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A Sulfoxide-Promoted, Catalytic Method for the Regioselective Synthesis of Allylic Acetates from Monosubstituted Olefins via C−H Oxidation

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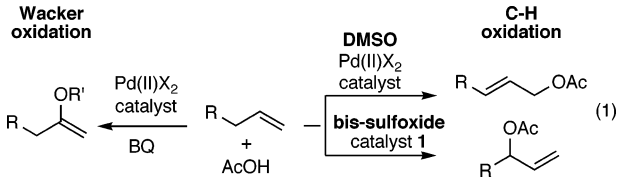
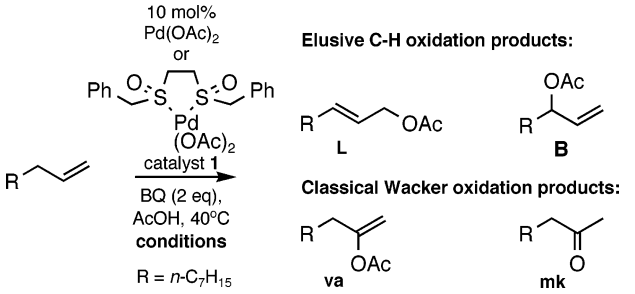
The development of selective methodologies for the oxidation of saturated C−H bonds would enable the direct installation of functionality into preassembled hydrocarbon frameworks, thereby providing alternatives to methods that rely upon C−C bond forming reactions between preoxidized fragments. A method for the selective oxidation of monosubstituted olefins to yield versatile, α-functionalized olefins would be highly useful in this context. Advances have been made in identifying catalytic allylic oxidation systems[1g,h] that form branched alcohols or acetates α to monosubstituted olefins; however, these are limited by low conversions and/or lack of substrate generality due to poor functional group tolerance. Well-known, mild allylic oxidation methods using palladium(II) salts in acetic acid (AcOH)[1a−f] are available for transforming *internal olefins* into regioisomeric mixtures of allylic acetates. These reactions are



thought to proceed via substitution of π-allyl intermediates generated through allylic C−H cleavage.[1a−f,2a,b] For reasons that are not clear, under these same conditions *monosubstituted olefins* predominantly undergo Wacker oxidation (Markovnikov oxypalladation/β-hydride elimination) to yield mixtures of vinyl acetates and methyl ketone.[1e,2c,d] Herein, we disclose that addition of dimethyl sulfoxide (DMSO) to the $Pd(OAc)_2$/benzoquinone (BQ)/AcOH catalyst system results in a general C−H oxidation method for converting monosubstituted olefins to linear (*E*)-allylic acetates with high regio- and stereoselectivities and in preparatively useful yields. Although DMSO has been widely used in Pd(II)-mediated oxidation systems to promote reoxidation of Pd(0) with O_2,[3] this is the first report of DMSO significantly altering both the reaction pathway selectivity and regioselectivity in a Pd(II)-catalyzed oxidation. We believe these effects result from sulfoxide ligation to palladium. In support of this, we demonstrate that a bis-sulfoxide Pd(II) acetate complex **1** is an effective allylic oxidation catalyst for monosubstituted olefins in the absence of DMSO. Moreover, **1** results in a reversal of regioselectivity, favoring formation of branched allylic acetates.

In the process of investigating the catalytic $Pd(OAc)_2$/BQ/AcOH-mediated oxidation of 1-decene, we discovered that addition of DMSO significantly shifts the reaction's product distribution from predominant formation of mixtures of vinyl acetates and methyl ketone to favor formation of linear (*E*)- allylic acetate ([*E*:*Z*] = 12:1, Table 1).[4] We considered that this effect may be due to stabilization of a charged intermediate in the catalytic cycle for C−H oxidation by the highly polar DMSO solvent. However, when we evaluated the reaction in a diverse range of dielectric media

Table 1. Effect of DMSO and Bis-sulfoxide Ligation on the Pd(II)-Catalyzed Oxidation of Monosubstituted Olefins

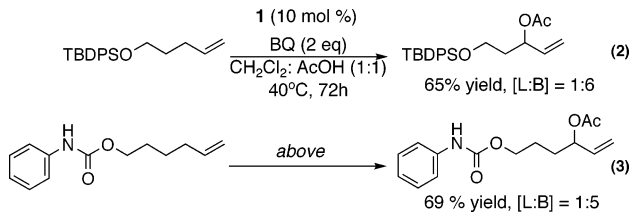


		% yield (GC),[a] 48 h				
entry	conditions	L[b]	B[c]	va[d]	mk[e]	[L:B]
1	AcOH	3	5	17	14	1:2
2	DMSO:AcOH (1:1)	40	2	3	6	20:1
3	**1** (10 mol %) CH_2Cl_2:AcOH (1:1)	8	66	<1	<1	1:8

[a] Yields determined by GC for an average of 2−3 runs from reactions carried out on a 0.2 mmol scale. Yields are corrected for response factor variations. [b] Linear (*E*)-allylic acetate. [c] Branched allylic acetate. [d] Vinyl acetate. [e] Methyl ketone.

