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

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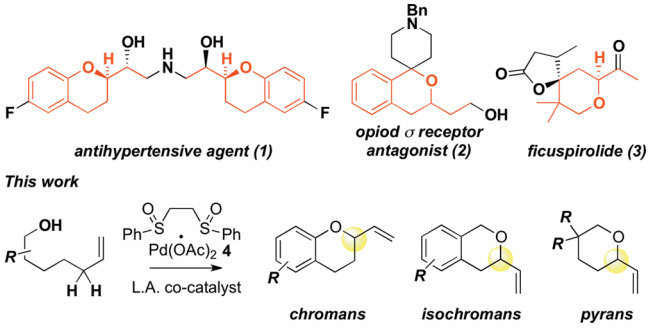
Supporting Information

ABSTRACT: The synthesis of chroman, isochroman, and pyran motifs has been accomplished via a combination of Pd(II)/bis-sulfoxide C−H activation and Lewis acid co-catalysis. A wide range of alcohols are 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 functionalization pathway. Consistent with this, the reaction shows reactivity trends orthogonal to those of traditional Pd(0)-catalyzed allylic substitutions.

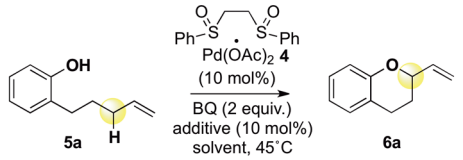
Selective C−H oxidation reactions enable streamlining synthetic routes due to their ability to introduce oxygen and nitrogen functionality under conditions orthogonal to those of traditional acid−base methods.[1] Often, this is because novel metal-promoted pathways are accessed to effect electrophile and nucleophile activation. Here 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 benzopyran and pyran motifs.

Chart 1



Oxygen-containing heterocycles are widely sought for their significant biological properties.[2] Pyrans and benzopyran motifs, such as chromans and isochromans, are pervasive structural elements in biologically relevant small molecules (Chart 1), as displayed by antihypertensive agent **1**, opiod σ receptor antagonist **2**, and *Ficus microcarpa* natural product ficuspirolide **3**.[3] Reported methods for accessing such oxygen heterocycle motifs are highly varied and generally necessitate the use of preoxidized starting materials.[4] Prominently, much work has focused on processes that proceed via Pd(II) oxypalladation or Pd(0) allylic substitution methods, in some cases with high levels of asymmetric induction,[5b,c,6b−d] utilizing stereochemically defined internal olefins as precursors.[5,6]

Table 1. Reaction Development



Entry	Additive	Catalyst	Solvent	Time	Yield [%][a]
1	none	**4**	THF	72 h	18
2	DIPEA	**4**	THF	24 h	0
3	$B(C_5F_6)_3$	**4**	THF	16 h	22
4	Cr(salen)Cl	**4**	THF	16 h	48
5	Cr(salen)Cl	**4**	DCE	16 h	79[d]
6	$Cr(salen)BF_4$	**4**	DCE	16 h	47[d]
7	Cr(TPP)Cl	**4**	DCE	16 h	72[d]
8	Mn(salen)Cl	**4**	DCE	16 h	45[d,e]
9	none	**4**	DCE	16 h	24
10	Cr(salen)Cl	$Pd(OAc)_2$	DCE	16 h	<5
11[b]	Cr(salen)Cl	**4**	DCE	16 h	9
12[c]	Cr(salen)Cl	**4**	DCE	72 h	67[d]
13	Ag(OTf)	**4**	THF	16 h	18

[a] Yields determined by ^{1}HNMR with an internal standard (nitrobenzene). [b] 2,6-dimethylbenzoquinone substituted for 1,4-benzoquinone. [c] 5 mol% **4**. [d] Average of two isolated yields. [e] 43% recovered starting material.

