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Asymmetric Dihydroxylation of Olefins Containing Sulfur: Chemoselective Oxidation of C–C Double Bonds in the Presence of Sulfides, 1,3-Dithianes, and Disulfides.

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Abstract: *Osmium tetroxide catalyzed oxidation of sulfide containing olefins in the presence of the chiral ligands (DHQD)$_2$PHAL and (DHQ)$_2$PHAL resulted in the chemoselective oxidation of the C–C double bond rather than oxidation at sulfur. The enantioselectivity is dependent on the substitution pattern of the olefin and ranges from 61-98%. The AD can be performed in the presence of the disulfide and 1,3-dithiane functional groups, also.*

The ever increasing scope of the osmium tetroxide/cinchona alkaloid catalyzed asymmetric dihydroxylation (AD) of alkenes depends, in large part, on its functional group tolerance.[1] Here we report the catalytic AD of olefins possessing the sulfide, disulfide and 1,3-dithiane groups.

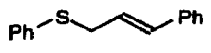
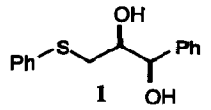
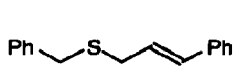
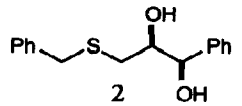
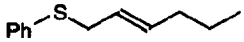
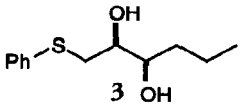
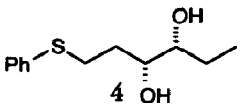
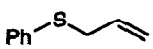
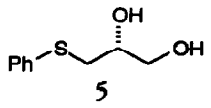
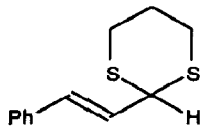
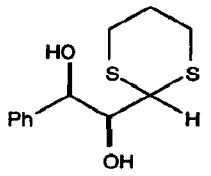
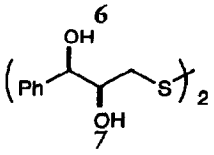
Sulfides are selectively oxidized to sulfoxides[2] by an array of reagents including peracetic acid,[3] sodium metaperiodate,[4] and manganese dioxide.[5] Further oxidation of the sulfoxides to sulfones is slow, allowing isolation of the sulfoxides. In contrast, permanganate ion or osmium tetroxide (OsO_4) oxidize sulfoxides to sulfones rapidly, but react slowly with sulfides.[6] Recently, the clean conversion of sulfides to sulfones using catalytic OsO_4 and *N*-methylmorpholine-*N*-oxide (NMO) as the terminal oxidant has been reported.[7] These reactions appear to require a tertiary amine and show moderate[7a] to good[7b] selectivity for sulfur oxidation *versus* olefin oxidation.

Standard asymmetric dihydroxylations[8] of sulfide containing olefins (entries 1-5) gave the corresponding sulfide-diols (**1-5**) in good yields and good to excellent enantiomeric excesses (ee).[9] A 1,3-dithiane[10] (entry 6) and a disulfide (entry 7) also reacted at the double bonds rather than the sulfur atoms with good chemical and stereo yields.[11]

Benzyl sulfide under standard AD conditions (room temperature, 24 h) produced a mixture of starting sulfide (92%) and combined sulfoxide and sulfone (8%), suggesting that sulfides oxidize slowly under AD conditions. While a catalytic amount (1 mol%) of alkaloid ligand is sufficient to accelerate olefin dihydroxylation greatly,[13] it appears insufficient to bring about sulfide oxidation.[14]

In summary, we have found that in olefins containing sulfide, 1,3-dithiane or disulfide units, the sulfur containing functional group is significantly less reactive than C–C double bonds toward osmium

Table. Chemoselective AD of Olefinic Sulfides.

