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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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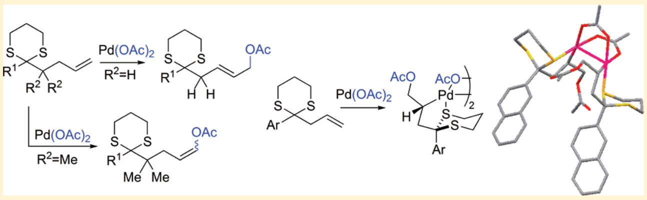
S *Supporting Information*

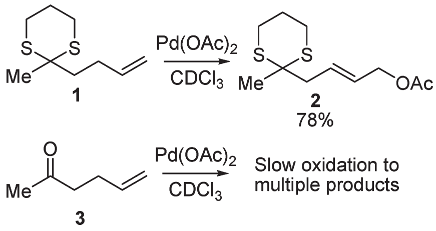
ABSTRACT: The Pd-mediated oxidation of unsaturated thioacetals gives either allyl or vinyl esters, depending on the substrate structure. We report the characterization of a range of sulfur-stabilized palladium intermediates via a combined computational and experimental NMR approach, demonstrating that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

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] When the reaction mixture was allowed to stand 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] 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 the two isomeric complexes **4** and **5** (Figure 1). Over the course of around 15 min at room temperature, this mixture of complexes was converted into the single new species **6**.

Scheme 1. Reaction of Unsaturated Dithianes with $Pd(OAc)_2$



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

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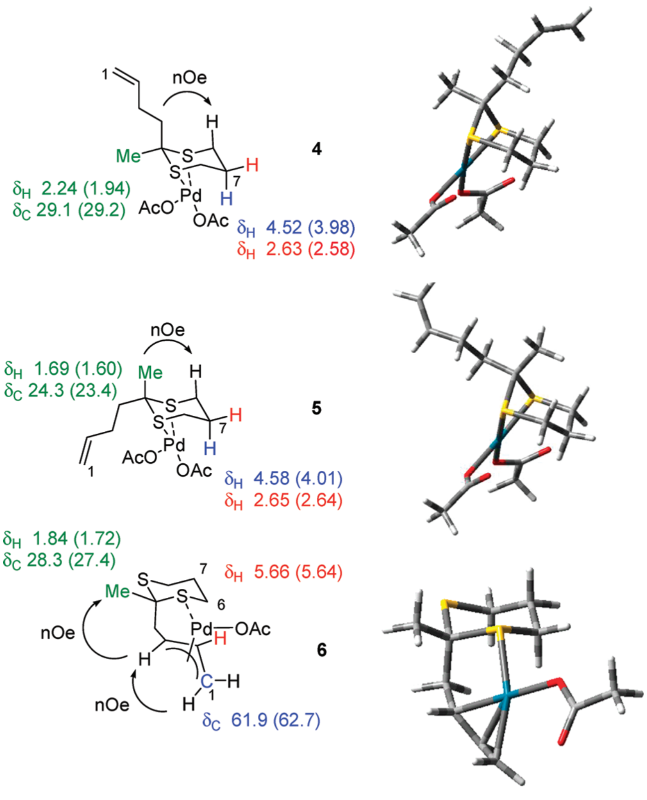
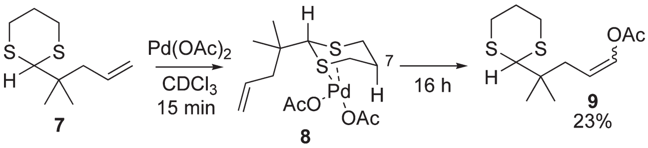


Figure 1. Structures of complexes **4**−**6**. Observed chemical shifts for selected atoms are shown, with calculated values from DFT in parentheses.[13]

