

Combined Oxypalladation/C–H Functionalization: Palladium(II)-Catalyzed Intramolecular Oxidative Oxyarylation of Hydroxyalkenes**

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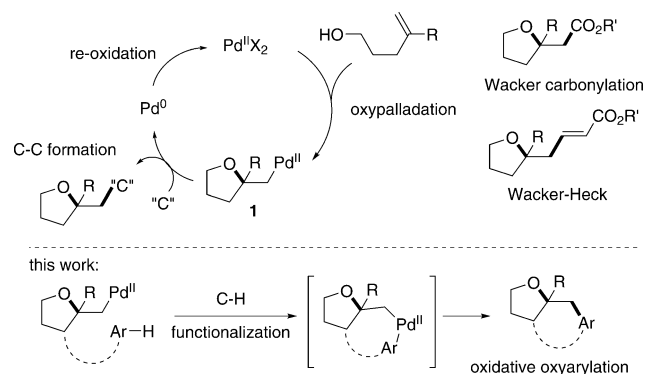
Originating from the classic Wacker process,^[1] the palladium(II)-catalyzed oxidative difunctionalization of alkenes has emerged as an attractive strategy for the rapid generation of molecular complexity due to its ability to form multiple carbon–carbon/carbon–heteroatom bonds and stereogenic centers in a single step.^[2–4] This versatility, combined with the broad functional-group compatibility and air- and moisture-tolerance, renders the Pd^{II}-catalyzed oxidative difunctionalization a powerful tool for synthetic chemists. One of the most synthetically relevant transformations of this class is the Pd^{II}-catalyzed oxidative carboetherification of hydroxyalkenes, which leads to a variety of interesting oxygenated heterocycles.^[5] Pioneered by Semmelhack,^[6] the oxidative carboetherification in the presence of CO or electronically biased olefins has been developed with wide application to complex-molecule synthesis.^[7] Mechanistically such reactions are believed to proceed through a β -alkoxy-alkylpalladium(II) intermediate **1** generated from nucleophilic oxypalladation (Scheme 1). Compared to the more often reported carbon–heteroatom bond forming processes, the scope of

oxidative carbon–carbon bond formation from **1** is still limited.^[8] It is both synthetically and mechanistically interesting to expand the scope of this type of transformation in order to access more structurally diverse molecules.

Aiming to develop a viable method for the catalytic oxidative oxypalladation/arylation of unactivated hydroxyalkenes, we were inspired by the recent development in the field of Pd^{II}-catalyzed directed arene C–H activation/C–C bond formation.^[9] Noting that **1** could undergo cyclopalladation with a proximate arene ring under similar conditions (Scheme 1), we envisioned the possibility of merging the two Pd^{II}-catalyzed transformations, namely the oxypalladation and C–H activation/C–C bond formation.

The success of this strategy lies in the identification of a catalytic system efficient for both the oxypalladation and C–H functionalization steps, as well as the ability to avoid oxidation of the alcohol functional group.^[10] Herein we report a simple and mild Pd^{II}-catalyzed method for the efficient construction of the tetrahydro-2*H*-indeno-[2,1-*b*]furan framework from acyclic hydroxyalkenes bearing unactivated arenes.

We began our study by subjecting 4-methyl-3-phenylpent-4-en-1-ol (**2a**) to a catalytic amount of palladium acetate and a variety of different stoichiometric oxidants. Several



Scheme 1. Scope of the Pd^{II}/Pd⁰-catalyzed oxidative carboetherification.

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Table 1: Representative optimization of the reaction conditions.^[a]

Entry	Ligand (x mol %)	Oxidant (y equiv)	Yield [%] ^[b]
1	none	CuCl ₂ (2)	< 5
2	none	AgOAc (2)	18
3	none	PhI(OAc) ₂ (2)	< 5
4	none	O ₂ (1 atm)	22
5	pyridine (20)	O ₂ (1 atm)	66
6	2,2'-bipyridyl (10)	O ₂ (1 atm)	13
7	1,10-phen (10)	O ₂ (1 atm)	5
8	3-cyanopyridine (20)	O ₂ (1 atm)	71
9	4-DMAP (20)	O ₂ (1 atm)	82
10	ethyl nicotinate (20)	O ₂ (1 atm)	88
11 ^[c]	ethyl nicotinate (20)	O ₂ (1 atm)	< 5
12	ethyl nicotinate (6)	O ₂ (1 atm)	89

