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Intercepting Wacker Intermediates with Arenes: C–H Functionalization and Dearomatization

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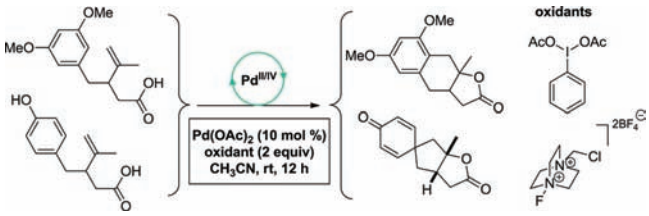
ABSTRACT



An intramolecular cyclization cascade reaction has been developed utilizing a high valent palladium intermediate that generates a carbon–carbon and carbon–oxygen bond in a single transformation. This method provides rapid access to highly functionalized tricyclic scaffolds, including spirocyclic cyclohexadienones. Good yields and mild conditions are reported with high tolerance toward oxygen and water.

High valent palladium mediated olefin difunctionalizations are versatile transformations in organic chemistry. Recent examples of palladium mediated amino acetoxylations,[1] dihydroxylations,[2] and diaminations[3] have greatly expanded the scope of synthetic methods available to organic chemists.[4] Seminal contributions by Semmelhack and Hegedus exploited Wacker intermediates generated from Pd^{II}-mediated cyclization reactions to make the key C–C bonds (Figure 1).[5] Methods inspired by their synthetic strategies have been successful in generating a high degree of molecular diversity[6] and found application in natural product synthesis.[7] Although C–C bond forming olefin difunctionalizations have been well developed in the context of Heck[8] and π-allyl palladium[9] chemistry, high valent palladium mediated C–C bond

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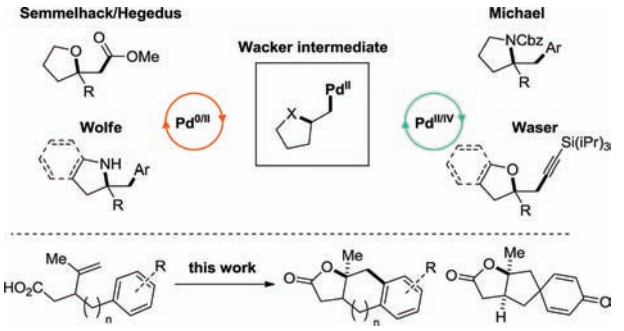

Figure 1. Pd-mediated oxidative C−C bond forming cyclizations.

forming alkene difunctionalization has not been studied to the same extent.

Recently, the Michael group reported an intermolecular carboamination reaction using $Pd(OAc)_2$ and *N*-fluorobenzenesulfonimide (NFSI) to synthesize substituted pyrrolidines from tethered amino alkenes in moderate to high yields.[10] Another report by Waser and co-workers described an intermolecular oxyalkynylation of olefins employing an alkynyl λ^3-iodane oxidant, which enabled them to generate substituted tetrahydrofuran and benzofuran derivatives.[4f] Furthermore, the groups of Kita[12b,d−f] and Swenton[12a,c] have synthesized spirocyclohexadieneones through chemical and electrochemical dearomatization of phenols, respectively. Hypervalent iodine or anodic oxidations are most effective in forging carbon−heteroatom bonds, although there are a few reported examples of C−C bond forming dearomatizations that produce *ipso* substituted dienones. With this in mind, we envisioned using the increased reactivity of high valent palladium obtained by oxidizing Wacker intermediates to allow for the formation of multiple bonds in a single operation, without the need to prefunctionalize our substrates.

Our research in transition metal catalyzed olefin difunctionalization was initiated during efforts directed toward the synthesis of the terpenoid antibiotic platensimycin.[11] The key transformation in our proposal was an oxidative dearomatization of a *para*-substituted phenol to form a spirocyclic cyclohexadienone as a precursor for a radical conjugate addition to efficiently provide the bicyclic fragment of platensimycin (Figure 2).

