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Allylic Oxidations of Terminal Olefins Using a Palladium Thioether Catalyst

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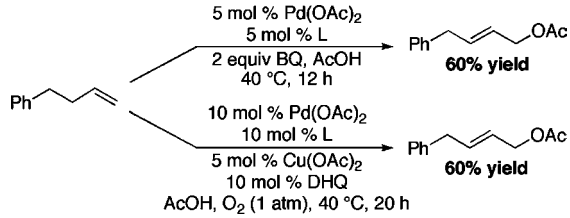
ABSTRACT



A palladium catalyst that converts terminal olefins to linear allylic acetates at lower catalyst loadings and faster reaction times than current systems is reported. This reaction can be conducted using benzoquinone as the oxidizing agent or catalytic amounts of copper and hydroquinone under one atmosphere of oxygen. Preliminary reactivity studies of π-allylpalladium complexes under our reaction conditions do not provide results similar to those obtained in the catalytic reaction, which may suggest an alternative reaction pathway. The palladium catalyst is ligated by an aryloxyalkyl aryl sulfide, which is identified as a new ligand for homogeneous catalysis.

The functionalization of allylic C−H bonds via selective oxidation reactions has the potential to greatly impact the synthesis of complex molecules.[1] Traditionally, allylic oxidations have been mediated by selenium[2a] and copper,[2b,c] but functional group tolerance and low selectivities are problematic for these metals. Other metals such as mercury[2d] and rhodium[2e] have also been investigated. Over four decades ago, a stoichiometric $Pd(OAc)_2$-promoted oxidation of the allylic C−H bond of 1-butene in neat AcOH was reported to give the corresponding vinyl acetate as the major product along with 9% of the linear allylic acetate.[3] However, the addition of DMSO provided an 8-fold increase of linear allylic acetate. Although much work has been done on allylic oxidations of disubstituted olefins since these findings,[4] few selective methods for allylic oxidation reactions of terminal olefins to allylic acetates have been reported.[5,6] White and co-workers showed that palladium(II) complexes ligated by sulfoxides catalyzed the conversion of terminal alkenes to either linear or branched allylic acetates with very good selectivities.[6] However, some of the challenges that remain include high catalyst loadings, long reaction times, and the requirement of excess benzoquinone (BQ). Herein, we present a unique aryloxyalkyl aryl sulfide palladium catalyst that converts terminal olefins to linear allylic acetates in good yields and regioselectivities. This allylic oxidation reaction

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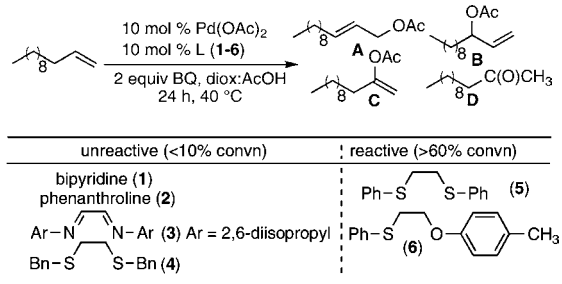
operates at decreased catalyst loadings, in shorter reaction times and without the need for excess benzoquinone.

In addition to the synthetic utility of oxidations of allylic C−H bonds,[7] we were attracted to the mechanism proposed for the palladium-catalyzed allylic oxidation reactions using sulfoxide ligands.[6b] Moreover, our group has a specific interest in the interaction of late transition metal complexes with sulfur,[8] which has been wrongly considered to operate solely as a poison in the presence of palladium. Using 1-dodecene as the test substrate, we investigated palladium-catalyzed allylic oxidation reactions using bidentate or hemilabile bidentate sulfur- and nitrogen-based ligands. We hypothesized that the tighter binding of the sulfur- and nitrogen-based ligands (relative to the sulfoxide ligands) may increase the overall reaction rate while still favoring the branched regioisomer. We reasoned that since the weaker binding DMSO ligand favored the linear product[3a,6a] and the stronger binding bis-sulfoxide ligand favored the branched product[6b] ligands that bound more tightly than bis-sulfoxides may also favor the branched product. The tighter binding would increase the overall reaction rate because of the probability that the ligand would spend more time at the metal center. Phosphines were not employed because both McMurry[5a] and White[6b] have shown that phosphines increase the overall reaction rate but provide approximately 1:1 mixtures of branched and linear allylic acetate products.