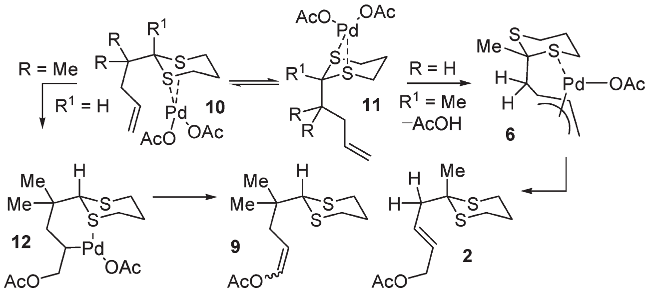
carbons 1−3 (Figure 1). Deshielding of the protons on C-6 but not C-8 suggested that the Pd atom was only coordinated to one of the sulfur atoms. The NMR spectrum of the mixture of complexes **4** and **5** suggested coordination of the Pd to both sulfur atoms, however, with the protons at C-6 and C-8 shifted downfield. 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 **4**−**6** were established using a combined application of NMR, semiempirical (PM6), and quantum-mechanical (QM) methods.[13] 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 ^{1}H 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 ^{1}H 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).

The oxidation of closely related dithiane **7** proceeded very differently from the reaction of dithiane **1** (Scheme 2). Initial formation of complex **8** was observed, which over time evolved to give the vinyl acetate **9** as the major oxidation product in 23% yield.[14] There was no evidence for the formation of allylic 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.[15]

Scheme 2. Reaction of Unsaturated Dithiane 7 with $Pd(OAc)_2$



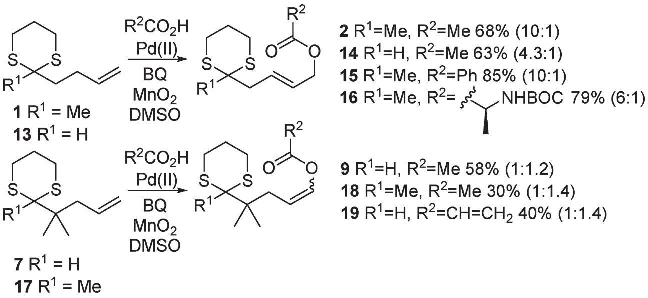
Scheme 3. Proposed Mechanism of the Pd-Mediated Oxidation Reactions



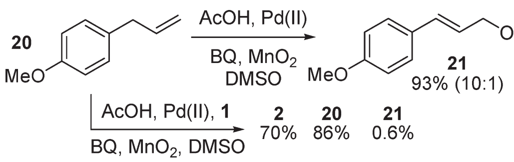
On the basis of these observations it seems that two divergent reaction mechanisms can operate during the oxidation of these unsaturated dithianes (Scheme 3). Initial formation of the palladium dithiane complexes **10** and/or **11** occurs prior to oxidation. Reaction can then occur via abstraction of an allylic hydrogen atom to give the π-allyl complex **6**, followed by attack of acetate to give the allyl acetate product **2**. The π-allyl complex **6** has the palladium coordinated to an equatorial lone pair on the sulfur, with the tether occupying an axial position. Alternatively, direct acetoxypalladation to give the 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.

We then sought to determine whether these mechanisms were also operative under catalytic conditions (Scheme 4). With MnO_2 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**

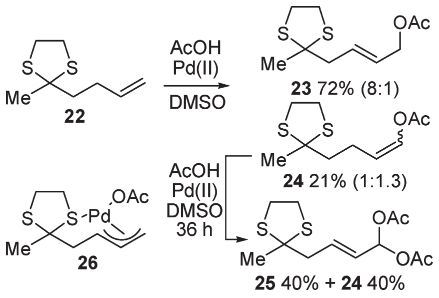
Scheme 4. Catalytic Oxidation Reactions of Unsaturated Dithianes



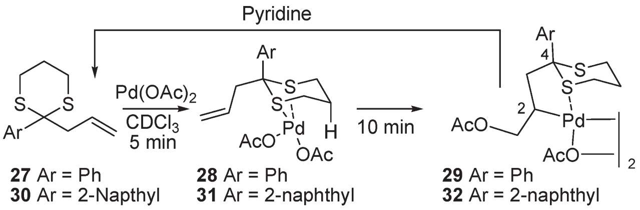
Scheme 5. Chemoselective Oxidation of an Unsaturated Dithiane in the Presence of Another Alkene



Scheme 6. Oxidation of an Unsaturated Dithiolane



Scheme 7. Formation of Stable Pd σ-Complexes



giving allyl and vinyl acetate products **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.[14]

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**.

