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Aromatic substituent effects in palladium-catalyzed intramolecular olefin oxyarylation reactions

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ABSTRACT

The effect of electron-donating groups on the palladium-catalyzed intramolecular oxyarylation reaction was studied. In the case of activation at the *ortho*-position, the reaction favors the formation of a tricyclic lactone via C—H insertion. However, when the *ipso*-position is activated, the major product is instead a novel α,β-unsaturated lactone formed by way of a stabilized phenonium intermediate followed by elimination.

Palladium-catalysis revolutionized the field of organic synthesis by facilitating the predictable formation of carbon-carbon and carbon-heteroatom bonds [1,2]. Aside from the standard direct coupling of organohalides and organometallic species, palladium-catalyzed olefin difunctionalizations have emerged as an adaptable and useful synthetic transformation, specifically for the formation of heterocycles [3,4]. More recently, several groups have investigated the use of high oxidation state palladium(IV) salts, which are unlikely to undergo β-hydride elimination, preventing competing Wacker oxidation [5]. The required use of a strong oxidizing agent limits the formation of highly sensitive Pd(0) species, meaning that these reactions typically can be run with no special precautions to exclude water or oxygen [5f]. Multiple variations of high-oxidation state palladium-catalyzed olefin difunctionalizations have since been reported, including both inter- and intramolecular variants [6,7].

In 2009, Michael and coworkers reported an interesting palladium-catalyzed intermolecular aminoarylation of an olefin utilizing *N*-fluorobenzenesulfonimide (NFSI) as an external oxidant [8]. The reaction was highly regiospecific with regards to the addition site on the aromatic ring. Mechanistic studies suggested that the reaction occurs by an initial aminopalladation followed by a C—H insertion through a highly electrophilic alkylpalladium intermediate [9]. Palladium(IV) has been found to undergo C—H insertion via an electrophilic aromatic substitution mechanism, supporting the observed regiochemical outcomes [10]. Stephenson and coworkers elaborated on these finding in 2011 while exploring the synthesis of the platensimycin core, demonstrating that electron-rich aromatic rings can directly displace the alkylpalladium, forming a series of interesting dearomatized products in an intramolecular fashion [11].

Our research program is aimed at further exploring the scope of palladium-catalyzed heteroarylations in an effort to synthesize highly constrained ring systems. In addition, we hoped to expand the scope of the heteroarylation reaction to the formation of lactones. As such, we were delighted to find that treatment of 2,2-diphenylpent-4-enoic acid (**1a**) with catalytic palladium(II) trifluoroacetate and two equivalents of the oxidant Selectfluor leads to moderate yields of the tricyclic lactone **2a**, as shown in Scheme 1. Mass balance for our early reactions was relatively poor, and the product was initially difficult to characterize due to slow rotation of the exocyclic aromatic ring due to steric congestion around the quaternary center.

In an effort to increase the chemical yield, we sought to utilize the previously reported increased reactivity of electron-rich aromatic systems [8,11]. By increasing the electron density, we hoped to further favor the desired addition of the aromatic ring. Somewhat surprisingly, when substrate **1b** containing a strongly donating methoxy group in the *para*-position was submitted to the reaction, only trace formation of a tricyclic lactone **2** was observed. Instead, novel α,β-unsaturated lactone **3b** was formed as the major product in 49% yield. The structure of **3b**, where an aryl group has been transferred from C2 to C5 of the pent-4-enoic acid structure with a concurrent β-hydrogen elimination, was proposed following

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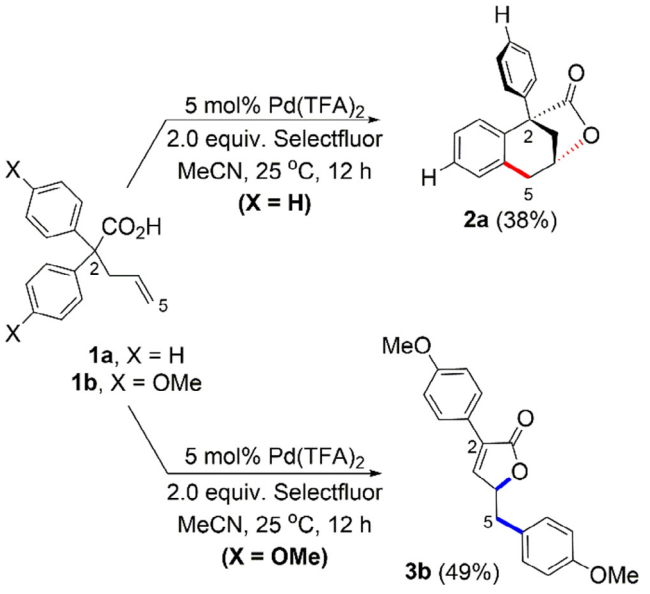


Scheme 1. Diverging reactivity of the palladium-catalyzed intramolecular oxyarylation reaction.

