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Sulfur-Directed Olefin Oxidations: Observation of Divergent Reaction Mechanisms in the Palladium-Mediated Acetoxylation of Unsaturated Thioacetals

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Summary: The Pd-mediated oxidation of unsaturated thioacetals gives either allyl or vinyl esters depending on the substrate structure. We report the characterization of a range of sulfur-stabilized palladium intermediates via a combined computational and experimental NMR approach, demonstrating that the oxidation proceeds via two divergent reaction mechanisms. We were also able to synthesize an unusual σ-bound Pd complex, via

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acetoxypalladation of an unsaturated dithiane, which was characterized by X-Ray crystallography.

Palladium-mediated oxidation reactions play an important role in synthetic chemistry, providing methods for the conversion of alkenes to methyl ketones or aldehydes (Wacker process),[1,2] and ketones to enones (Saegusa oxidation).[3] More recently, there has been considerable interest in the Pd-mediated oxidation of alkenes to allylic esters,[4-9] and in oxidative alkene functionalisation reactions.[10] Typically these processes require a co-oxidant (e.g. benzoquinone/BQ, MnO_2, Cu salts, O_2) and these co-oxidants often play a complex role in the catalytic cycle. As a consequence, mechanistic studies using stoichiometric quantities of Pd salts are not always consistent with the results obtained from catalytic reactions.[5,6,8] A good understanding of the reaction mechanism can be extremely valuable for optimizing reaction procedures and developing new transformations. In recent reports sulfur ligands have been employed for controlling the outcome of the Pd-catalysed oxidation of alkenes, to give either linear or branched allylic esters selectively.[7,8] Even in very early reports, the important effect of DMSO as a solvent in stoichiometric palladium oxidations was noted.[9] The oxidation of alkenes to give allyl acetates is thought to proceed via a π-allyl Pd complex, although mechanistic studies have often given conflicting results.[5,8,11] In this communication we report a study of the oxidation of unsaturated thioacetals with $Pd(OAc)_2$. The reaction can proceed via two divergent mechanisms to give either allylic or vinylic ester products, and these oxidation processes are operative under both stoichiometric and catalytic reaction conditions. In addition, the intermediate palladium complexes are stabilized by the thioacetal unit and can be observed and characterized by NMR, providing a detailed understanding of the reaction pathways.

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Scheme 1 Reaction of unsaturated dithianes with Pd(OAc)$_2$.
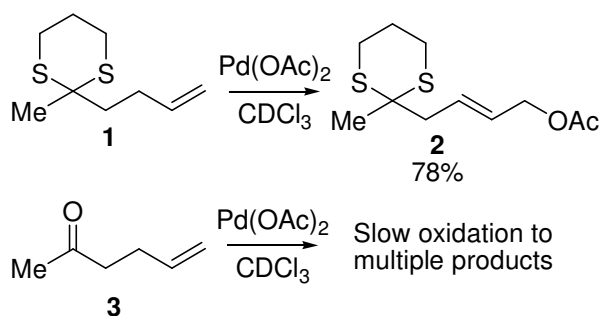
As part of an ongoing project on the development of new transformations of acetals, we examined the reaction of unsaturated dithiane **1** with 1 equiv. of Pd(OAc)$_2$ (Scheme 1).[2,12] On standing overnight at room temperature, the allylic acetate **2** was observed as the major product, and was isolated in 78% yield. No trace of the corresponding branched acetate was observed in the crude NMR spectrum.[7,13] The parent ketone **3** was not oxidized under similar reaction conditions to any significant extent, although after prolonged reaction times (ca. 48 h) a complex mixture of products was observed by NMR. In order to determine how the thioacetal group was directing the oxidation reaction, we carefully monitored the reaction by NMR in order to study any intermediate complexes. Upon treatment of **1** with Pd(OAc)$_2$ in CDCl$_3$, we observed immediate formation of an approximately 1:1 mixture of two isomeric complexes **4** and **5** (Figure 1). Over the course of around 15 minutes at room temperature, this mixture of complexes was converted into a single new species **6**.