[a] Reaction conditions: Pd(OAc)₂ (5 mol %), ligand (x mol %), oxidant (y equiv), K₂CO₃ (0.5 equiv), **2a** (0.1 mmol), toluene (1 mL), 100 °C, 19 h. [b] GC yield using dodecane as an internal standard. [c] Without Pd(OAc)₂.

common combinations for Pd^{II}-catalyzed oxidative C–H activations such as Pd^{II}/Cu^I, Pd^{II}/Ag^I, and Pd^{II}/PhI(OAc)₂ were shown to be ineffective for this transformation (Table 1, entries 1–3).^[8,11] Simple Pd(OAc)₂/pyridine/O₂ (1 atm) system,^[12] however, was able to efficiently catalyze the desired transformation, affording **3a** in moderate yield (entry 5). The use of bidentate pyridine-based ligands were found to significantly retard the reaction (entries 6 and 7).^[13] Tuning the substituents on the pyridine ligand (entries 8–10) led to the identification of ethyl nicotinate^[14] as the optimal ligand. The ligand loading could also be lowered to 6 mol % without loss of yield (entry 12).

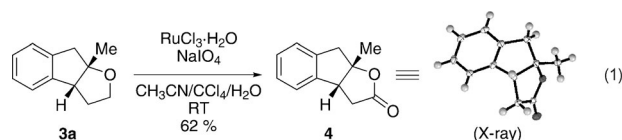
Table 2: Pd^{II}-catalyzed oxidative oxyarylation of hydroxyalkenes.^[a]

Entry	Substrate	Product	Yield [%] ^[b]
1			81
2			58
3			74
4			74
5			80
6			66
7			87
8			69
9			48 ^[c]
10			67
11			73

[a] Reaction conditions: Pd(OAc)₂ (5 mol %), ligand (x mol %), oxidant (y equiv), K₂CO₃ (0.5 equiv), **2a** (0.1 mmol), toluene (1 mL), 100 °C, 19 h. [b] GC yield using dodecane as an internal standard. [c] Without Pd(OAc)₂. [d] Reaction conditions: Pd(OAc)₂ (5 mol %), ethyl nicotinate (6 mol %), O₂ (1 atm), K₂CO₃ (0.5 equiv), **2** (0.5 mmol), toluene (5 mL), 100 °C, 19 h. [e] Yields of isolated products, average of two runs. [f] With 5 mol % CuCl₂ as co-oxidant and 30 mol % ethyl nicotinate. [g] Ratio determined by ¹H NMR spectroscopy.

A variety of α-aryl-γ-hydroxyalkenes could be cyclized to the corresponding tetrahydro-2*H*-indeno-[2,1-*b*]furan derivatives using this Pd^{II}-catalyzed intramolecular tandem oxy-palladation/C–H activation protocol. Illustrative examples of the reaction scope are shown in Table 2. Both alkyl and aryl substituents on the carbon–carbon double bond were tolerated (**3b**, **3c**), as well as tertiary alcohol nucleophile (**3d**).^[15] In addition, a wide range of electron-rich, -neutral and -deficient arenes were found to participate in the C–H activation process (**3e–h**, **3j**). An aryl bromide-containing substrate afforded the desired product (**3i**) in modest yield, although additional quantities of copper(II) chloride proved to be necessary.^[16] This observed orthogonal reactivity relative to the Pd⁰-catalyzed cross-coupling chemistry is useful for the further elaboration of the arene ring. A *meta*-substituted arene (entry 10) cyclized to give a 3:1 mixture of regioisomers favoring the cleavage of the less hindered C–H bond (**3j**, **3j'**). Finally it was found that a pyridyl group could also participate in the C–H activation process with functionalization solely at the 4-position (**3k**).

