Published in final edited form as:

J Am Chem Soc. 2011 November 23; 133(46): 18566–18569. doi:10.1021/ja208068w.

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*

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

Abstract

This communication describes the development of a room temperature ligand-directed C–H arylation reaction using aryl diazonium 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.¹ 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.² 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.² However, despite this progress, the vast majority of C–H arylation methods still require elevated temperatures (>80 °C).³ The development of general room temperature C–H arylation reactions (particularly in non-acidic solvents) remains an important challenge for the field.^{3,4}

In 2005, our group reported the Pd-catalyzed ligand-directed C–H arylation of amide and arylpyridine substrates with diaryliodonium salts.⁵ These transformations proceed in high yield at 100 °C; however, as shown in Scheme 1, very little product was 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]BF₄ (Scheme 1).⁶ This 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 has suggested that phenyl radicals can participate in Pd-catalyzed C–H arylation reactions.⁷ However, high temperatures were required in this system in order to generate Ph• from dibenzoylperoxide via decarboxylation (eq. 1b).⁷ We sought to identify reagents that could form aryl radicals at room temperature, and a literature survey uncovered Deronzier's Ru(bpy)₃Cl₂-photocatalyzed generation of aryl radicals at 25 °C from aryl

*mssanfor@umich.edu .

Supporting Information Available: 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>.

diazonium salts.^{8a-c} 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).⁹

Initial investigations focused on the Pd-catalyzed C–H arylation of **2** with phenyldiazonium tetrafluoroborate. $\text{Ru(bpy)}_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ 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 % of Pd(OAc)_2 , 2.5 mol % of $\text{Ru(bpy)}_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$, and 2 equiv of PhN_2BF_4 in MeOH (Table 1, entry 1). The yield was improved to 84% by using 4 equiv of PhN_2BF_4 in conjunction with 10 mol % of Ag_2CO_3 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 yield of **2a** ($\leq 8\%$) was observed (Table 1, entries 4–6). This transformation has several attractive features compared to most current C–H arylation methods,² including a low operating temperature (25°C),¹⁰ a non-acidic solvent (MeOH), and the generation of innocuous nitrogen and easily removable HBF_4 as the only stoichiometric byproducts. In addition, this is the first example of palladium-catalyzed C–H functionalization using visible light photoredox catalysis.

With optimal conditions in hand, we next explored the functional group compatibility of this transformation with a series of 2-arylpyridine derivatives. As shown in Table 2, C–H phenylation proceeded at room temperature in modest to good yield with a variety of electronically diverse pyridine substrates. In all cases, Pd(OAc)_2 , $\text{Ru(bpy)}_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$, and visible light were required to achieve $>9\%$ yield (see Supporting Information for control reactions). Electron donating and electron withdrawing substituents were well-tolerated on both the pyridine (entries 1–6) and aryl ring undergoing functionalization (entries 7 and 8). Additionally, aryl chloride and bromide substituents on the pyridine ring were compatible with the reaction conditions, suggesting against the intermediacy of Pd^0 in this transformation (entries 3 and 4).

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 (Table 3, entry 6). This functional group typically undergoes rapid hydrolysis in the acidic solvents and at the elevated temperatures required for most related reactions.¹¹ 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.^{11b} Again, for the examples in Table 3, Pd(OAc)_2 , Ru, and visible light were all critical for achieving good yields of the products (see Supporting Information 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 yield with electron deficient, electron rich, and relatively sterically hindered arylating reagents. Interestingly, the electron deficient derivatives **17–19** showed modest to high photoreactivity with 1-phenylpyrrolidin-2-one (**10**) in the absence of Ru(bpy)₃Cl₂•6H₂O. In one of the most pronounced cases, **10** underwent Pd-catalyzed photoreaction with [4-CF₃C₆H₄N₂]BF₄ to afford **23** in 97% calibrated GC yield without [Ru] (Scheme 2). This yield was comparable to that obtained using 2.5 mol % of Ru(bpy)₃Cl₂•6H₂O under otherwise analogous conditions (92% by GC). Interestingly, this uncatalyzed photoreaction was highly substrate dependent; for example, relatively little reaction was observed between [4-CF₃C₆H₄N₂]BF₄ and oxime ether **14** in the absence of [Ru] (Scheme 2).¹²

Although the mechanistic details of Pd/Ru photo-catalyzed C–H arylation remain to be elucidated, a possible catalytic cycle is shown in Figure 1. The key steps involve: (i) photo-excitation of the Ru catalyst to generate Ru(bpy)₃^{2+*}, (ii) reduction of the diazonium salt to Ar• and concomitant oxidation of the Ru center to Ru(bpy)₃³⁺,⁸ (iii) reaction of Ar• with palladacycle **29** (generated by C–H activation of the substrate) to afford the Pd^{III} intermediate **30**, (iv) one electron oxidation of **30** by Ru(bpy)₃³⁺ to regenerate the photocatalyst and form Pd^{IV} intermediate **31**, and finally (v) C–C bond-forming reductive elimination to release the arylated product and regenerate the Pd^{II} catalyst. Efforts to obtain a detailed mechanistic understanding of this transformation are currently underway.