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Figure 1 Structures of complexes **4**, **5** and **6**. Observed chemical shifts for selected atoms are shown, with calculated values from DFT in parentheses.[14]
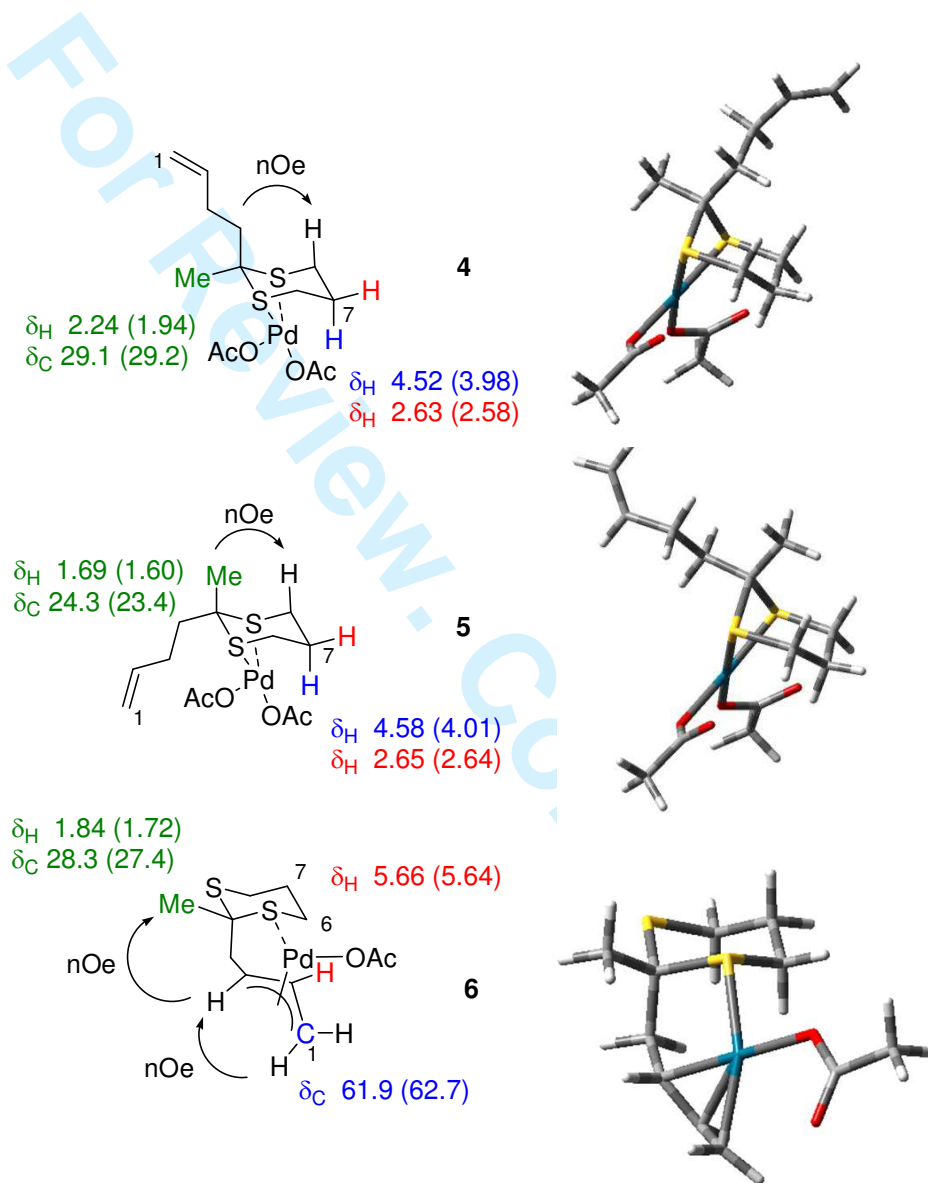