The use of 10 mol % $Pd(OAc)_2$ in combination with nitrogen ligands **1**−**3** or sulfur ligand **4** failed to produce more than trace amounts of allylic acetate products by GC (Table 1). However, 1,2-bis(phenylthio)ethane (**5**) and

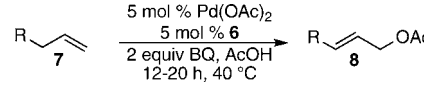
Table 1. Ligands Tested in Pd-Catalyzed Allylic Oxidation of 1-Dodecene



$Pd(OAc)_2$ gave 65% conversion of 1-dodecene to allylic acetates **A** and **B** (40:1), along with trace amounts of vinyl acetate **C** and methyl ketone **D**. After this result, we quickly discovered that a catalyst formed from 2-tolyloxylethyl phenyl sulfide (**6**) and $Pd(OAc)_2$ completely converted 1-dodecene to **A**−**D** in a 19:2:3:1 ratio, respectively. Further optimization of this catalyst found acetic acid to be the optimal solvent as 5 mol % $Pd(OAc)_2$ and **6** gave 85% conversion of 1-dodecene to products **A**−**D** with a 23:1 ratio of linear to branched products, while suppressing side products **C** and **D** (Supporting Information). The use of $Pd(OAc)_2$/**6** allowed for lower catalyst loadings, which lessened the amount of side products formed. Our hypothesis was partially correct: the reaction rate increased, but the favored product was the linear allylic acetate, not the branched. To our knowledge, this class of ligand has never been used in any transition-metal-catalyzed reactions.

With optimized conditions in hand, the scope of this catalyst system was probed (Table 2). All of the compounds

Table 2. Scope of Allylic Oxidation Reactions Using 5 mol % of $Pd(OAc)_2$ and **6**



entry	alkene	time (h)	product	yield(%)[a]
1	**7a**	16	**8a**	68
2	**7b**	14	**8b**	68
3	**7c**	20	**8c**	65
4	**7d**	12	**8d**	60
5	**7e**	15	**8e**	52
6	**7f**	14	**8f**	78[b]
7	**7g**	15	**8g**	59
8	**7h**	16	**8h**	70[c]
9	**7i**	14	**8i**	32
10	**7j**	12	**8j**	53
11	**7k**	20	**8k**	42
12	**7l**	14	**8l**	49

[a] Isolated yields shown are of only the (*E*) isomer (>95% by ^{1}H NMR spectroscopy) and are an average of two (1 mmol) reactions. [b] Product is a 2:1 mixture of linear and branched isomers. [c] Yield is a mixture of 10:1 (*E*:*Z*) isomers and contains a trace of an unidentified side product.

in the table were isolated as the pure (>95% by ^{1}H NMR spectroscopy) linear (*E*)-allylic acetate unless noted, and the yields are an average of two reactions. The reaction times were optimized to favor the greatest conversion with the least amount of branched allylic acetate, vinyl acetate, and ketone side products (Table 1, **B**−**D**). Nonetheless, all of the alkenes underwent ≥85% conversion in all reactions. Most of the reactions were highly selective for

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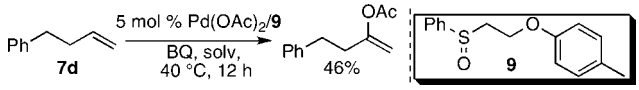
linear allylic oxidation products. Allylic (entries 1−3) and homoallylic (entry 4) arenes provided the corresponding linear products in good yields regardless of the substitution present on the arene. The reaction conditions also tolerated amides, carbamates, esters, ethers, and acetals (entries 6−12). The only substrate that did not provide good L:B selectivity contained an amide, which likely coordinates to the metal center and disrupts the Pd−S dative bond present in the high selectivity catalyst in these reactions (entry 6). The low yield obtained for the PMB-ester (entry 9) may be a result of some type of oligomerization or other side reaction as ≥90% conversion of the alkene was observed. The GC spectrum contained only minor amounts of the corresponding vinyl acetate and methyl ketone products, and attempts to isolate any other major products were fruitless. In a separate experiment, 1-dodecene was submitted to the catalytic conditions in the absence of benzoquinone or air, and <5% of the terminal alkene was isomerized to 2-dodecene. Therefore, it is not likely that the unknown side products are emanating from oxidation products formed from the corresponding internal alkene.