Unfortunately, hypervalent iodine, halocyclization, or conventional Wacker cyclization conditions proved to be

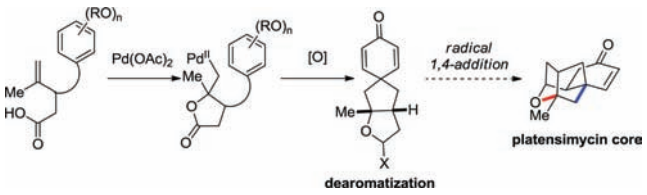

Figure 2. Natural product synthesis as inspiration for methods development.

ineffective toward oxidative dearomatization, often causing extensive substrate oligomerization or decomposition.[12,13] Consequently, we decided to address these shortcomings using a $Pd^{II/IV}$ catalytic cycle.

As illustrated in Table 1, our initial results provided only trace quantities of the desired dearomatized cyclohexadienes (Table 1, entries 1−3). After extensive optimization, the electrophilic fluorination reagent Selectfluor was found to provide the best results, affording spirocycle **2** in 43% yield as a single diastereoisomer. Treating substrate **1** with oxidants in the absence of a Pd^{II} source (Table 1, entries 5 and 6) afforded only the oxygen trapping product **2a**. We proceeded to screen for the optimal nucleopalladation coupling partners other than pendant alcohols (Figure 3). Unfortunately, carboxylic acid and cyanohydrin derivatives (see **3** and **4**, respectively, for representative examples) gave comparable yields without providing deeper insight into reaction optimization alternatives. In spite of low isolated yields, this transformation remains a useful method of generating complex polycyclic compounds and represents a unique example of a high valent palladium-mediated C−C bond forming oxidative dearomatization reaction.[14]

We subsequently explored the effects of different substituents on the arene moiety. In the event, we decided to investigate substrates with pendant carboxylic acids due to their known ability to participate in nucleopalladation processes. Thus, upon exposure of **7** to our reaction conditions, we isolated the desired adduct **8a** in only

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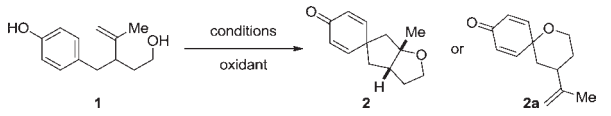
Table 1. Optimization for Oxidative Dearomatization



entry	conditions	yield of **2**[a]
1	$Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2.0 equiv), PhMe, rt, 12 h	0%
2	$Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2.0 equiv), CH_3CN, rt, 12 h	5−10%
3	$Pd(OAc)_2$ (10 mol %), PhI=O, (3.0 equiv), CH_3CN, rt, 12 h	N. R.
4	$Pd(OAc)_2$ (10 mol %), Selectfluor (2.0 equiv), CH_3CN, rt, 12 h	43%
5	$PhI(OAc)_2$ (1.1 equiv), CH_3CN	0%[b]
6	$PhI(O_2CCF_3)_2$ (1.1 equiv), $(F_3C)_2CHOH$	0%[b]

[a] Isolated yield (%) after purification by chromatography on SiO_2. [b] **2a** was the only isolable product.

20% yield. Further analysis of the reaction mixture revealed C−H insertion product **8** to be the major product (isolated in 68% yield). Intrigued by the crossover between oxidative dearomatization and C−H functionalization, we sought to explore the possibility of utilizing the ω-unsaturated carboxylic acids for oxidative C−H functionalization reactions. We sought to favor this transformation by varying the substitution pattern and electronic properties of the arene and to suppress the formation of dearomatization products.[15,16]

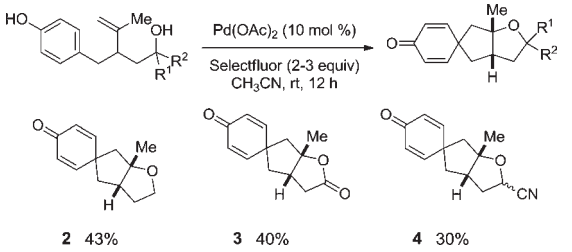


Figure 3. Examples of Wacker cyclization/dearomatization.

Upon screening oxidants and palladium complexes to promote C−H functionalization (not shown), it was found that $PhI(OAc)_2$ (2 equiv) and $Pd(OAc)_2$ (10 mol %) in CH_3CN provided optimal conditions for this transformation. These reactions were unsucessful when performed under traditional $Pd^{0/II}$ wacker oxidation conditions (stoichiometric and catalytic). Applying these conditions to substrate **5** afforded tricyclic compound **6** in excellent yield (92%) with a 1.75:1 diastereomeric ratio (Table 2, entry 1). High conversions were observed for electron-rich and -neutral substrates providing the tricyclic products in good to moderate yields (Table 1). Substrates that formed smaller fused ring systems (entries 3−9) showed a consistent decline in yield compared with entries 1 and 2. Further analysis of the reaction mixture obtained upon conversion of **11** to **12** (Table 2, entry 4) indicated that the attenuated yield was due to the competitive formation of pyranone (**24**) and olefin acetoxylation (**23**) side products. Prevention of these side products proved challenging; however they provided some mechanistic insight for this reaction (*vide infra*).