In summary, this communication describes a mild approach for the 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 aryl diazonium 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 this new concept will find application in the development of many new synthetically useful transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge the NIH NIGMS (GM073836) as well as an ARRA supplement to this grant for financial support of this work.

REFERENCES

1. Hassan J, Sevignon M, Gozzi C, Schulz E, Lemaire M. Chem. Rev. 2002; 102:1359. [PubMed: 11996540]
2. For representative reviews on C–H arylation, see: (a) Alberico D, Scott ME, Lautens M. Chem. Rev. 2007; 107:174. [PubMed: 17212475] (b) Kakiuchi F, Kochi T. *Synthesis*. 2008:3013. (c) McGlacken GP, Bateman L. Chem. Soc. Rev. 2009; 38:2447. [PubMed: 19623360] (d) Chen X, Engle KM, Wang D-H, Yu J-Q. Angew. Chem. Int. Ed. 2009; 48:5094. (e) Lyons TW, Sanford MS. Chem. Rev. 2010; 110:1147. [PubMed: 20078038] (f) Daugulis O. Top. Curr. Chem. 2010; 292:57. [PubMed: 21500403] (g) Chiusoli GP, Catellani M, Costa M, Motti E, Ca' ND, Maestri G. Coord. Chem. Rev. 2010; 254:456.
3. Wencel-Delord J, Droge T, Liu F, Glorius F. Chem. Soc. Rev. 2011; 40:4740. [PubMed: 21666903]
4. For isolated examples of room temperature Pd-catalyzed C–H arylation, see: (a) Hull KL, Lanni EL, Sanford MS. J. Am. Chem. Soc. 2006; 128:14047. [PubMed: 17061885] (b) Xiao B, Fu Y, Xu J, Gong T-J, Dai J-J, Yi J, Liu L. J. Am. Chem. Soc. 2010; 132:468. [PubMed: 20020760] (c)

- Nishikata T, Abela AR, Huang S, Lipshutz BH. *J. Am. Chem. Soc.* 2010; 132:4978. [PubMed: 20307066] (d) Nishikata T, Abela AR, Lipshutz BH. *Angew. Chem. Int. Ed.* 2010; 49:781. (e) Haffemayer B, Gulias M, Gaunt MJ. *Chem. Sci.* 2011; 2:312. (f) Tredwell MJ, Gulias M, Bremeyer N, Johansson CCC, Collins BSL, Gaunt MJ. *Angew. Chem. Int. Ed.* 2011; 50:1076.
5. Kalyani D, Deprez NR, Desai LV, Sanford MS. *J. Am. Chem. Soc.* 2005; 127:7330. [PubMed: 15898779]
6. (a) Deprez NR, Sanford MS. *J. Am. Chem. Soc.* 2009; 131:11234. [PubMed: 19621899] (b) Ariafard A, Hyland CJT, Canty AJ, Sharma M, Yates BF. *Inorg. Chem.* 2011; 50:6449. [PubMed: 21671562]
7. Yu W-Y, Sit W, Zhou Z, Chan ASC. *Org. Lett.* 2009; 11:3174. [PubMed: 19583200]
8. (a) Cano-Yelo H, Deronzier A. *J. Chem. Soc., Perkin Trans. 2.* 1984:1093. (b) Cano-Yelo H, Deronzier A. *J. Chem. Soc., Faraday Trans. 1.* 1984:3011. (c) Cano-Yelo H, Deronzier A. *Tetrahedron Lett.* 1984; 25:5517. (d) Cano-Yelo H, Deronzier A. *J. Photochemistry.* 1987; 37:315. (e) Cano-Yelo H, Deronzier A. *New J. Chem.* 1987; 11:479. (f) Lalevee J, Blanchard N, Tehfe M-A, Peter M, Morlet-Savary F, Fouassier JP. *Macromol. Rapid Commun.* 2011; 32:917. [PubMed: 21520323]
9. (a) Narayanam JMR, Stephenson CRJ. *Chem. Soc. Rev.* 2011; 40:102. [PubMed: 20532341] (b) Yoon TP, Ishchay MA, Du J. *Nature Chem.* 2010; 2:527. [PubMed: 20571569] (c) Nicewicz D, MacMillan DWC. *Science.* 2008; 322:77. [PubMed: 18772399]
10. Regulation of the reaction temperature at 25 °C was found to be important for obtaining reproducible yields in these reactions. See Supporting Information for details.
11. (a) Desai LV, Hull KL, Sanford MS. *J. Am. Chem. Soc.* 2004; 126:9542. [PubMed: 15291549] (b) Neufeldt SR, Sanford MS. *Org. Lett.* 2010; 12:532. [PubMed: 20041702]
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.