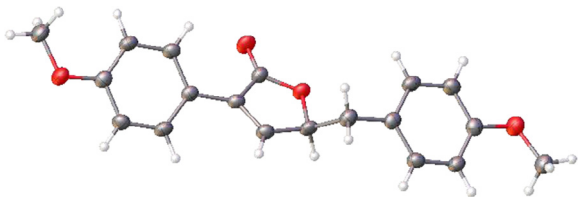


Fig. 1. Projection of **3b**. Carbon atoms shown in grey, oxygen in red, and hydrogen in white.

extensive NMR analysis and confirmed by X-ray crystallography, shown in Fig. 1 [12].

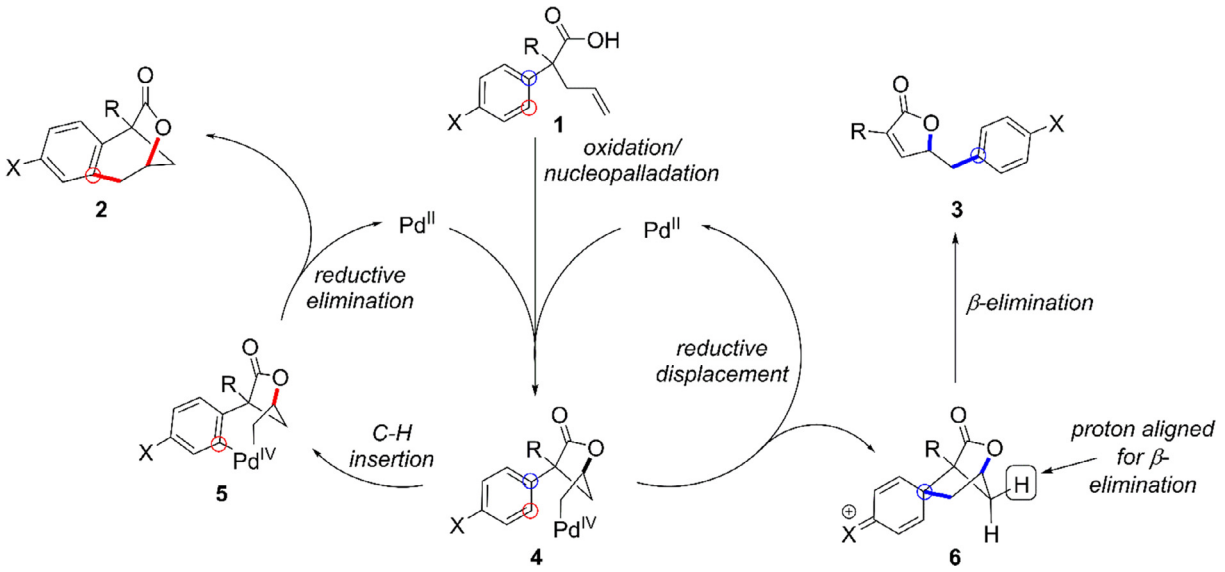
Intrigued by this divergence in reactivity, we set about to formulate a mechanistic hypothesis (Scheme 2). Based on literature precedent [6,11], we propose than an initial carboxypalladation and oxidation of carboxylic acid **1** would form lactone **4**. Reaction by the *ortho* position (red) of the aromatic ring *via* C—H insertion as proposed by Michael and coworkers [9], would produce the originally observed tricyclic compound **2** following reductive elimination.