Pd(II)/bis-sulfoxide-catalyzed allylic C−H functionalizations of terminal olefins have shown broad applicability in synthetic methodology.[7] 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_a's under 6.[7−9] Higher-basicity nucleophiles impede the catalytic cycle either by deactivating the Pd catalyst or failing to undergo deprotonation under the reaction conditions whose only sources of base (the acetate counterion and dihydroquinone generated upon Pd reoxidation) are weak and catalytic.[7e] With pK_a's ranging from ∼10 for phenol to >15 for aliphatic alcohols, alcohols represented a major hurdle for allylic oxidations. Initial intermolecular experiments with

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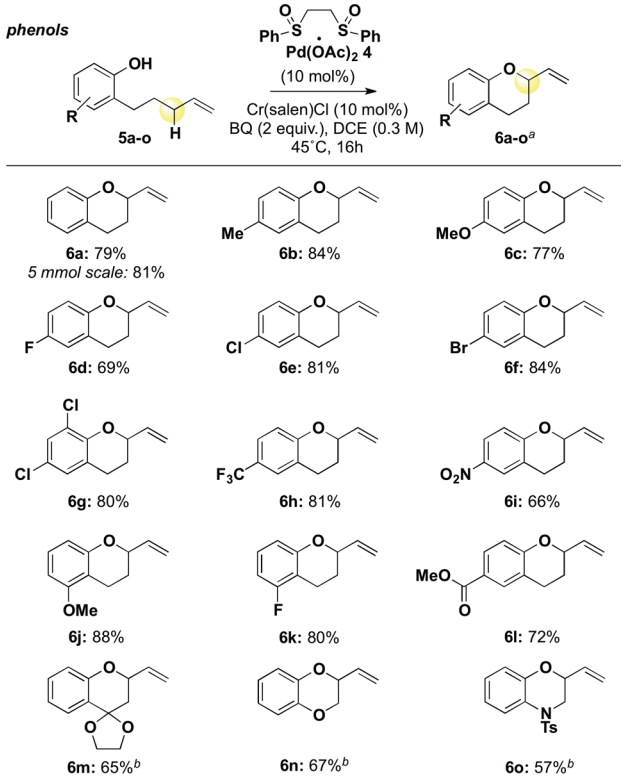
terminal olefins and excess phenols consistently showed no desired products. Inspired by our oxidative macrolactonization and diol-forming reactions, we envisioned that rendering the reaction intramolecular might promote alcohol complexation to the Pd, with concomitant acidification enabling deprotonation under neutral conditions.[8,9] 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.[8a,10]

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).[11] We have previously demonstrated that catalytic amounts of both aza- and oxophilic Lewis acids (LAs) enhance the reactivity of allylic C−H functionalizations. Whereas the addition of catalytic amounts of $B(C_6F_5)_3$ did not increase the yield (entry 3),[12] inclusion of the oxophilic LA Cr(salen)Cl resulted in an increase to 40% yield (entry 4)[7b,9,13] that was further enhanced in 1,2-dichloroethane solvent (79% yield, entry 5). Use of a less-coordinating BF_4 counterion on the Cr LA diminished reactivity; however, use of an analogous, square planar porphyrin ligand resulted in nearly identical yields of **6a** (entries 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).[7b] Removal of the co-catalyst from these optimized reaction conditions resulted in a dramatic decrease in yield (entry 9). Substitution of catalyst **4** for $Pd(OAc)_2$ resulted in only trace yield (<5%) of product, supporting the hypothesis that the reaction proceeds via a C−H cleavage/π-allylPd functionalization pathway (entry 10). Consistent with the need for a π-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).[13] Significantly, the loading of Pd catalyst **4** may be cut in half (5 mol%) with only a minor decrease in yield if reaction times are extended (entry 12).

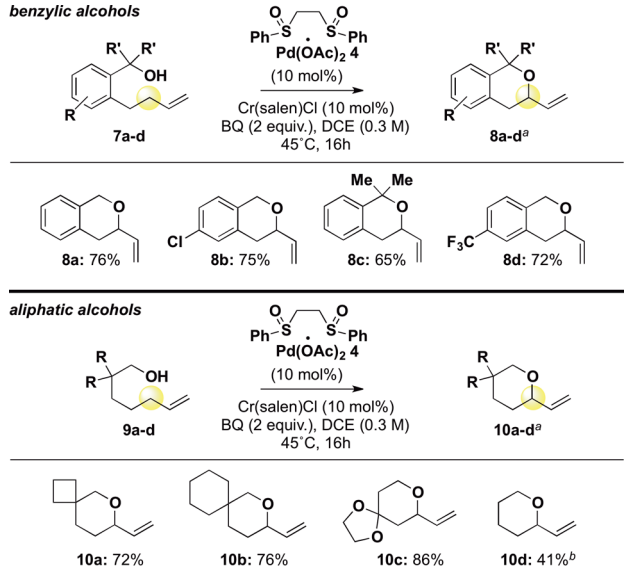
We next examined the scope of this method for furnishing the 2-vinylchroman motif. Gratifyingly, aromatic substitution shows broad tolerance for both electron-donating substituents (Table 2, products **6b**, **6c**, **6j**) and electron-withdrawing substituents (products **6d**−**6i**, **6k**, **6l**). 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 the reaction under Pd(0) allylic substitution conditions, where poor reactivity was observed with weakly nucleophilic phenols (*vide infra*).[14] 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** is obtained in 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 2. Chroman Formation



