

Communication

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# Terminal Olefins to Chromans, Isochromans, and Pyrans via Allylic C–H Oxidation

Stephen E. Ammann, Grant T. Rice, M. Christina White\*

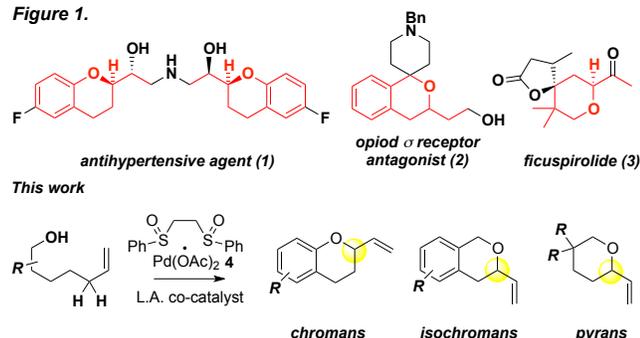
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## Supporting Information Placeholder

**ABSTRACT:** The synthesis of chroman, isochroman, and pyran motifs has been accomplished via a combination of palladium(II)/bis-sulfoxide C–H activation and Lewis acid co-catalysis. A wide range of alcohols were found to be competent nucleophiles for the transformation under uniform conditions (catalyst, solvent, temperature). Mechanistic studies suggest that the reaction proceeds via initial C–H activation followed by a novel inner-sphere reductive elimination functionalization pathway. Consistent with this, the reaction shows orthogonal reactivity trends to traditional Pd(0)-catalyzed allylic substitutions.

Selective C–H oxidation reactions increasingly enable the streamlining of synthetic routes due to their ability to introduce oxygen and nitrogen functionality under conditions orthogonal to those of traditional acid-base methods.<sup>1</sup> In many cases, this is because novel metal-promoted pathways are accessed to effect electrophile and nucleophile activation. Herein we report a Pd(II)/sulfoxide-catalyzed allylic C–H oxidation reaction that proceeds under neutral and uniform conditions to provide access to a wide range of oxygen heterocycles including chromans, isochromans and pyrans.

Figure 1.



Oxygen-containing heterocycles comprise a class of compounds that are widely sought-after for their significant biological properties.<sup>2</sup> Pyrans and benzopyran motifs, such as chromans and isochromans, are pervasive structural elements in biologically relevant small molecules (Figure 1), as displayed by antihypertensive agent **1**, opioid  $\sigma$  receptor antagonist **2**, and *Ficus Microcarpa* natural product ficuspirolide **3**.<sup>3</sup> Reported methods for accessing

such oxygen heterocycle motifs are highly varied, and generally necessitate the use of preoxidized starting materials.<sup>4</sup> Prominently, much work has focused on processes that proceed via Pd(II) oxy-palladation or Pd(0) allylic substitution methods, in some cases with high levels of asymmetric induction,<sup>5b,c</sup> 6b-d utilizing stereochemically defined internal olefins as precursors.<sup>5,6</sup>

Table 1. Reaction Development

Entry	Additive	Catalyst	Solvent	Time	Yield [%] <sup>a</sup>
1	none	<b>4</b>	THF	72 h	18
2	DIPEA	<b>4</b>	THF	24 h	0
3	B(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub>	<b>4</b>	THF	16 h	22
4	Cr(salen)Cl	<b>4</b>	THF	16 h	48
5	Cr(salen)Cl	<b>4</b>	DCE	16 h	79 <sup>d</sup>
6	Cr(salen)BF <sub>4</sub>	<b>4</b>	DCE	16 h	47 <sup>d</sup>
7	Cr(TPP)Cl	<b>4</b>	DCE	16 h	72 <sup>d</sup>
8	Mn(salen)Cl	<b>4</b>	DCE	16 h	45 <sup>d,e</sup>
9	none	<b>4</b>	DCE	16 h	24
10	Cr(salen)Cl	Pd(OAc) <sub>2</sub>	DCE	16 h	<5
11 <sup>b</sup>	Cr(salen)Cl	<b>4</b>	DCE	16 h	9
12 <sup>c</sup>	Cr(salen)Cl	<b>4</b>	DCE	72 h	67 <sup>d</sup>

<sup>a</sup> Yields determined by <sup>1</sup>HNMR with an internal standard (nitrobenzene).