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 diacetate **25** after prolonged reaction times. These experiments provide further evidence that the two types of oxidation products are produced via divergent reaction pathways and not via Pd-mediated isomerization 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**.

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. However, we found that treatment of dithiane **27** with Pd(OAc)$_2$ (Scheme 7) gave the stable Pd σ-complex **29** via the initial short-lived dithiane complex **28**.[16] 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).[17] Interestingly, these complexes are formed as single diastereisomers (on the basis of the NMR spectrum), despite the fact that three stereogenic centers are generated during the reaction.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 coordinated to a single sulfur atom via the axial lone pair and adopts a square-planar geometry. This dimeric structure appears to 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 1 equiv of pyridine only led to β-acetoxyelimination and regeneration of the starting dithiane **27** (Scheme 7).

We were also able to generate the analogous σ complex **33** by carbopalladation of dithiane **27** using phenyltributylstannane in the presence of a Pd(II) salt (Scheme 8).[10] 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**

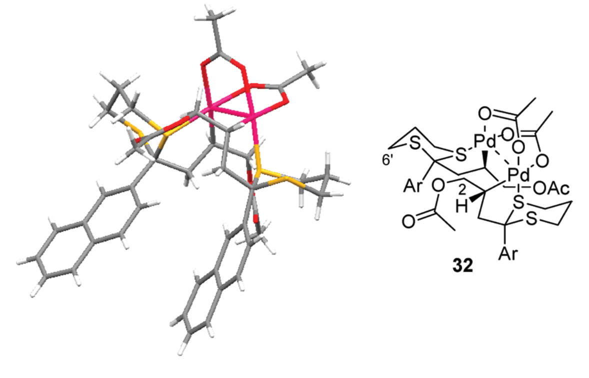
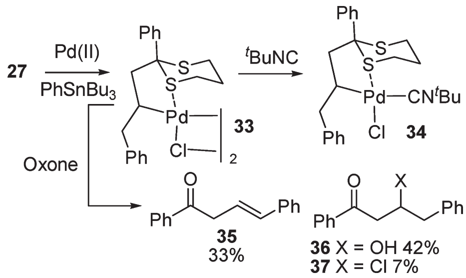


Figure 2. X-ray crystal structure of **32**.

Scheme 8. Carbopalladation of Dithiane 27



with oxone[18] proceeded smoothly, with concomitant deprotection of the dithiane, to give a mixture of the alkene **35**, the alcohol **36**, and the chloride **37**[19] in 82% overall yield.

In summary, we have demonstrated 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.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. 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** (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Muzart, J. *Tetrahedron* **2007**, *63*, 7505–7521. (b) Anderson, B. J.; Keith, J. A.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 11872–11874. (c) Keith, J. A.; Henry, P. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9038–9049.

(2) For Wacker oxidation of unsaturated thioethers, see: Raghavan, S.; Krishnaiah, V.; Rathore, K. *Tetrahedron Lett.* **2008**, *49*, 4999–5002.

(3) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013.

(4) (a) Bäckvall, J. E.; Hopkins, R. B.; Grennberg, H.; Mader, M. M.; Awasthi, A. K. *J. Am. Chem. Soc.* **1990**, *112*, 5160–5166. (b) Heumann, A.; Åkermark, B. *Angew. Chem., Int. Ed.* **1984**, *23*, 453–454.(c) Popp, B. V.; Stahl, S. S. *Topics in Organometallic Chemistry*; Springer-Verlag: Berlin, Heidelberg, 2006.