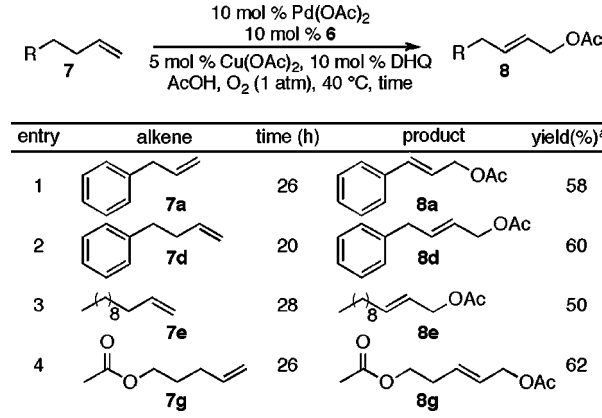
The oxidation of sulfides to sulfoxides is facile, and thus it is reasonable to believe that the reaction conditions employed may oxidize sulfide ligand **6** to the corresponding sulfoxide ligand **9** and that **9** binds to palladium to form the active catalyst. Sulfide ligand **6**, not sulfoxide ligand **9**, is observed in the GC spectrum upon analysis of the oxidation reaction under our standard conditions shown in Table 2. Nonetheless, we prepared ligand **9** and tested its reactivity with $Pd(OAc)_2$ under optimal reaction conditions. The major product of this reaction was the corresponding vinyl acetate, which was isolated in 46% yield. The reaction did not go to completion as approximately 30% of the starting alkene was observed in the GC spectrum (Scheme 1).

Scheme 1. Allylic Oxidation with Sulfoxide Version of **6**



The requirement of excess BQ is one drawback to this catalytic process. For example, allylic oxidation of 10 g of 4-phenyl-1-butene requires approximately 16 g of BQ. We recently discovered that our reaction conditions can be modified to replace the 2 equiv of BQ with a catalytic amount of copper and dihydroquinone (DHQ) under 1 atm of O_2.[9] The catalyst loading had to be increased to 10 mol % in $Pd(OAc)_2$ and ligand (**6**). However, these conditions allowed the production of the corresponding linear allylic acetates from a range of terminal alkenes (Table 3). The products shown in the table are of the (*E*) isomer. The yields of linear allylic acetates are equivalent

Table 3. Pd-Catalyzed Allylic Oxidations Without Excess BQ



[a] Isolated yields shown are of only the (*E*) isomer (>95% by ^{1}H NMR spectroscopy) and are an average of two (1 mmol) reactions.

to or slighly decreased in comparison to the yields obtained using 2 equiv of BQ shown in Table 2.

The mechanism of this process is unclear at this stage of our research. Although Pd complexes coordinated to mixed (*S,O*) ligands have been previously isolated,[10] aryloxyalkyl aryl sulfide palladium complexes have not. Observation of the interaction of **6** with $Pd(OAc)_2$ showed coordination of **6** to Pd by ^{1}H NMR spectroscopy (Supporting Information); however, any attempts to isolate the complex that gave rise to these resonances only produced intractable oils. The expected coordination of ligand **6** to palladium is mainly through sulfur with the aryl ether providing only moderate support as a potential hemilabile ligand. Surprisingly, we were able to isolate **10** $Pd[PhS(CH_2)_2OAr]_2Cl_2$ (Ar = *p*-$CH_3C_6H_4$) (Figure 1). The X-ray structure of this complex

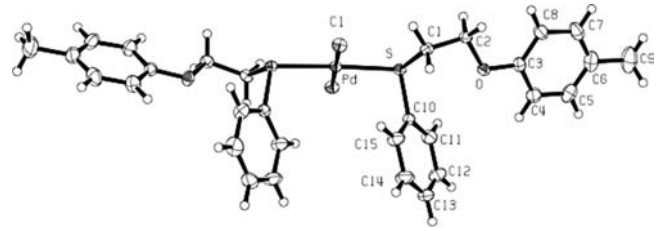


Figure 1. ORTEP structure of **10** shown at 50% ellipsoid probability.