To explain the formation of **3**, we propose a reductive displacement by the nucleophilic *ipso* position of the arene to form phenonium ion **6**, stabilized by the donating methoxy group. Baekvall and coworkers have previously studied the highly reactive phenonium ion formed by the direct displacement of an alkyl palladium species [13]. Subsequently, several groups have utilized the highly electrophilic palladium(IV) to form a series of interesting dearomatized products [11,14]. In **6**, the phenonium ion is anti-coplanar with the indicated bridge proton facilitating facile β-elimination to form α,β-unsaturated lactone (**3**) driven by the restoration of aromaticity. All attempts to observe or isolate the proposed intermediates were unsuccessful.

To further explore the nature of this novel reaction, we began a series of experiments to determine the optimal conditions for the intramolecular aryl-transfer. As shown in Table 1, the choice of external oxidant proved crucial. Reduction in the stoichiometric quantity of Selectfluor to 1.2 equivalents significantly increased reaction yield, likely by reducing the prevalence of competing side reactions. *N*-Fluorobenzenesulfonimide (NFSI), a fluorine based oxidant used successfully in related aminoarylations [7], effects the aryl transfer product, albeit at a reduced yield relative to Selectfluor. Hypervalent iodine oxidants, such as $PhI(OAc)_2$ and $PhI(O_2CCF_3)_2$, suffered from competing dioxygenation of the olefin and reduced yields overall.

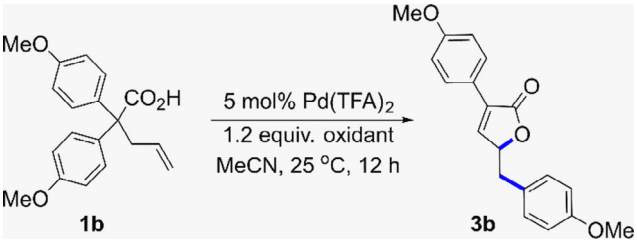
The reaction is exceptionally fast with total consumption of starting material observed by NMR and TLC after only 5 min (entry 7). A reaction time of one hour proved optimal, ensuring complete reaction while minimizing potential decomposition (entry 6). While all attempted palladium sources produced similar yields, the non-nucleophilic counterions of $Pd(TFA)_2$ were ideal in reducing competing side reactions that complicated purification observed with other catalysts. Additives, such as radical inhibitors or drying agents had little effect on reaction yields. Full details of the reaction optimization can be found in the Supplementary Material.

With optimized conditions in hand, we sought to further understand the impact of electronic effects on the formation of **2** and **3**,



Scheme 2. Proposed mechanism for the formation of **2** and **3**.

Table 1
Optimization of the formation of **3b**.



Entry	Oxidant	Time	Yield[b] (%)
1	Selectfluor	12 h	59
2	*N*-Fluorobenzenesulfonimide	12 h	37
3	$PhI(OAc)_2$	12 h	6
4	$PhI(O_2CCF_3)_2$	12 h	13
5	PhI = O	12 h	8
6	**Selectfluor**	**1 h**	**84 (82)[c]**
7	Selectfluor	5 min	78

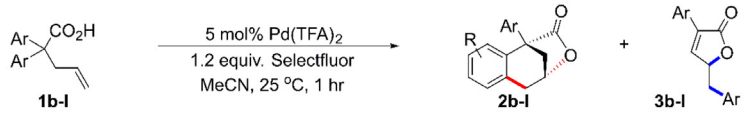
[a]Reaction conditions: **1b** (0.2 mmol), Selectfluor (0.24 mmol), and $Pd(TFA)_2$ (0.01 mmol) were combined in 1.0 mL of acetonitrile and stirred for the indicated amount of time at room temperature.
[b]Yield by ^1H NMR versus 1,3-dinitrobenzene as internal standard.
[c]Isolated yield.