(e.g., CH_3CN, dioxane, CH_2Cl_2, benzene), we observed no correlation between the polarity of the added solvent and its ability to promote the C−H oxidation pathway [Table S3, Supporting Information (SI)].

To explore the potential role of sulfoxide as a ligand in promoting the palladium(II) catalyzed C−H oxidation pathway, we formed bis-sulfoxide palladium(II) acetate complex **1** via routine metal complexation with 1,2-bis(phenylmethanesulfinyl)ethane in CH_2Cl_2 at 40 °C.[5] In the absence of DMSO, complex **1** was found to be an effective catalyst for allylic C−H oxidation in a variety of standard solvents (CH_2Cl_2, dioxane, THF, Et_2O, DME, benzene, toluene, see Table S4), leading to formation of < 1% of the undesired Wacker oxidation products (Table 1). Moreover, a reversal in regioselectivity was observed with **1** for a variety of substrates to give the branched allylic acetates as the major products with good selectivities and yields (e.g., eqs 2, 3). It is remarkable



that the regioselectivities reported in entries 4 and 8 (Table 2) and eqs 2 and 3 represent a turnover from 31:1 to 1:6 and 13:1 to 1:5 (respectively). These results demonstrate for the first time that sulfoxide ligation of Pd(II) salts can selectively promote C−H

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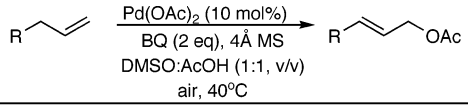
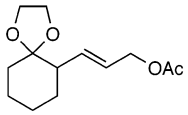
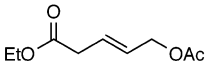
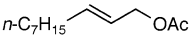
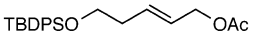
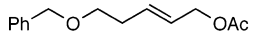
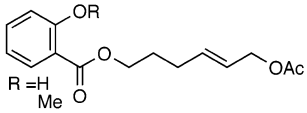
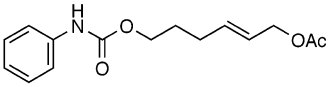
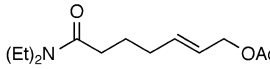
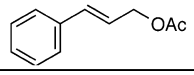
Table 2. Allylic Oxidation of Terminal Olefins to (*E*)-Allylic Acetates[a]



entry	major product	linear: branched[c]	*E*:*Z*[d]	yield[e]
1		>99:1	>20:1	50% (72h)
2[b]		>20:1[d]	13:1	54% (48h)
3		24:1	12:1	52% (48h)
4[b]		31:1	11:1	50% (72h)
5[b]		31:1	11:1	57% (48h)
6		14:1	11:1	61% (72h)
7	R =H, Me	17:1	13:1	56% (72h)
8		13:1	12:1	64% (72h)
9		23:1	12:1	62% (48h)
10		>99:1	13:1	65% (48h)

[a] All data reported ([**L**:**B**], [*E*:*Z*] ratios, yields) based on an average of two runs. Minor peaks consistent with diene byproducts were detected by ^{1}H NMR analysis of the crude. [b] 10 mol % of $Pd(TFA)_2$. [c] Ratio based on GC analysis of crude. Not corrected for small response factor variations. [d] Ratio based on 1H NMR analysis of crude. [e] Isolated yields after chromatography from reactions carried out on a 1.0 mmol scale (0.17 M).

oxidation versus Wacker oxidation chemistry and control the regioselectivity in the C−H oxidation products. Further studies will probe the effects of steric and electronic tuning of the C_2-symmetric, bis-sulfoxide ligand framework on the reactivity and selectivity of the C−H oxidation reaction and on its amenability to asymmetric catalysis.