Lactone **4** can be accessed by one-step oxidation of the oxyarylation adduct **3a** [Equation (1)]. The relative configuration of **4** was confirmed by X-ray diffraction. Lactone **4** is also structurally related to a class of sulindac-derived biologically active molecules which have been used for “precancerous treatment.”^[17]



To gain an insight into the reaction mechanism, deuterium labeling experiments were performed. The observed kinetic isotope effect for both intermolecular and intramolecular cases were found to be approximately 2 (Figure 1).^[18] This

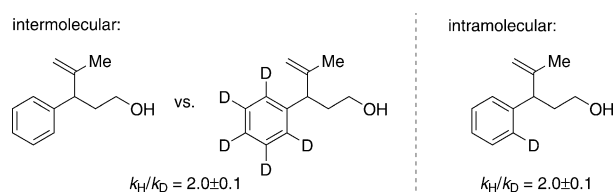
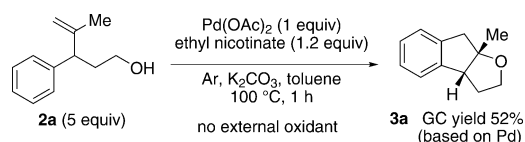


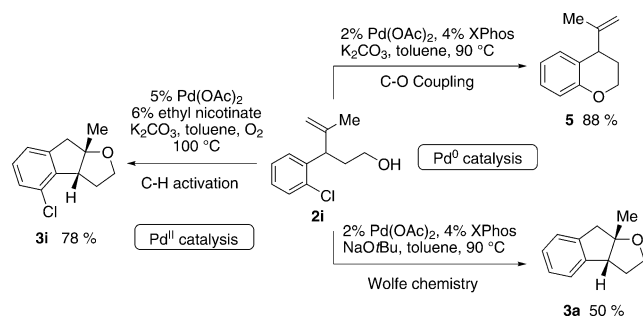
Figure 1. Observed kinetic isotope effect.

observation is consistent with a reaction mechanism in which irreversible C–H bond cleavage is rate-limiting. Next, treating **2a** with palladium acetate under an argon atmosphere in the presence of ethyl nicotinate also afforded cyclization product **3a** (Scheme 2). The formation of **3a** in the absence of external re-oxidant is consistent with the Pd^{II}/Pd⁰ catalytic cycle depicted in Scheme 1.

One of the most interesting aspects of the Pd^{II}-catalyzed oxidative process is its orthogonal reactivity compared with Pd⁰-catalyzed transformations (Scheme 3). Treating hydroxy-



Scheme 2. Oxyarylation in the absence of external oxidant.



Scheme 3. Divergent Pd^{II} catalysis and Pd⁰ catalysis.

alkene **2i** with a catalytic amount of palladium acetate and XPhos in the presence of K₂CO₃ afforded chroman derivative **5** by a classic Pd⁰-catalyzed C–O coupling.^[19] The alkene functional group remained intact. However, switching the base to NaOtBu resulted in the formation of cyclization product **3a** through Pd⁰-catalyzed carboetherification of the alkene originally developed by Wolfe and co-workers.^[5] On the other hand, subjecting **2i** to the standard conditions described in this work led to exclusive formation of **3i** through the desired Pd^{II}-catalyzed oxypalladation/C–H functionalization pathway. Dechlorinated material was not detected. This demonstrates the potential of diversified modification of a single compound containing multiple functional groups using different palladium catalyst systems.

In conclusion, we have developed an efficient protocol for the intramolecular oxidative oxyarylation of hydroxyalkenes by using a Pd^{II}-catalyzed tandem oxypalladation/C–H functionalization strategy. This methodology allows rapid access to tetrahydro-2*H*-indeno-[2,1-*b*]furan framework from simple acyclic hydroxyalkene bearing unactivated arenes or heteroarenes. Further mechanistic studies and application of this strategy to the synthesis of other heterocyclic systems are currently under investigation.

Experimental Section

An oven-dried 50 mL Schlenk tube equipped with a Teflon-coated magnetic stir bar was charged with palladium acetate (5.6 mg, 0.05 equiv) and potassium carbonate (34.5 mg, 0.5 equiv). The tube was then briefly evacuated and backfilled with oxygen (this sequence was repeated a total of four times). Ethyl nicotinate (4.5 mg, 0.06 equiv) and hydroxyalkene (0.50 mmol, 1.0 equiv) were added to the tube followed by anhydrous toluene (5.0 mL) through a syringe. The sealed tube was placed in a pre-heated 100 °C oil bath. After stirring at the same temperature for 19 h the mixture was allowed to cool to room temperature. Diethyl ether (5 mL), methanol (0.25 mL), and sodium borohydride (9.5 mg, 0.5 equiv) were then added and the resulting mixture was stirred for a further 5 min at room temperature. The mixture was then filtered through a short plug

of silica gel and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (EtOAc/hexane) to afford the cyclization product.

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