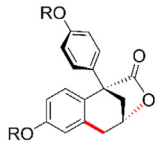
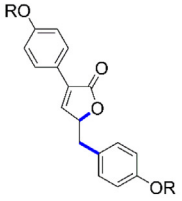
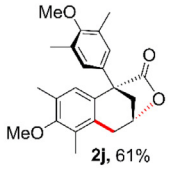
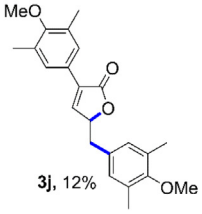
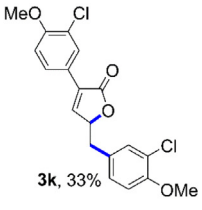
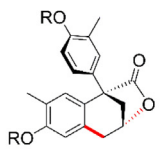
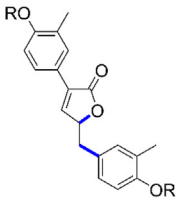
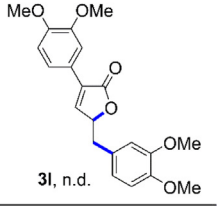
shown in Table 2. The pendant alkyl group on the phenolic oxygen had little effect on product formation (**1b–e**), producing almost exclusively the α,β-unsaturated lactone **3** in reasonable yields. Yields are slightly reduced for the *t*-butoxy substrate (**3e**), possibly due to the labile nature of the *t*-butyl ethers under cationic conditions. Though peaks consistent with the presence of tricyclic lactones (**2b–e**) could be observed in the baseline of crude ^1H NMR, we were unable to successfully isolate or purify the species. Attempts to perform the reaction on a phenolic substrate, such as **1f** where R = H, resulted only in decomposition of the starting material.

From our mechanistic hypothesis, we predicted that increasing the electron density at the position *ortho* to the ring attachment would increase the relative formation of the tricyclic lactone. Indeed, the incorporation of additional electron-donating groups (**1g–k**) in the *meta*-position of the aromatic ring increased the preference for the tricyclic lactone **2**. In fact, as the donating capability of the group was increased to a methoxy group (**1l**), the tricyclic product was formed exclusively. We conclude that the specific reaction pathway is determined by the relative degree of activation of the *ortho*-carbon (to form **2**) and the *ipso*-carbon (to form **3**).

We next explored a variety of other substitution patterns to better understand the factors that bias the ratio of **2** and **3** (Table 3). In general, the reaction appears to follow the selectivity observed in a standard electrophilic aromatic substitution reaction, with addition occurring preferentially at the most electron-rich site on the aromatic ring. In the absence of an oxygen substituent, alkyl groups can be used to direct the reaction (**1m–o**), though product

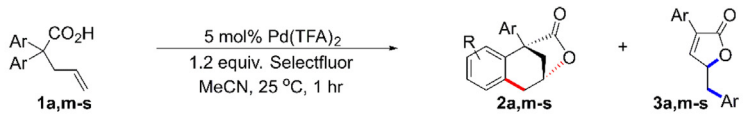
Table 2
Substrate Scope.

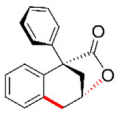
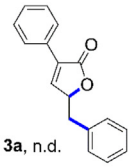
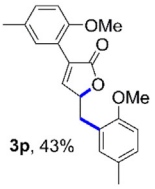
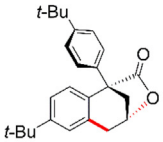
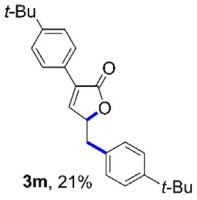
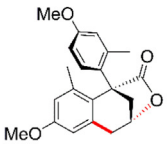
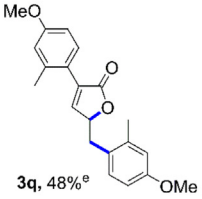
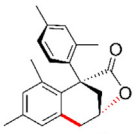
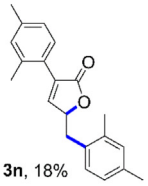
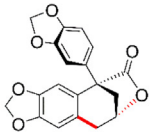
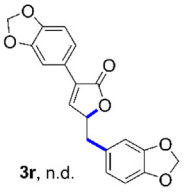
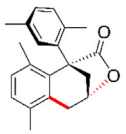
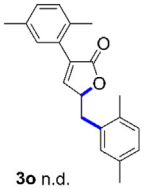
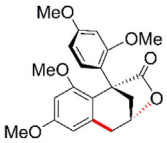
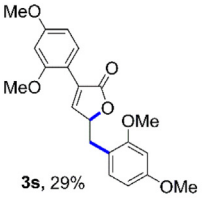