A plausible catalytic cycle is outlined in Figure 4. Beginning with the C−H functionalization pathway (Section I, **Path A**), Pd^{II} coordinates to the olefin of the substrate and undergoes an oxypalladation to form a Wacker intermediate. A Pd^{II} C−H metalation, followed by oxidation by $PhI(OAc)_2$ provides a palladacycle that undergoes reductive elimination, producing the C−H insertion product.[17] For phenols, the catalytic cycle proceeds through a dearomatization pathway (**Path B**). In turn, the Wacker intermediate undergoes oxidation by Selectfluor, generating the highly electrophilic alkylpalladium^{IV} intermediate. This undergoes a direct reductive nucleophilic substitution by the phenol to form the spirocyclohexadienone product.

With the proposed mechanistic hypothesis established, we began to formulate an explanation for the unavoidable formation of the olefin acetoxylation (**23**) and pyranone (**24**) side products (Figure 4, Section II). Using substrate **11** as a representative example, we hypothesized that **23** and **24** were generated as a consequence of the relative configuration of the Wacker intermediate formed during the initial nucleopalladation step, which can result in either a *trans* or *cis* substituted lactone (intermediates **A** and **B**, Figure 4, Section II). Since the subsequent reductive elimination of **B** would yield a highly strained *trans*-fused [3.3.0] bicyclic system (compound **C**),[18] intermediate **B** can undergo a Meerwein−Wagner shift[19,20] to form an oxocarbenium intermediate with concomitant trapping by

(15) (a) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (b) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5993. (c) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520.

(16) Engle, K. M.; Mei, T.-S.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 1478.

(17) The oxidation of the alkylpalladium complex may occur prior to C−H metallation. Control experiments on substrate **5** revealed the necessity of a high valent palladium cycle. Stoichiometric $Pd(OAc)_2$ or catalytic variants using Cu^{II} salts failed to produce any of **6**. For an example of a Pd^{IV} mediated C−H metallation, see: Racowski, J. M.; Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, DOI: 10.1021/ja2051099.

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(19) (a) Boontanonda, P.; Grigg, R. *J. Chem. Soc., Chem. Commun.* **1977**, 583. (b) Clark, G. R.; Thiensathit, S. *Tetrahedron Lett.* **1985**, *26*, 2503.

(20) This byproduct may also be the result of β-carbon elimination/endo cyclization. For examples of β-carbon elimination, see: (a) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645. (b) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 11010. For a review on the subject, see:(c) Leemans, K.; D'hooge, M.; De Kimpe, N. *Chem. Rev.* **2011**, *111*, 3268.

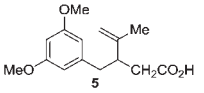
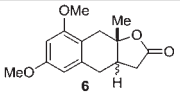
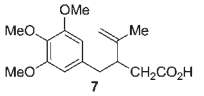
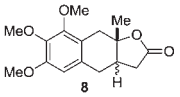
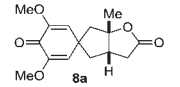
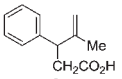
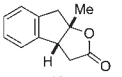
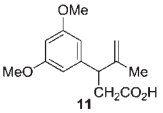
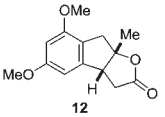
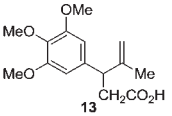
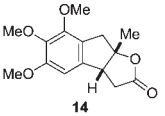
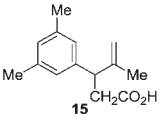
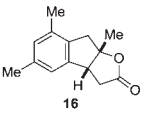
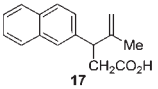
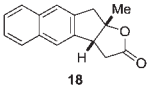
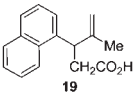
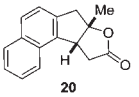
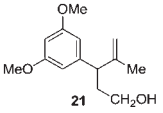
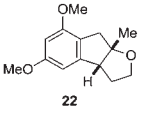
(21) When Selectfluor was used as the stoichiometric oxidant, there was extensive decomposition of the starting material.

acetate (i.e., **22**). As an alternative pathway, intermediate **B** can also undergo acetoxylation to form acetate **23**.