[a] Average isolated yields of two runs at 0.1 mmol. [b] Reaction run for 72 h.

Table 3. Isochroman and Pyran Formation



[a] Average isolated yields of two runs at 0.1 mmol. [b] ^{1}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 (pK_a = 15−16). We were delighted to discover that benzyl alcohol **7a** is converted into 3-vinyl-2-isochroman **8a** in good yield under reaction conditions *identical* 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 yields (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

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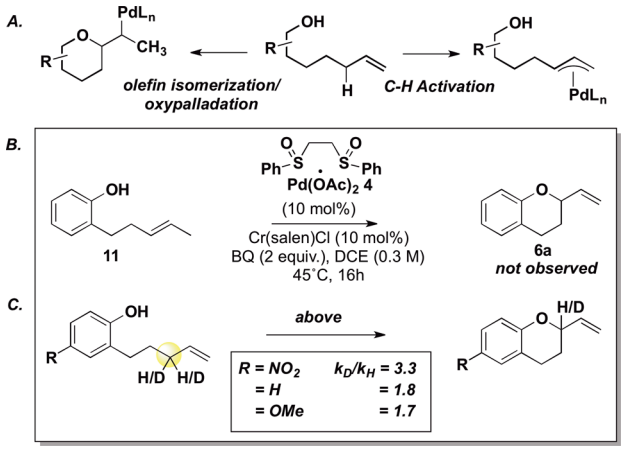
nucleophile, aliphatic alcohols may also function as nucleophiles to furnish pyran motifs. We found that the reaction of primary alcohols **9a**–**9c** proceeds under conditions identical to those employed for phenols and benzyl alcohols to furnish 2-vinylpyran products **10a**–**10c** in good yields. While gem-disubstitution is beneficial for cyclization, it is not a requirement for reactivity (Table 3, **10d**).

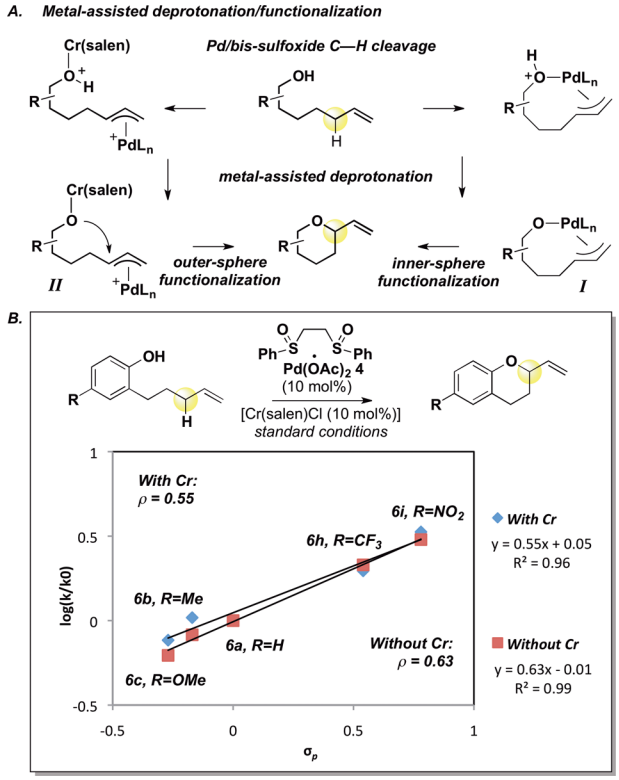
Scheme 1. Mechanistic Experiments: Oxypalladation versus C–H Cleavage