(5) Åkermark, B.; Hansson, S.; Rein, T.; Vagberg, J.; Heumann, A.; Bäckvall, J. E. *J. Organomet. Chem.* **1989**, *369*, 433–444.

(6) (a) Grennberg, H.; Bäckvall, J. E. *Chem. Eur. J.* **1998**, *4*, 1083–1089. (b) Grennberg, H.; Simon, V.; Bäckvall, J. E. *Chem. Commun.* **1994**, 265–266. (c) Jabre-Truffert, S.; Delmas, A. M.; Grennberg, H.; Åkermark, B.; Waegell, B. *Eur. J. Org. Chem.* **2000**, 219–224. (d) Kozitsyna, N. Y.; Bukharkina, A. A.; Martens, M. V.; Vargaftik, M. N.; Moiseev, I. I. *J. Organomet. Chem.* **2001**, *636*, 69–75. (e) Lin, B. L.; Labinger, J. A.; Bercaw, J. E. *Can. J. Chem.* **2009**, *87*, 264–271. (f) Yang, H.; Khan, M. A.; Nicholas, K. M. *J. Mol. Catal.* **1994**, *91*, 319–334. (g) Zanoni, G.; Porta, A.; Meriggi, A.; Franzini, M.; Vidari, G. *J. Org. Chem.* **2002**, *67*, 6064–6069. (h) Campbell, A. N.; White, P. B.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 15116–15119.

(7) (a) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970–6971. (b) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346–1347.

(8) Henderson, W. H.; Check, C. T.; Proust, N.; Stambuli, J. P. *Org. Lett.* **2010**, *12*, 824–827.

(9) Kitching, W.; Rappopor., Z; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1966**, *88*, 2054–2055.

(10) (a) Kalyani, D.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 2150–2151. (b) Kalyani, D.; Satterfield, A. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 8419–8427. (c) Urkalan, K. B.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 3146–3149. (d) Werner, E. W.; Urkalan, K. B.; Sigman, M. S. *Org. Lett.* **2010**, *12*, 2848–2851.

(11) (a) Hansson, S.; Heumann, A.; Rein, T.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 975–984. (b) Jia, C. G.; Muller, P.; Mimoun, H. *J. Mol. Catal. A: Chem.* **1995**, *101*, 127–136.

(12) For the Pd-mediated isomerization of an unsaturated thioether, see: McCrindle, R.; Alyea, E. C.; Ferguson, G.; Dias, S. A.; McAlees, A. J.; Parvez, M. *J. Chem. Soc., Dalton Trans.* **1980**, 137–144.

(13) For full details of the calculations, see the Supporting Information.

(14) The vinyl acetate products undergo further oxidation in the presence of excess Pd (see Scheme 6), in some cases to a complex mixture of products.

(15) (a) Kozitsyna, N. Y.; Vargaftik, M. N.; Moiseev, I. I. *J. Organomet. Chem.* **2000**, *593*, 274–291. (b) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298–5300. (c) Minami, T.; Nishimoto, A.; Nakamura, Y.; Hanaoka, M. *Chem. Pharm. Bull.* **1994**, *42*, 1700–1702. (d) Tanaka, M.; Urata, H.; Fuchikami, T. *Tetrahedron Lett.* **1986**, *27*, 3165–3168.

(16) An analogous Pd σ complex appeared to form from the corresponding alkyl dithiane (**27**, Me in place of Ph), but the NMR spectrum was less clean.

(17) For a recent example of a stable Pd σ complex containing β-hydrogen atoms, see: Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662–13663.

(18) (a) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141–1144. (b) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439–2463. (c) Powers, D. C.; Geibel, M. A. L.; Klein, J.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050–17051.

(19) (a) Carr, K.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1984**, 1227–1228. (b) Ramos, S. S.; Almeida, P.; Santos, L.; Motherwell, W. B.; Sheppard, T. D.; Costa, M. C. *Tetrahedron* **2007**, *63*, 12608–12615.