Entry	Substrate[a]	Product[a]	Yield[b]	ee[c]	Config.[d]
1		 1	75%	98%	*2S,3R*
2		 2	72%	98%	*2S,3R*
3		 3	68%	84%	*2S, 3R*
4		 4	74%	98%	*3R,4R*
5[e]		 5	87%	61%	*2R*
6		 6	78%	97%	*2S, 3R*
7		 7	80%	95% de	*1R, 2S, 7S, 8R*

[a] Spectroscopic data is listed in ref. 11. [b] Yields are for isolated products. [c] The ee's of the products were determined using chiral column HPLC (1-6) and the de of 7 was determined by NMR: (retention time of major enantiomer in *italics)* 1: Chiralcel OD-H, λ = 254 nm, 2.5% isopropanol/hexane, 1 mL/min: 52.8 min, *57.3 min*; 2: Chiralcel OB, λ = 254 nm, 10% isopropanol/hexane, 1 mL/min: 25.5 min, *30.9 min*; 3: Chiralcel OD-H, λ = 254 nm, 5.0% isopropanol/ hexane, 1 mL/min: 13.1 min, *16.5 min*; 4: Chiralcel OD-H, λ = 254 nm, 2.5% isopropanol/hexane, 1 mL/min: 39.6 min, *44.4 min*; 5: Chiralcel OG, λ = 254 nm, 5.0% isopropanol/hexane, 1 mL/min: 39.2 min, *44.7 min*; 6: Chiralcel OD-H, λ = 254 nm, 10% isopropanol/hexane, 1 mL/min: *17.0 min*, 26.3 min. [d] All configurations are based on our mnemonic (for which there have been no exceptions to date for prochiral olefins). [e] AD-mix α [$(DHQ)_2$-PHAL] was used for this entry.

tetroxide in the presence of the chiral ligands PHAL(DHQD)$_2$ and PHAL(DHQ)$_2$.[15] The dihydroxylation products are formed selectively and the yields and enantioselectivities are good to excellent.

Acknowledgments

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8. Typical AD reactions are run as follows: dissolve 1 mmol of olefin in 10 mL of 1:1 *t*-BuOH/H_2O and cool to 0 °C. Add AD-mix β (1.5 g, Aldrich) and stir at 0 °C until complete (may take several days). (AD-mix α [(DHQ)$_2$-PHAL] used for entry 5, allyl phenyl sulfide.) Add Na_2SO_3 until two clear phases form and no further gas is evolved. Separate phases, extract aqueous with ethyl acetate (3 x 10 mL), then wash organics with brine. Flash chromatograph on silica gel with hexane/ethyl acetate. The disulfide reaction was not treated with Na_2SO_3.
9. Phenyl cinnamyl sulfone and the diol derived from osmylation of its C–C double bond were independently synthesized. These compounds were not observed in the crude reaction mixture of the AD of phenyl cinnamyl sulfide, as judged by TLC.
10. Because α,β-unsaturated aldehydes have not proven good substrates for the AD reaction, the high enantioselectivity with this dithiane substrate is promising. Aldehydes protected as acetals have also been shown to be good substrates for the asymmetric dihydroxylation reaction: see Lohray, B.B.; Kalantar, T.H.; Kim, B.M.; Park, C.Y.; Shibita, T.; Wai, J.S.M.; Sharpless, K.B. *Tetrahedron Lett.* **1989** *30*, 2041.
11. Data for compounds 1-7. 1: ^{1}H NMR (acetone-d_6) δ 7.3 (m, 10H), 4.75 (m, 1H), 4.53 (d, J = 4.5, 1H), 4.25 (d, J = 5.4, 1H), 3.82 (m, 1H), 3.13 (dd, J = 13.4, J = 4.3, 1H), 2.89 (dd, J = 13.4, J = 7.5, 1H) ppm; ^{13}C{^{1}H} NMR (acetone-d_6) δ 143.1, 137.8, 129.6, 129.1, 128.7, 128.0, 127.6,