<sup>b</sup> 2,6-dimethylbenzoquinone substituted for 1,4-benzoquinone. <sup>c</sup> 5 mol% **4**.

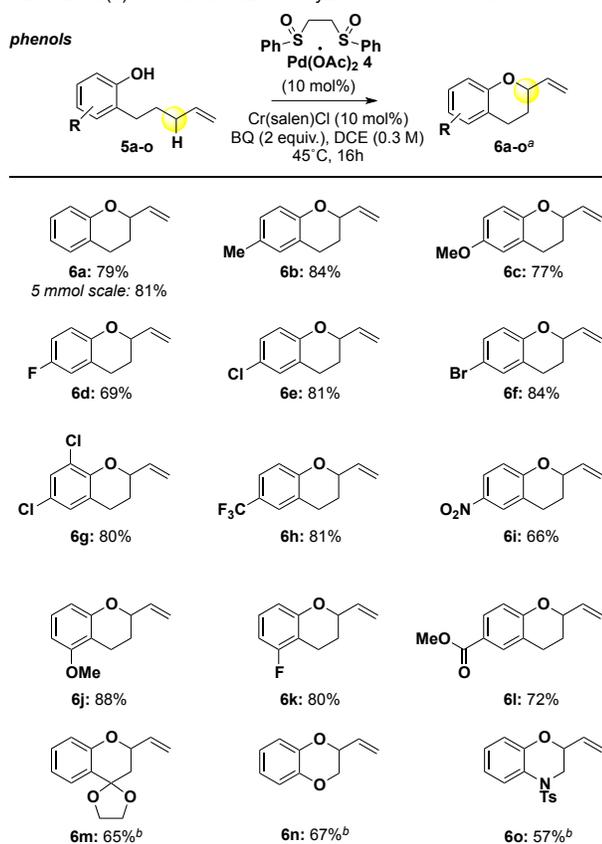
<sup>d</sup> Average of two isolated yields. <sup>e</sup> 43% recovered starting material.

Palladium(II)/bis-sulfoxide catalyzed allylic C–H functionalizations of terminal olefins have shown broad applicability in synthetic methodology.<sup>7</sup> We sought to apply a C–H activation strategy toward a general method for the synthesis of cyclic ether motifs starting from monooxygenated terminal olefin substrates. However, nucleophiles used for allylic C–H functionalization under the mild conditions of palladium sulfoxide catalysis have uniformly possessed pK<sub>a</sub>'s under 6.<sup>7–9</sup> Higher-basicity nucleophiles impede the catalytic cycle, either by deactivation of the Pd catalyst or by failing to undergo deprotonation under the reaction conditions whose only sources of base (the acetate counterion and dihydroquinone generated upon palladium reoxidation) are weak

and catalytic.<sup>7e</sup> With pKa's ranging from ~ 10 for phenol to above 15 for aliphatic alcohols, alcohols represented a major hurdle for allylic oxidations. Initial intermolecular experiments with terminal olefins and excess phenols consistently showed no desired products. Inspired by our oxidative macrolactonization and diol forming reactions, we envisioned rendering the reaction intramolecular might promote alcohol complexation to the palladium, with concomitant acidification enabling deprotonation under neutral conditions.<sup>8,9</sup> Moreover, functionalization (C—O bond formation) may proceed via an inner-sphere reductive elimination mechanism that could have orthogonal scope to classic Pd(0) methods.<sup>8a,10</sup>