Intermediate **6** has an NMR spectrum consistent with a π-allyl species, showing ^{13}C resonances at 61.9, 115.2 and 77.5 ppm for carbons 1-3 (Figure 1). Deshielding of the protons on C-6 but not C-8 suggested that the Pd atom was only co-ordinated to one of the sulfur atoms. The NMR spectrum of the mixture of complexes **4** and **5** suggested co-ordination of the Pd to both sulfur atoms, however, with the protons at C-6 and C-8 shifted downfield in comparison to dithiane **1**. An unusually high chemical shift of around 4.5 ppm was seen for the axial proton at C-7 on the dithiane ring in both isomers of this complex. The structures of

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4-6 were established using a combined application of NMR, semi-empirical (PM6) and quantum mechanical (QM) methods.[14] Initially, molecular structures were built satisfying the experimentally measured nuclear Overhauser effects (NOEs) and vicinal J-couplings. The geometries of these structures were optimized subsequently using PM6 calculations, followed by QM DFT (density functional theory) calculations. The final structures elucidated in this manner are shown in Figure 1. The observed NOEs suggest a chair conformation of the six-membered ring, the presence of which is further supported by the large values of ^3J couplings for *trans*-diaxial protons. The equatorial/axial orientations of the 5-Me group in **4** and **5** are further supported by their ^1H and ^{13}C chemical shifts. Significant high-frequency shifts of the 7-H_{ax} proton in **4** and **5** can be attributed to its spatial proximity to the oxygen atoms of the nearby acetates (around 3.4 Å in the structures shown). The ^1H and ^{13}C NMR shifts for the proposed structures of **4-6** were calculated using DFT and these values showed good agreement with those observed experimentally, including the unusual high-frequency shifts for the 7-H_{ax} proton in **4** and **5** (Figure 1 and Supporting Information).

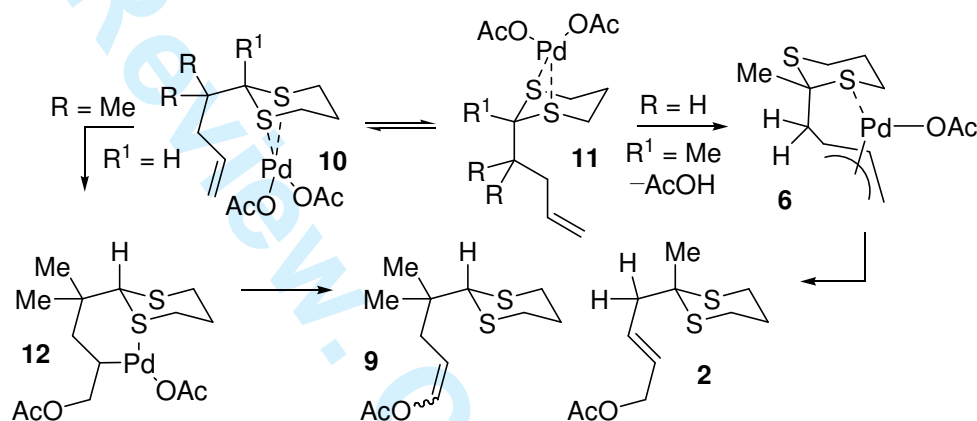**Scheme 2** Reaction of unsaturated dithiane **7** with Pd(OAc)$_2$
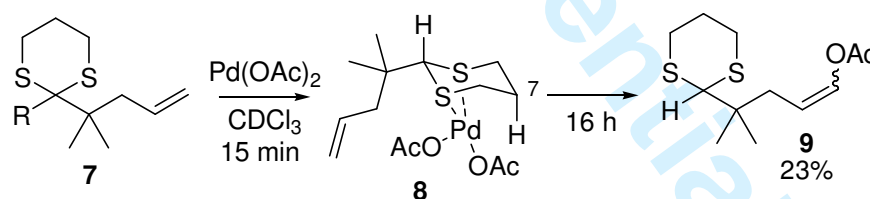
The oxidation of closely related dithiane **7** proceeded very differently to the reaction of dithiane **1** (Scheme 2). Initial formation of a single complex **8** was observed, which over time evolved to give the vinyl acetate **9** as the major oxidation product in 23% yield.[15] There was no evidence for the formation of allyl acetate products or the internal vinyl acetate, which might be expected to form via a Wacker-type oxidation.[1,2]

