Scheme 2. Background Reactions with Electron-Deficient Aryldiazonium Salts



that this new concept will find application in the development of many new synthetically useful transformations.



**Figure 1.** Possible mechanism for the Pd/Ru-catalyzed C–H arylation reaction.

## ■ ASSOCIATED CONTENT

**S Supporting Information.** Experimental details and spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## ■ AUTHOR INFORMATION

### Corresponding Author

mssanfor@umich.edu

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(10) Regulation of the reaction temperature at 25 °C was found to be important for obtaining reproducible yields in these reactions. See the SI for details.

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(12) The origin of this photoreactivity in the absence of [Ru] is currently under investigation. We tentatively hypothesize that certain palladacyclic intermediates may participate in photoinduced electron transfer to electron-deficient aryldiazonium salts to initiate this transformation.