Preliminary evaluation of standard Pd(II)/bis-sulfoxide conditions using commercial catalyst **4** furnished chroman **6a** in a modest 18% yield from phenol **5a** (Table 1, entry 1). Increasing the concentration of weak base in solution via addition of catalytic DIPEA shut down reactivity (entry 2).<sup>11</sup> We have previously demonstrated that catalytic amounts of both aza- and oxophilic Lewis acids enhance the reactivity of allylic C—H functionalizations. Whereas the addition of catalytic amounts of B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> did not increase the desired yield (entry 3),<sup>12</sup> inclusion of the oxophilic Lewis acid Cr(salen)Cl resulted in an increase in yield to 40% (entry 4).<sup>7b,9,13</sup> that was further enhanced in 1,2-dichloroethane solvent (79% yield, entry 5). Use of a less-coordinating BF<sub>4</sub> counterion on the Cr Lewis acid diminished reactivity, however use of an analogous, square planar porphyrin ligand results in nearly identical yield of **6a** (entry 6,7). Significantly, a Mn(salen)Cl co-catalyst, previously shown to promote **4**-catalyzed intermolecular C—H aminations, also effected a promising improvement in yield (entry 8).<sup>7b</sup> Removal of the co-catalyst from these optimized reaction conditions resulted in a dramatic decrease in yield (entry 9). Substitution of catalyst **4** for Pd(OAc)<sub>2</sub> resulted in only trace yield

**Table 2.** Pd(II)/bis-sulfoxide/LA Catalyzed Chroman Formation

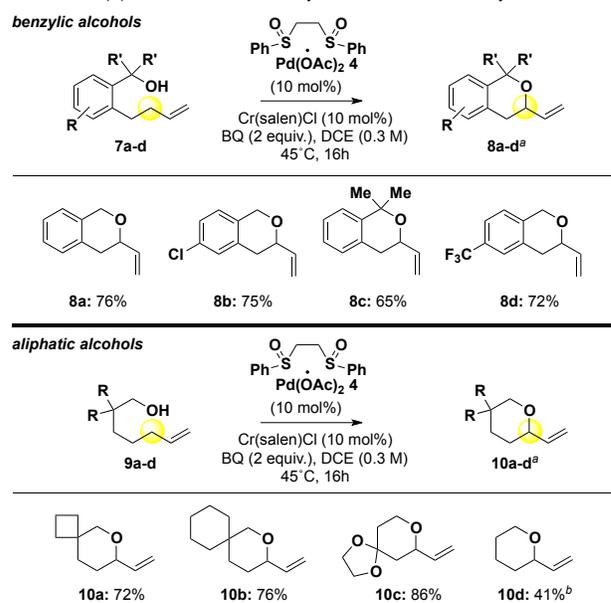


<sup>a</sup> Average isolated yields of two runs at 0.1 mmol. <sup>b</sup> Reaction run for 72 h.

(< 5%) of product, supporting the hypothesis that the reaction proceeds via a C—H cleavage/ $\pi$ -allylpalladium functionalization pathway (entry 10). Consistent with the need for a  $\pi$ -acidic ligand capable of binding to Pd for the Cr co-catalyst effect, the more sterically bulky 2,6-dimethylbenzoquinone caused the reaction to proceed with greatly diminished yield (entry 11).<sup>13</sup> Significantly, the loading of palladium catalyst **4** may be cut in half (5 mol%) with only a minor decrease in yield if reaction times are extended (entry 12).