Dithiane complex **8** had an NMR spectrum similar to **5**, with a high chemical shift for the axial proton at C-7 (4.53 ppm). This complex was formed *as a single stereoisomer* with the

palladium complexed to the same face as the carbon chain (Scheme 2). Over time **8** did not react to form a π-allyl complex but was instead slowly converted into the vinyl acetate **9** as the major oxidation product. The formation of terminal vinyl acetates in this type of oxidation reaction is highly unusual.[16]

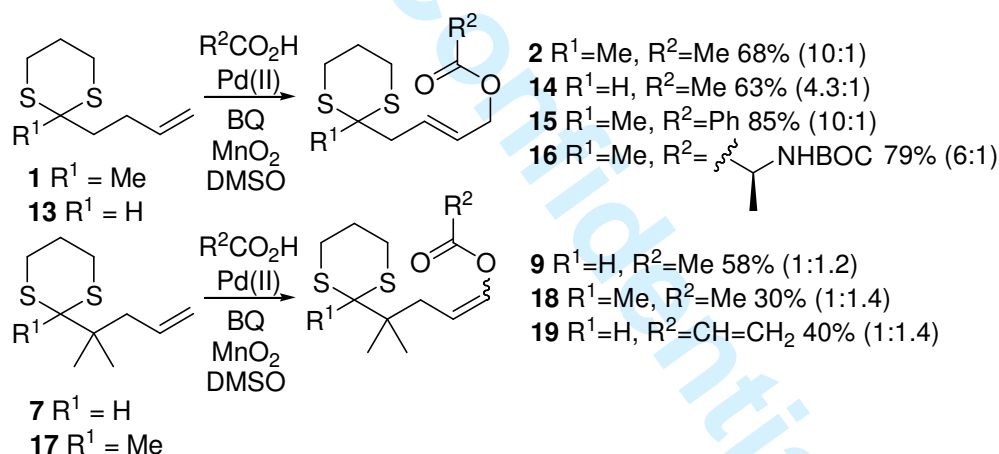**Scheme 3** Proposed mechanism of the Pd-mediated oxidation reactions.

On the basis of these observations it seems that two divergent reaction mechanisms can operate during the oxidation of these unsaturated dithianes (Scheme 3). Initial formation of the palladium dithiane complexes **10** and/or **11** occurs prior to oxidation. Reaction can then occur via abstraction of an allylic hydrogen atom to give π-allyl complex **6**, followed by attack of acetate to give the allyl acetate product **2**. The π-allyl complex **6** has the palladium co-ordinated to an equatorial lone pair on the sulfur, with the tether occupying an axial position. Alternatively, direct acetoxypalladation to give σ-complex **12** can occur, followed by β-hydride elimination to give the vinyl acetate product **9**. This latter process presumably becomes more favorable with a bulkier chain (R=Me) for two reasons: (i) abstraction of the allylic hydrogen atom to form a π-allyl complex is more difficult; (ii) complex **10**, with the bulky chain occupying an equatorial position, becomes favored over **11**. This latter effect may prevent access to the intermediate conformer necessary for the formation of a π-allyl complex similar to **6**, which contains the unsaturated chain in an axial position.

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We then sought to determine whether these mechanisms were also operative under catalytic conditions (Scheme 4). With MnO_2 and benzoquinone (BQ) as co-oxidants,[4b] and we found that unsaturated thioacetals **1** and **7** could be oxidized to give the corresponding acetates **2** and **9**. The R^1 group (H or Me) did not appear to affect the reaction outcome, with dithianes **13** and **17** giving analogous allyl and vinyl acetate products to **14** and **18** respectively. Other esters could readily be introduced by addition of 2 equiv. of the carboxylic acid to the reaction mixture (**15-16** and **19**). Although the vinyl acetate products were only obtained in moderate yields, it is notable that the isolated yield of **9** is significantly higher than that obtained in the stoichiometric reaction. This is likely to be a consequence of the instability of these vinyl acetates in the presence of excess Pd salts.[15]

Scheme 4 Catalytic oxidation reactions of unsaturated dithianes.