126.3, 75.9, 75.1, 37.3 ppm; HRMS (FAB) expected 283.0769 (M + Na^+), observed 283.0769; $[\alpha]_D$ = –2.81° (*c* 1.10 EtOH), mp 71-72 °C; **2**: ^1H NMR (acetone-d_6) δ 7.3 (m, 10H), 4.64 (m, 1H), 4.43 (d, *J* = 4.5, 1H), 4.07 (d, *J* = 5.0, 1H), 3.70 (m, 3H), 2.53 (dd, *J* = 13.8, *J* = 6.4, 1H), 2.36 (dd, *J* = 13.7, *J* = 7.6, 1H) ppm; $^{13}C\{^1H\}$ NMR (acetone-d_6) δ 142.2, 139.7, 129.7, 129.0, 128.7, 127.9, 127.6, 127.4, 76.2, 75.9, 36.7, 35.0 ppm; HRMS (FAB) expected 297.0925 (M + Na^+), observed 297.0917 $[\alpha]_D$ = –40.0° (*c* 1.06, EtOH), mp 62-64 °C; **3**: ^1H NMR ($CDCl_3$) δ 7.30 (m, 5H); 3.20 (m, 2H); 3.15 (dd, *J* = 15.6, 4.6, 1H); 3.01 (dd, *J* = 7.9, 3.7, 1H); 2.91 (s, 2H), 1.48 (m, 4H); 0.89 (t, *J* = 7.0, 3H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 135.1, 129.9, 126.5, 72.5, 71.7, 38.2, 35.7, 18.8, 13.9 ppm; $[\alpha]_D$ = –8.85° (*c* 1.04, EtOH), mp 69-70 °C; **4**: ^1H NMR ($CDCl_3$) δ 7.40 (m, 4H); 7.15 (t, *J* = 7.0, 1H); 3.53 (m, 1H); 3.28 (m, 1H); 3.03 (m, 4H); 1.75 (m, 2H); 1.40 (m, 1H); 0.93 (t, *J* = 7.4, 3H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 136.1, 129, 128.8, 125.9, 72.6, 32.7, 29.9, 26.2, 9.86 ppm; $[\alpha]_D$ = –55.1° (*c* 1.04, EtOH), oil; **5** ^1H NMR ($CDCl_3$) δ 7.3 (m, 5H); 3.68 (m, 2H); 3.50 (m, 1H); 3.00 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 134.8, 129.9, 129.0, 126.7, 69.8, 65.0, 37.6 ppm; HRMS (FAB) expected 207.0456 (M + Na^+), observed 207.0464; $[\alpha]_D$ = –11.2° (*c* 1.00, EtOH), mp 64-65 °C;[12] **6**: ^1H NMR ($CDCl_3$) δ 7.20 (m, 5H); 4.94 (d, *J* = 14.3, 1H); 3.85 (m, 1H); 3.78 (d, *J* = 6.0, 1H); 2.80 (m, 6H); 1.90 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 140.9, 128.4, 127.9, 126.4, 77.1, 73.1, 47.8, 28.2, 27.4, 25.3 ppm; HRMS (FAB) expected 388.9646 (M + Cs^+), observed 388.9646; $[\alpha]_D$ = –20.4 (*c* 1.09, EtOH), mp 88-89 °C; **7**: ^1H NMR ($CDCl_3$) δ 7.25-7.35 (m, 10H), 4.53 (d, *J* = 6.3, 2H), 3.92 (ddd, *J* = 8.9, 5.6, 3.6, 2H), 3.50 (s, 2H), 3.34 (s, 2H), 2.74 (dd, *J* = 14.0, 3.6, 2H), 2.63 (dd, *J* = 14.0, 8.3, 2H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 140.2, 128.6, 128.5, 126.8, 76.2, 74.4, 42.1, ppm; HRMS (FAB) expected 389.0857 (M + Na^+), observed 389.0860; $[\alpha]_D$ = +58.8° (*c* 2.0, EtOH); oil.

12. Recrystallization from benzene gives enatiopure **5**, mp 89-90 °C, $[\alpha]_D^{23}$ = –20.7° (*c* 1.0 EtOH): Fujisawa, T.; Itoh, T.; Nakai, M.; Sato, T. *Tetrahedron Lett.* **1985**, *26*, 771.
13. Kolb, H.C.; Andersson, P.G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1994**, *116*, 1278.
14. Sulfide oxidation is rapid in the presence of *stoichiometric* amounts of cinchona alkaloid ligand (King, S.B. and Sharpless, K.B. unpublished results). *N*-Methylmorpholine is known *not* to catalyze the osmylation of olefins (Jacobsen, E.N., Markó, I.É. and Sharpless, K.B. unpublished results).
15. The reader will no doubt be wondering what the difference is between these osmium-based oxidation systems which so affects the preference for olefin *vs.* sulfide oxidation or *vice versa*. A mechanistic rational for this selectivity dichotomy is still elusive, so for the present, we must be content with its synthetic utility which is clear enough.

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