We next examined the scope of this method for furnishing the 2-vinyl-chroman motif. Gratifyingly, aromatic substitution shows broad tolerance for both electron-donating substituents (Table 2, products **6b**, **6c**, **6j**) and electron-withdrawing substituents (products **6d-6i**, **6k**, **6l**). It is significant to note that even the highly electron-withdrawing trifluoromethyl and nitro groups furnish chroman products in good yields. This is in contrast to what has been observed under Pd(0) allylic substitution conditions where poor reactivity is observed with weakly nucleophilic phenols (*vide infra*).<sup>14</sup> Chloride- and bromide-substituents are well tolerated under these oxidative conditions (products **6e-6g**), and serve as handles for further manipulation. Importantly, representative substrates were selected to illustrate tolerance for substitution on the alkyl chain. The bulky ketal-substituted product **6m** was obtained in a 65% yield, serving as a masked ketone to access chromanone motifs. Oxygen substitution on the alkyl chain furnishes benzodioxan **6n**; similarly, nitrogen substitution allows for formation of dihydro-2,4-benzoxazine product **6o**. Additionally, we were gratified to find that the reaction may be scaled-up 50-fold without any diminishment in yield (product **6a**).

**Table 3.** Pd(II)/bis-sulfoxide/LA Catalyzed Isochroman and Pyran Formation

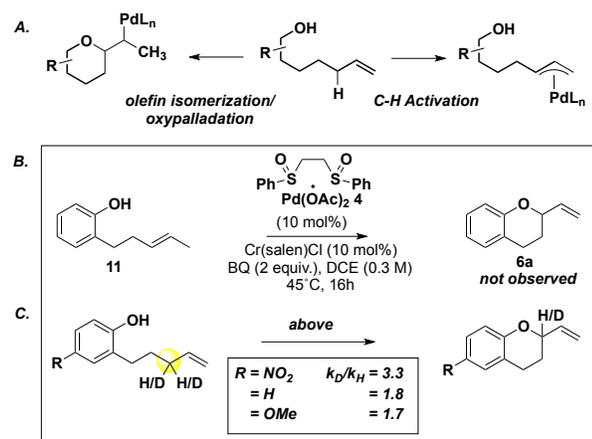


<sup>a</sup> Average isolated yields of two runs at 0.1 mmol. <sup>b</sup> <sup>1</sup>HNMR yield, 48% recovered **9d**.

We hypothesized that such a chelation approach to nucleophile activation may extend beyond phenols to other, significantly less acidic alcohols such as benzylic and even aliphatic alcohols (pKa = 15-16). We were delighted to discover that benzyl alcohol **7a** is converted into 3-vinyl-2-isochroman **8a** in good yield under identical reaction conditions to those used for chroman synthesis (Table 3). Electronic substitution of the aromatic ring is also well tolerated, with chloride- and trifluoromethyl-substituted isochromans produced in good yield (products **8b** and **8d**, respectively).

Additionally, we were pleased to observe that bulky geminal dimethyl-substituted product **8c** is furnished in 65% yield. Given the facile nature of this reaction irrespective of the electronic nature of the alcohol nucleophile, aliphatic alcohols may also function as nucleophiles to furnish pyran motifs. We were delighted to find that the reaction of primary alcohols **9a-c** proceeds under identical conditions to those employed for phenols and benzyl alcohols to furnish 2-vinylpyran products **10a-c** in good yields. While gem-disubstitution is beneficial for cyclization, it is not a requirement for reactivity (Table 3, **10d**).

**Scheme 1.** Mechanistic Experiments: Oxypalladation versus C—H Cleavage

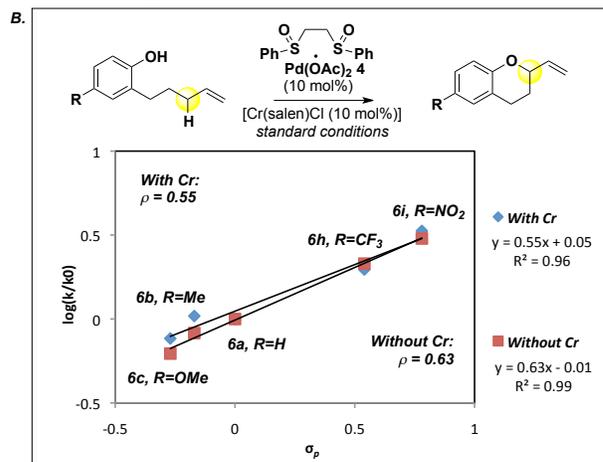
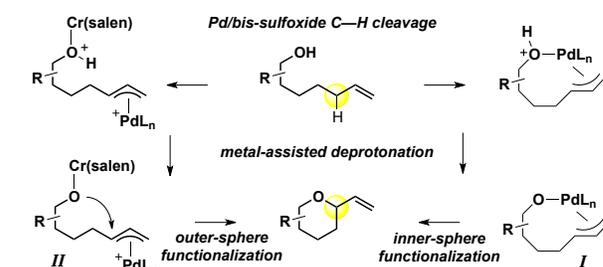