2 R^1=Me, R^2=Me 68% (10:1)
14 R^1=H, R^2=Me 63% (4.3:1)
15 R^1=Me, R^2=Ph 85% (10:1)
16 R^1=Me, R^2= ⟍NHBOC 79% (6:1)

9 R^1=H, R^2=Me 58% (1:1.2)
18 R^1=Me, R^2=Me 30% (1:1.4)
**19** R^1=H, R^2=CH=CH$_2$ 40% (1:1.4)

We also found that the dithiane-directed oxidation reaction could be carried out chemoselectively in the presence of another oxidizable alkene, allyl anisole **20** (Scheme 5). In the absence of dithiane **1**, **20** was oxidized to give the corresponding allylic acetate **21** in 93% yield.[8] However, only the unsaturated dithiane was oxidized to any significant extent, when a mixture of **1** and **20** was treated under the same conditions, with **20** being recovered in 86% yield together with a trace of the corresponding oxidation product **21**.

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Scheme 5 Chemoselective oxidation of an unsaturated dithiane in the presence of another alkene.
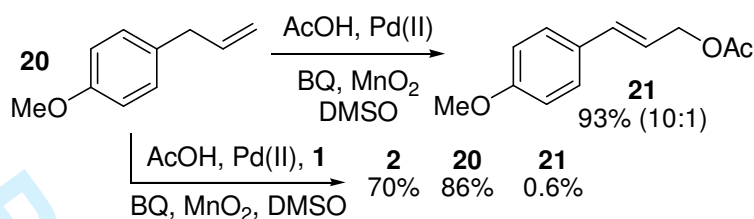
Given that the oxidation pathway seems to be significantly affected by the conformation of the dithiane ring, we also examined the reaction of dithiolane **22**. This gave a mixture of the allyl and vinyl acetate products **23** and **24** in 93% overall yield (Scheme 6). The two isolated products **23** and **24** were shown not to interconvert under the reaction conditions, although vinyl acetate **24** was slowly oxidized to give geminal acetate **25** after prolonged reaction times. These experiments provide further evidence that the two types of oxidation product are produced via divergent reaction pathways and not via Pd-mediated isomerisation processes. A stoichiometric reaction of **22** with Pd(OAc)$_2$ in CDCl$_3$ led to the formation of small quantities of **24**, together with the π-allyl complex **26** which gradually reacted to give **23**.
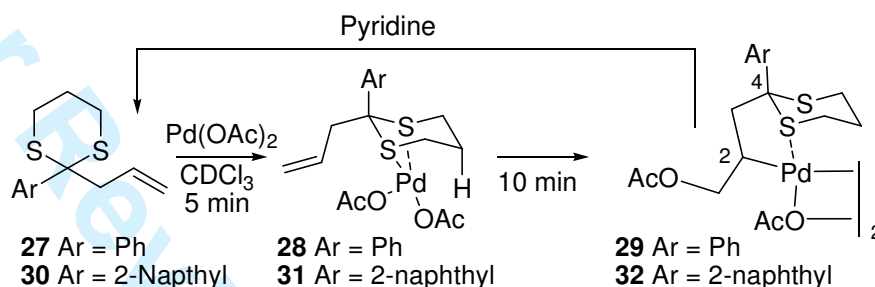
Scheme 6 Oxidation of an unsaturated dithiolane.
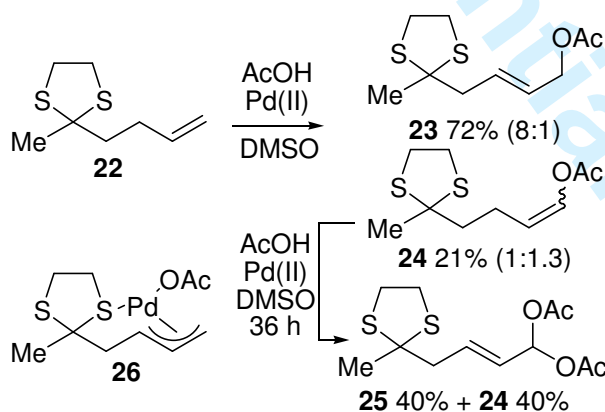
Although the formation of the vinyl acetate products **9** (and **24**) appears to proceed via an intermediate Pd σ-complex such as **12**, we were unable to observe this intermediate by NMR.