Substrate	Ratio (**2**:**3**)[b]	Yield **2** (%)[c]	Yield **3** (%)[c]	Substrate	Ratio (**2**:**3**)[b]	Yield **2** (%)[c]	Yield **3** (%)[c]
				**1j**	6:1	 **2j**, 61%	 **3j**, 12%
1b	1:16	**2b**, R = Me, n.d.	**3b**, R = Me, 82%				
1c	1:17	**2c**, R = Et, n.d.	**3c**, R = Et, 84%				
1d	1:16	**2d**, R = *i*Pr, n.d.	**3d**, R = *i*Pr, 80%				
1e	1:18	**2e**, R = *t*-Bu, n.d.	**3e**, R = *t*-Bu, 54%				
1f	N/A	decomposition	decomposition	**1k**	1:1.5	 **2k**, 26%	 **3k**, 33%
							
1g	1:6	**2g** R = Me, 11%	**3g** R = Me, 63%				
1h	1:4	**2h** R = Et, 16%	**3g** R = Et, 59%				
1i	1:5	**2i**, R = *i*Pr, 12%	**3i**, R = *i*Pr, 52%	**1l**	>20:1	 **2l**, 72%	 **3l**, n.d.

[a]Reaction conditions: **1** (0.5 mmol), Selectfluor (0.6 mmol), and $Pd(TFA)_2$ (0.025 mmol) were combined in 2.0 mL of acetonitrile and stirred for 1 h at room temperature.
[b]Ratio determined by crude ^1H NMR analysis.
[c]Isolated yield.

Table 3
Substrate Scope.



Substrate	Ratio (2:3)[b]	Yield 2 (%)[c]	Yield 3 (%)[c]	Substrate	Ratio (2:3)[b]	Yield 2 (%)[c]	Yield 3 (%)[c]
1a	>20:1	 **2a**, 43%	 **3a**, n.d.	**1p**	1:15	 **2p**, n.d.	 **3p**, 43%
1m	3:1	 **2m**, 64%	 **3m**, 21%	**1q**	1:3	 **2q**, 16%[d,e]	 **3q**, 48%[e]
1n	2.7:1	 **2n**, 52%[d]	 **3n**, 18%	**1r**	>20:1	 **2r**, 74%	 **3r**, n.d.
1o	>20:1	 **2o**, 68%[d]	 **3o** n.d.	**1s**	<1:20	 **2s**, n.d.	 **3s**, 29%

[a]Reaction conditions: **1** (0.5 mmol), Selectfluor (0.6 mmol), and $Pd(TFA)_2$ (0.025 mmol) were combined in 2.0 mL of acetonitrile and stirred for 1 h at room temperature.
[b]Ratio determined by crude ^1H NMR analysis.
[c]Isolated yield.
[d]Isolated as a mixture of stable rotational isomers.
[e]Yield determined by ^1H NMR analysis.

mixtures are generally formed. In cases of relatively equal activation between the two sites (**1m**), the tricyclic lactone **2m** is the preferred product by a significant margin. The reaction is generally tolerant of groups in the *ortho*-position (**1n–q,s**); however, this generally results in reduced yields and a slight increase in preference for the formation of the tricyclic product. The decreased reactivity is likely due to the increased steric demand around the reacting *ipso* carbon.

As a note, purification and characterization of the tricyclic lactones (**2**) was complicated by the previously observed restricted rotation of the exocyclic aromatic ring. Though the ^{13}C NMR spectra of the compounds exhibit complete coalescence at room temperature, elevated temperature was required to resolve peaks in the ^1H NMR. Compounds with substitution *ortho* to the ring junction (**2n,o,q**) exhibited locked rotation of the exocyclic aromatic ring and formed as stable and isolable mixtures of rotational isomers.

While the substrate scope for the aryl-transfer reaction is relatively limited due to restrictions on the aromatic rings, the reaction provides interesting insight into high-oxidation state palladium reactions. The substrate scope with respect to the influence of electron-donating groups on the ring supports our proposed mechanism, indicating that the relative nucleophilic activation of the *ipso*- and *ortho*-positions determines the product ratio. Further work to explore our mechanistic hypothesis in more detail is ongoing.

Despite the moderate yields, we have discovered and elaborated on an interesting and novel rearrangement catalyzed by high oxidation state palladium. The extreme sensitivity to the position and nature of the functional groups on the aromatic ring may limit the synthetic utility; however, it does provide an interesting model for additional research in the field of high oxidation state palladium-catalysis. It provides additional evidence for the highly electrophilic nature of alkyl palladium(IV) intermediates. Further study into the mechanism and intermediates has the potential to lead to the development of new and interesting transformations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151674.

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