The unexpectedly broad nucleophile scope prompted us to examine the reaction mechanism. Benzopyrans have been generated via Pd(II)-mediated oxypalladation mechanisms from internal olefins, prompting us to evaluate an olefin isomerization/oxypalladation mechanism (Scheme 1A).<sup>5</sup> When internal olefin **11** was subjected to the reaction conditions, minimal conversion and, critically, no chroman product was observed (entry B). Previous studies support that Pd(II)/bis-sulfoxide promotes C—H cleavage from terminal olefins to furnish  $\pi$ -allylPd intermediates and we sought to evaluate if such a mechanism operates here.<sup>7b,8a,13</sup> Isotope labelling studies were undertaken, where separate rate constants were measured for reactions proceeding with allylic hydrogen or deuterium. Interestingly, a range of isotope effects were observed depending on the nature of the alcohol (entry C). With phenol nucleophiles of weak nucleophilicity and modest acidity, isotope effects in the range of 1.7–1.8 were measured, whereas an isotope effect of 3.3 was measured for phenol **5i** with a significantly lower pKa. This is consistent with a scenario where neither C—H cleavage nor deprotonation/functionalization (C—O bond formation) are completely rate-determining and the observed KIE reflects multiple steps.<sup>15</sup>

In considering the functionalization mechanism, metal assisted alcohol deprotonation is necessary to acidify the O—H bond and enable soft deprotonation with the weak acetate and/or dihydroquinone base.<sup>16</sup> Significantly, the course for functionalization may be determined depending on the metal assisting in deprotonation:  $\pi$ -allylPd coordination/deprotonation generates **I**, the precursor for inner-sphere functionalization at the palladium, whereas Cr(salen) assisted deprotonation would promote in an outer-sphere delivery to the  $\pi$ -allylPd via **II** (Scheme 2A). To evaluate the latter possibility, a Hammett analysis of the reaction catalyzed by both Pd(II)/bis-sulfoxide **4** and Cr(salen)Cl was compared to a second Hammett analysis of the background reaction catalyzed only by **4** (Scheme 2B). The absence of a signifi-

**Scheme 2.** Functionalization Step: Mechanistic Examination

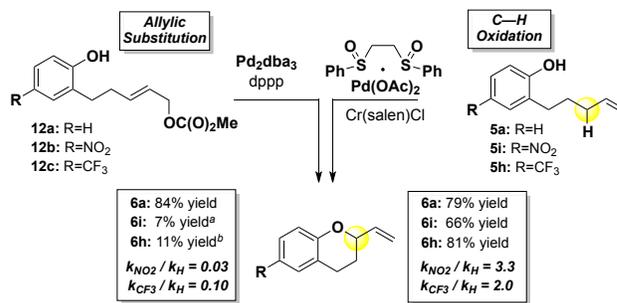
**A. Metal-assisted deprotonation/functionalization**



cant change in rho values leads us to favor a mechanism whereby deprotonation and functionalization occur at palladium.