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However, we found that treatment of dithiane **27** with Pd(OAc)$_2$ (Scheme 7) gave a stable Pd

σ-complex **29** via an intial short-lived dithiane complex **28**.[17]

Scheme 7 Formation of stable Pd σ-complexes.

27 Ar = Ph   28 Ar = Ph   29 Ar = Ph
30 Ar = 2-Napthyl   31 Ar = 2-naphthyl   32 Ar = 2-naphthyl

The σ-complex complex **29** has a distinctive signal for the proton at C$_2$ (3.26 ppm, dddd).

The structure of this σ-complex was subsequently confirmed for the naphthalene-substituted

analogue **32** via single crystal X-ray diffraction (Figure 2).[18] Interestingly, these complexes

are formed as single diastereisomers (based on the NMR spectrum), despite the fact that three

stereogenic centers are generated during the reaction.

**Figure 2** X-ray crystal structure of **32**.

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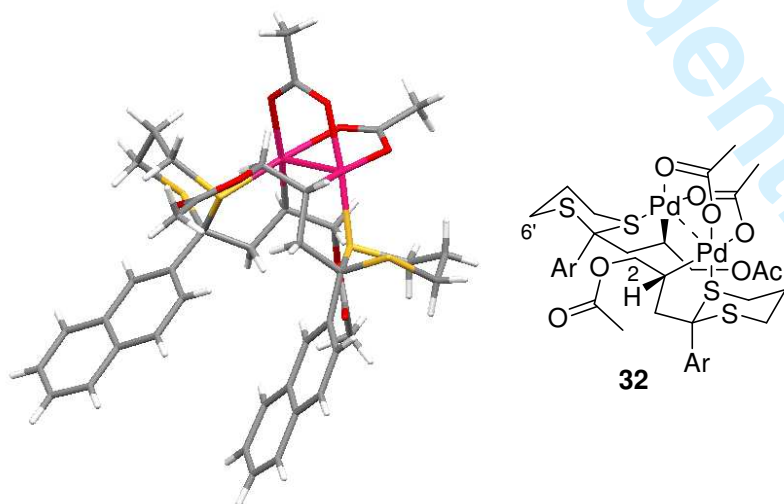
The complex is dimeric with two bridging acetate ligands linking the Pd atoms with an

intermetallic distance of only 2.959 Å. Each Pd atom is co-ordinated to a single sulfur atom

via the axial lone pair, and adopts a square-planar geometry. This dimeric structure appears to

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be maintained in solution as an NOE was observed between the protons at C-2 and C-6`

(Figure 2). This highly rigid structure presumably accounts for the fact that the complexes do

not readily undergo β-hydride elimination. In fact, treatment of **29** with an equivalent of

pyridine only led to β-acetoxyelimination and regeneration of the starting dithiane **27**

(Scheme 7).