Because (*E*)-allylic acetates and their corresponding alcohols are valuable synthetic intermediates, we explored the generality and synthetic utility of the DMSO-promoted C−H oxidation reaction (Table 2). Evaluation of reaction parameters (Tables S1−S8) indicated that the reaction conditions $Pd(OAc)_2$ (10 mol %)/BQ (2 equiv)/4 Å MS/DMSO:AcOH (1:1, v/v) at 40 °C are presently optimal. Palladium(II) trifluoroacetate [$Pd(TFA)_2$] gave similar results in the presence of 4 Å MS and, in general, the addition of 4 Å MS increased formation of linear (*E*)-allylic acetate (Tables S1, S2). Notably, these conditions are operationally simple and tolerant of a wide range of functionality. Benzyl and silyl ether-, ketal-, ester-, carbamate-, and amide-functionalized monosubstituted olefins underwent direct oxidation with excellent regio- and stereoselectivities to generate the corresponding linear (*E*)-allylic acetates in preparatively useful yields (Table 2). The high selectivity, functional group compatibility, and directness of this method make it a powerful alternative to C−C bond forming procedures that require multistep routes for accessing the majority of products in Table 2.[6]

Consistent with a mechanism involving π-allyl intermediates, stoichiometric formation of bis[chloro(1,2,3-*trihapto*-1-decene)-palladium(II)][2d] and subsequent exposure of it to our DMSO[7] acetoxylation conditions generated the linear and branched allylic acetates observed in the catalytic reaction (SI). Regioisomeric ratios for both the DMSO and bis-sulfoxide catalytic $Pd(OAc)_2$ acetoxylation systems decrease slowly over the course of the reaction.[8] This suggests a mechanism involving sulfoxide ligand-directed regioselective acetate substitution of a π-allyl intermediate with background Pd(II)-catalyzed allylic acetate isomerization.[8,9] Investigation of the reaction mechanism and studies toward an understanding of the role of sulfoxide ligation on selectivity are in progress.

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Supporting Information Available: General experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Pd(II)/AcOH: (a) Hansson, S.; Heumann, A.; Rein, T.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 975. (b) Heumann, A.; Reglier, M.; Waegell, B. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 366. (c) Heumann, A.; Åkermark, B. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 453. (d) McMurry, J. E.; Kocovsky, P. *Tetrahedron Lett.* **1984**, *25*, 4187. (e) Åkermark, B.; Larsson, E. M.; Oslob, J. D. *J. Org. Chem.* **1994**, *59*, 5729. (f) Macsari, I.; Szabo, K. J. *Tetrahedron Lett.* **1998**, *39*, 6345. SeO_2/*t*-BuOOH: (g) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. Cu(I)/*tert*-butyl perbenzoate: (h) Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, *58*, 845.

(2) (a) Grennberg, H.; Backvall, J.-E. *Chem. Eur. J.* **1998**, *4*, 1083. (b) Wolfe, S.; Campbell, P. G. C. *J. Am. Chem. Soc.* **1971**, *93*, 1497, 1499. (c) Kitching, W.; Rappoport, Z.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1966**, *88*, 2054. (d) Trost, B. M.; Metzner, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 3572.

(3) Pd(II)/DMSO/O_2: (a) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766. (b) Grennberg, H.; Gogoll, A.; Backvall, J.-E. *J. Org. Chem.* **1991**, *56*, 5808.

(4) A similar observation in a stoichiometric $Pd(OAc)_2$ system, ref 2c.

(5) S−Pd coordination mode is tentatively assigned based on other Pd(II) bis-sulfoxide complexes. Pettinari, C.; Pellei, M.; Cavicchio, G. Crucianelli, M.; Panzeri, W.; Colapietro, M.; Cassetta, A. *Organometallics* **1999**, *18*, 555.

(6) For a standard HWE-based 5−6 step synthetic route toward functionalized (*E*)-allylic acetates, see: (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743. Cross-metathesis has been used to directly synthesize entry 10 in 51% yield: (b) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(7) Neutral, strongly coordinating Pd(II) ligands (e.g., DMSO, PPh_3) have been used to activate stoichiometric π-allyl chloride complexes toward alkylation: (a) Collins, D. J.; Jackson, W. R.; Timms, R. N. *Tetrahedron Lett.* **1976**, 495. (b) Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292. (c) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385.

(8) Table 1, entry 2 (w/MS): 24 h, [**L**:**B**] = 34:1; 72 h, [**L**:**B**] = 11:1. Table 1, entry 3: 24 h, [**L**:**B**] = 1:10; 72 h, [**L**:**B**] = 1:7 (Table 2 and eqs 2, 3 see SI). Submission of regioisomerically pure (*E*)-acetic acid dec-2-enyl ester to the DMSO reaction conditions resulted in the same trend. Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, *4*, 321.

(9) An alternative mechanism involving anti-Markovnikov oxypalladation/β-hydride elimination/Pd−H isomerization to the linear (*E*)-allylic acetate followed by Pd(II)-mediated allylic isomerization to the branched acetate is not consistent with the observed trend of progressively decreased branched:linear ratios over the course of the reaction with catalyst **1**.

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