The unexpectedly broad nucleophile scope led 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).[5] When internal olefin **11** was subjected to the reaction conditions, minimal conversion and, critically, no chroman product was observed (Scheme 1B). Previous studies support that Pd(II)/bis-sulfoxide promotes C–H cleavage from terminal olefins to furnish π-allylPd intermediates, and we sought to evaluate if such a mechanism operates here.[7b,8a,13] Isotope labeling studies were undertaken, where separate rate constants were measured for reactions proceeding with allylic hydrogen or deuterium. Interestingly, a range of kinetic isotope effects (KIEs) were observed, depending on the nature of the alcohol (Scheme 1C). With phenol nucleophiles of weak nucleophilicity and modest acidity, KIEs of 1.7–1.8 were measured, whereas a KIE of 3.3 was measured for phenol **5i**, with a significantly lower pK_a. This is consistent with a scenario where neither C–H cleavage nor deprotonation/functionalization (C–O bond formation) is completely rate-determining, and the observed KIE reflects multiple steps.[15]

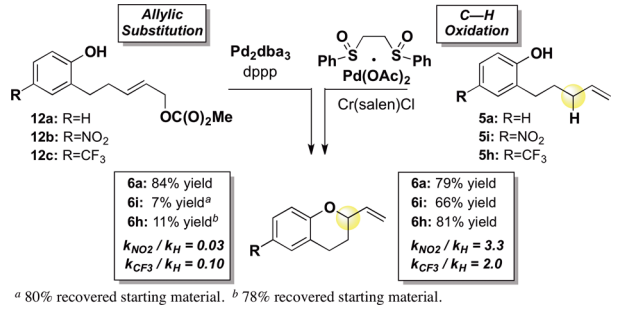
In considering the functionalization mechanism, metal-assisted alcohol deprotonation is necessary to acidify the O–H bond and enable soft deprotonation with the weak acetate and/or dihydroquinone base.[16] Significantly, the course for functionalization may be determined by the metal assisting in deprotonation: π-allylPd coordination/deprotonation generates ***I***, the precursor for inner-sphere functionalization at the Pd, whereas Cr(salen)-assisted deprotonation would promote in an outer-sphere delivery to the π-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 significant change in ρ values leads us to favor a mechanism whereby deprotonation and functionalization occur at Pd.

Scheme 2. Functionalization Step: Mechanistic Examination



Dissociation of the alkoxide from π-allylPd ***I*** followed by an outer-sphere π-allylPd functionalization should show a reactivity trend analogous to that of Pd(0)-mediated allylic substitution reactions known to proceed via outer-sphere alkoxide functionalization of π-allylPd.[6,14,17] 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 them to those of 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-vinylchroman **6a** was formed in good yield (84%); however, when *p*-nitrophenol and *p*-trifluoromethyl substrates **12b** and **12c** were exposed to

Scheme 3. Allylic C–H Oxidation versus Allylic Substitution



[a] 80% recovered starting material. [b] 78% recovered starting material.

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).[14] In contrast, chroman yields for allylic C–H oxidation do not show a significant dependence on the electronic properties of the alcohol, and the

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Hammett analysis of the Pd(II)/bis-sulfoxide/Cr(salen)Cl-catalyzed allylic C−H oxidation reaction reveals that the reaction rate is modestly *enhanced* by electron-withdrawing groups on the phenol pro-nucleophile, presumably reflecting a more facile deprotonation (k_{NO_2}/k_H = 3.3; k_{CF_3}/k_H = 2.0) (Schemes 2 and 3).[18] Such dramatic switches in reactivity and reaction rate trends are unlikely to be due to the different mechanisms for π-allylPd formation; thus, 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.[19] 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.[7a,8a,9] 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 Pd 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

Supporting Information

Experimental details and characterization data. 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.

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(18) A KIE of 5.2 for aliphatic alcohol **9b**, along with a 2-fold rate increase of **9b** compared to phenol **5a**, indicates that a trend based purely on nucleophile pK_a does not apply to all alcohols and different aspects of the nucleophilicity must be considered.

(19) Attack of protonated alcohol on the π-allylPd followed by deprotonation is also consistent with a faster rate for electron-deficient phenols.