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

Scheme 2.

Background Reactions with Electron Deficient Aryldiazonium Salts

Figure 1.
Possible Mechanism for Pd/Ru-Catalyzed C-H Arylation Reactions

Table 1

Optimization of Reaction Between **2** and $[\text{PhN}_2]\text{BF}_4$ ^[a]

Entry	$[\text{PhN}_2]\text{BF}_4$ (equiv)	Additive (equiv)	Yield ^[b]
1	2	None	31%
2	4	None	49%
3	4	Ag_2CO_3 (0.10)	84%
4 ^[c]	4	Ag_2CO_3 (0.10)	0%
5 ^[d]	4	Ag_2CO_3 (0.10)	8%
6 ^[e]	4	Ag_2CO_3 (0.10)	5%

^[a] General conditions: $\text{Pd}(\text{OAc})_2$ (0.1 equiv), $\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ (0.025 equiv), MeOH (0.1 M in substrate), rt, 4 h, 26 W compact fluorescent light bulb.

^[b] Calibrated yields determined by gas chromatographic analysis of the crude reaction mixtures.

^[c] General conditions, but with no $\text{Pd}(\text{OAc})_2$.

^[d] General conditions, but with no $\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$.

^[e] General conditions, but with no light.

Table 2

Substrate Scope of Room Temperature Pd/Ru-Catalyzed C–H Arylation of 2-Arylpyridine Derivatives

Entry	Substrate	Product	Isolated Yield ^a
1 ^b			76%
2 ^{c,d}			66%
3 ^{b,d,e,f}			62%
4 ^{b,c,d,e,f}			63%
5 ^{d,g}			59%
6 ^{c,d,e,h}			47%

Entry	Substrate	Product	Isolated Yield ^a
7 ^{d,f}			69%
8 ^{c,d,e,g}			60%

[a] General procedure: Substrate (1.0 equiv), Pd(OAc)₂ (0.1 equiv), Ru(bpy)₃Cl₂•6H₂O (0.025 equiv), PhN₂BF₄ (4.0 equiv), MeOH (0.1 M in substrate), rt, 4 h, 26 W compact fluorescent light bulb.

[b] Ag₂CO₃ (0.1 equiv) used as an additive.

[c] General conditions but with 0.15 equiv of Pd(OAc)₂.

[d] MeOH (0.05 M in substrate).

[e] 5.0 equiv of PhN₂BF₄

[f] Reaction run for 10 h.

[g] Reaction run for 8 h.

[h] Reaction run for 9.5 h.

Table 3

Scope of Directing Groups for Pd/Ru-Catalyzed C–H Arylation

Entry	Substrate	Product	Isolated Yield ^a
1			72%
2 ^b			79%
3 ^{c,d}			53%
4 ^d			44%
5 ^e			49%
6 ^{f,g,h}			50%

[^a] General procedure: Substrate (1.0 equiv), Pd(OAc)₂ (0.1 equiv), Ru(bpy)₃Cl₂•6H₂O (0.025 equiv), PhN₂BF₄ (4.0 equiv), MeOH (0.1 M in substrate), rt, 4 h, 26 W compact fluorescent light bulb.

[^b] General conditions but with 0.05 equiv of Ru(bpy)₃Cl₂•6H₂O.

[^c] Ag₂CO₃ (1.0 equiv) used as an additive.

[d] Reaction run for 5 h.

[e] 3.5 equiv of PhN_2BF_4

[f] General conditions but with 0.20 equiv of $\text{Pd}(\text{OAc})_2$.

[g] Reaction run for 5.5 h.

[h] MeOH (0.2 M in substrate).

Table 4

Scope for Aryldiazonium Salts for Pd/Ru-Catalyzed C–H Arylation

Entry	[Aryl-N ₂] ⁺ BF ₄ ⁻	Product	Isolated Yield ^a
1 ^b	(16)	(22)	76%
2 ^c	(17)	(23)	87%
3	(18)	(24)	76%
4	(19)	(25)	78%
5 ^d	(20)	(26)	79%
6 ^{d,e,f}	(21)	(27)	57%

[a] General procedure: Substrate (1.0 equiv), Pd(OAc)₂ (0.1 equiv), Ru(bpy)₃Cl₂•6H₂O (0.025 equiv), ArylN₂BF₄ (4.0 equiv), MeOH (0.1 M in substrate), rt, 4 h, 26 W compact fluorescent light bulb.

[b] Reaction run for 6 h.

[c] General conditions but with 3.4 equiv of ArylN₂BF₄.

[d] General conditions but with 0.05 equiv of Ru(bpy)₃Cl₂•6H₂O.

[e] Reaction run for 10 h.

[f] MeOH (0.2 M in substrate).