To further support our mechanistic hypothesis, we exposed acid **11** to our reaction conditions, using the deficient oxidant $PhI(O_2CCF_3)_2$ as the stoichiometric oxidant. As a result, the trifluoroacetate derivative of pyranone **24** was isolated as the major product in 30% yield along with trace amounts of the trifluoroacetate derivative of **23** which was also observed. We speculate that the poor level of substrate-directed diastereoselectivity in the nucleopalladation step is the most likely explanation for the low overall yield of the reaction (Table 2, entries 3–9), which is consistent with the observed side product.

In conclusion, we have developed a mild, C–C bond forming olefin difunctionalization methodology employing a $Pd^{II/IV}$ catalytic cycle. In addition, phenolic substrates underwent oxidative dearomatization in moderate yields, an unprecedented transformation in high valent palladium catalysis. Further investigations on the mechanism, scope, and applications of this reaction, especially in the context of the oxidative dearomatization, are currently being explored.

Table 2. Substrate Scope for C–H Functionalization[a]

entry	substrate	product	yield[b]
1	 **5**	 **6**	92%[c]
2	 **7**	 **8**	68%[d,c]
		 **8a**	20%
3	 **9**	 **10**	60%
4	 **11**	 **12**	61%
5	 **13**	 **14**	53%
6	 **15**	 **16**	57%
7	 **17**	 **18**	56%
8	 **19**	 **20**	51%
9	 **21**	 **22**	46%

[a] Reaction conditions: $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2.0 equiv), CH_3CN, rt, 12 h. [b] Isolated yield (%) after purification by chromatography on SiO_2. [c] dr 1.75:1. [d] dr 1.3:1. [e] See ref 21.

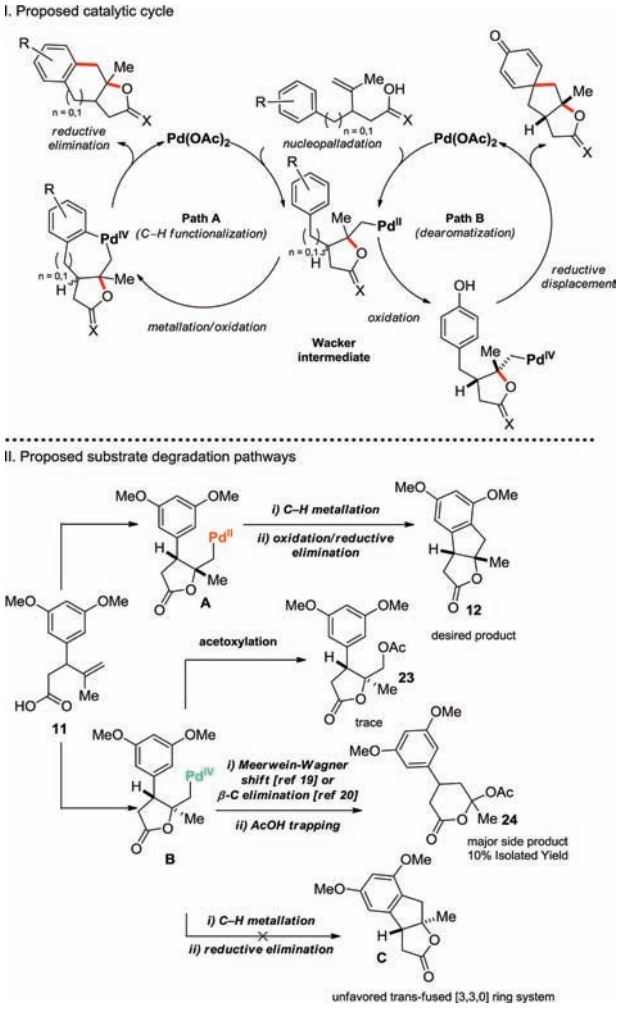


Figure 4. Proposed mechanisms for difunctionalization cascade and degradation pathways.

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Supporting Information Available. Experimental procedures, ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.