Dissociation of the alkoxide from  $\pi$ -allylPd **I** followed by an outer-sphere  $\pi$ -allylPd functionalization should have analogous trends in reactivity to Pd(0)-mediated allylic substitution reactions known to proceed via outer-sphere alkoxide functionalization of  $\pi$ -allylPd.<sup>6,14,17</sup> We examined the yields and initial rates of chroman formation for Pd(0)-mediated allylic substitution with electron-deficient and electron neutral substrates, and compared these to the allylic C—H oxidation reaction (Scheme 3). When allylic carbonate substrate **12a** containing an electron-neutral phenol was subjected to standard Pd(0) allylic substitution conditions, 2-vinyl-chroman **6a** was formed in good yield (84% yield); however, when *para*-nitrophenol or *para*-trifluoromethyl substrates

**Scheme 3.** Allylic C—H oxidation versus allylic substitution



<sup>a</sup> 80% recovered starting material. <sup>b</sup> 78% recovered starting material.

(**12b**, **12c**) were exposed to identical Pd(0) conditions, reactivity was significantly retarded (7% and 11% yields, respectively, Scheme 3). In both cases, this drop in reactivity correlates with a significant decrease in reaction rate ( $k_{NO_2} / k_H = 0.03$ ;  $k_{CF_3} / k_H = 0.10$ ).<sup>14</sup> In contrast, chroman yields for allylic C—H oxidation do not show a significant dependence on the electronic properties of

the alcohol, and the Hammett analysis of the Pd(II)/bis-sulfoxide/Cr(salen)Cl catalyzed allylic C—H oxidation reaction reveals that reaction rate is modestly *enhanced* by electron-withdrawing groups on the phenol pro-nucleophile, presumably reflecting a more facile deprotonation ( $k_{\text{NO}_2}/k_{\text{H}} = 3.3$ ; ( $k_{\text{CF}_3}/k_{\text{H}} = 2.0$ ) (Schemes 2 and 3).<sup>18</sup> Such dramatic switches in reactivity and reaction rate trends are unlikely to be due to the different mechanisms for  $\pi$ -allylPd formation, therefore, we take this as further evidence of a major deviation from the classical outer-sphere functionalization model. Although we cannot definitively rule out all outer-sphere functionalization pathways, on the basis of evidence presented we view it as highly unlikely.<sup>19</sup> Broad nucleophile scope is likely a consequence of such a metal-chelation approach, serving as a “dampening effect” for the nucleophiles’ electronic character. We have previously provided evidence that Pd(II)/sulfoxide-catalyzed C—H functionalizations with oxygen nucleophiles (e.g. carboxylates) proceed via an inner-sphere reductive elimination step.<sup>7a,8a,9</sup> The mechanistic findings herein constitute further evidence for such a pathway.

In summary, we have developed a general Pd(II)/bis-sulfoxide-catalyzed allylic oxidation method to afford for the first time direct access to chroman, isochroman, and pyran motifs starting from terminal olefins. This operationally simple method (open to air and moisture) proceeds with high substrate generality under uniform conditions (catalyst, solvent, temperature). Its low sensitivity to the electronic nature of the alcohol nucleophile along with inverse electronic trends observed for reaction rate relative to outer-sphere Pd(0)-catalyzed allylic substitutions, argues for an allylic C—H functionalization mechanism proceeding via inner-sphere palladium coordination/activation of the oxygen nucleophile and subsequent reductive elimination. We anticipate that this general strategy will help to broaden the scope of pro-nucleophiles used in C—H functionalization reactions.

## ASSOCIATED CONTENT

Experimentals, characterization data, and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest. GTR is now a student at Duke Law School.

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(18) A KIE of 5.2 for aliphatic **9b**, along with the fact that **9b** shows a more than two-fold rate *increase* when compared to phenol **5a**, indicates that a trend based purely on nucleophile pKa does not provide a complete picture for all alcohols and different aspects of the nucleophilicity of alcohols must be considered.

(19) For example, attack of the protonated nucleophile onto the  $\pi$ -allylPd electrophile followed by a deprotonation step would also be consistent with electron-deficient phenols reacting at a faster rate.