showed the ligands bound solely through sulfur with no close contact between the metal center and oxygen atoms. Submission of this complex to the standard reaction conditions did not provide any allylic acetate product until **10** was pretreated with 2 equiv of AgOAc (Scheme 2). The yield of this reaction is lower than observed under the standard reaction

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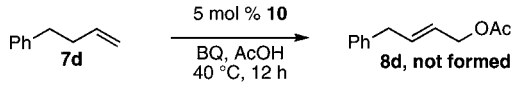
Scheme 2. Allylic Oxidations Using an Isolated Bisthioether Palladium Complex

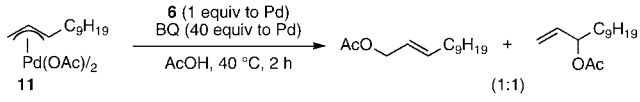


with 10 mol % AgOAc: **37% yield (*E*) isomer**

conditions that consist of a 1:1 ratio of metal to ligand. Complex **10** contains two thioether ligands on palladium, and the use of a 1:2 ratio of metal to ligand under the typical conditions shown in Table 2 provides the (*E*)-linear allylic acetate product in 50% yield. The slightly lower yield observed in Scheme 2 may be caused by insufficient formation of the $L_2Pd(OAc)_2$ (L = **6**) complex. The origin of this ligand effect is not known. However, when catalytic transformations proceed more slowly in the presence of excess ligand rather than an equimolar amount of ligand, it is sometimes because the presence of excess ligand retards the rate of the ligand dissociation step that may be a prerequisite for catalyst activation.[11] Therefore, the active catalyst in this system likely requires one ligand per palladium.

Palladium-catalyzed allylic oxidation reactions are expected to proceed via π-allylpalladium intermediates or through a mechanism that begins with an initial acetoxypalladation step.[12] To begin investigations into the reaction pathway, we prepared a π-allylpalladium acetate complex of dodecene (**11**) (Scheme 3). This complex was reacted with

Scheme 3. Intermediacy of a π-Allylpalladium Acetate Dimer



40 equiv of BQ and 1 equiv of **6** in AcOH at 40 °C for 4 h to mimic the actual reaction conditions.[6b] Observation of the crude reaction mixture by GC analysis did not reveal the expected allylic acetate in a 20:1 (L:B) ratio as observed in the catalytic reaction; rather, a 1:1 mixture of the linear and branched products was observed. The addition of 1 equiv of ligand **6** to π-allylpalladium complex **11** provided <4% of allylic acetate products, while the addition of 40 equiv of BQ favored the branched product in a 3:1 (B:L) ratio. The preliminary results obtained using this π-allylpalladium dimer along with the ability to conduct this reaction without excess benzoquinone suggests that the allylic oxidation of 1-dodecene under our reaction conditions does not proceed via this specific π-allylpalladium complex.

Under the optimized catalytic conditions shown in Table 2, isolated linear allylic acetate (48:1) L:B deteriorates to a 30:1 (L:B) ratio of allylic acetate over 12 h.[13] Under these identical conditions, isomerically pure branched allylic acetate is transformed to a mixture of branched and linear allylic acetates in a 2:1 (B:L) ratio over 12 h. However, monitoring the reaction progress of the allylic oxidation of 1-dodecene (Table 2, entry 5) by GC shows that the reaction does not begin to produce branched product until about 3 h when a 58:1 (L:B) ratio is observed in the GC spectrum. This high L:B ratio decreases to 43:1 after 5 h, 34:1 after 8 h, and ultimately around 20:1 after 12 h. Therefore, we do not believe that the catalyst is first producing branched allylic acetate product that is quickly isomerized to the linear allylic acetate.

In summary, we have demonstrated a palladium-catalyzed allylic oxidation of terminal olefins using a unique thioether catalyst that occurs at lower catalyst loadings, faster reaction times than previous systems, and without the need for superstoichiometric benzoquinone. Further studies involving the use of this catalyst in other processes as well as developing a clear mechanistic picture of this allylic oxidation reaction continue.

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Supporting Information Available: Experimental procedures and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For a potential mechanism of this process, see: Marion, N.; Gealageas, R.; Nolan, S. P. *Org. Lett.* **2007**, *9*, 2653, and references contained therein.