We were also able to generate analogous σ-complex **33** by carbo-palladation of dithiane **27**

using phenyltributylstannane in the presence of a Pd(II) salt (Scheme 8).[10]

Scheme 8 Carbo-palladation of dithiane **27**.
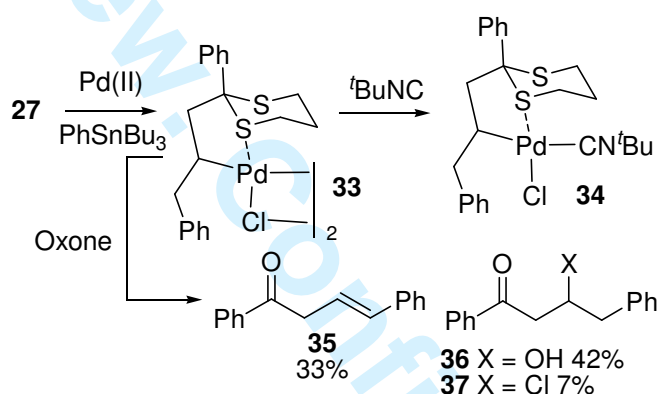
The NMR of complex **33** was somewhat broad, possibly due to monomer-dimer exchange.

However **33** could readily be converted to the monomeric complex **34**, which was more

easily characterized by NMR. Oxidation of the carbon-palladium bond in dimer **33** with

oxone[19] proceeded smoothly, with concomitant deprotection of the dithiane, to give a mixture

of the alkene **35**, the alcohol **36** and the chloride **37**[20] in 82% overall yield.

In summary, we have demsonstrated that two divergent reaction mechanisms operate

during the Pd-mediated oxidation of unsaturated thioacetals, leading to allyl and vinyl

acetates. The reaction intermediates can be characterized via NMR due to the useful

stabilizing effect of the thioacetal group, and the two reaction mechanisms operate under both

catalytic and stoichiometric conditions. We were also able to prepare a series of highly

unusual Pd σ-complexes containing β-hydrogen atoms, which could be charactized via NMR

studies, and in one case, single crystal X-ray diffraction. We anticipate that thioacetals can be used to control many other transition-metal catalyzed reactions and to facilitate the direct observation of a variety of reaction intermediates. Further work is underway to extend the scope of these sulfur-directed organometallic reactions, and the results will be reported in due course.

Supporting Information Available. Full experimental procedures and details of the NMR shift calculations for complexes **4**-**6**, spectroscopic data for all new compounds, and X-ray crystallographic data for complex **32**.

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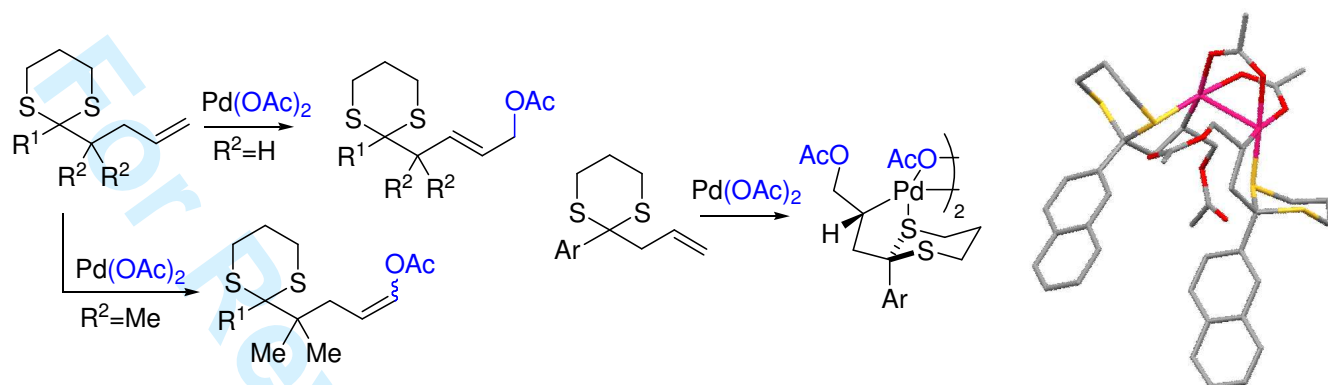
The Palladium-mediated oxidation of unsaturated thioacetals proceeds via two divergent

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