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Dihydroxylation and Oxidative Cleavage of Olefins in the Presence of Sulfur

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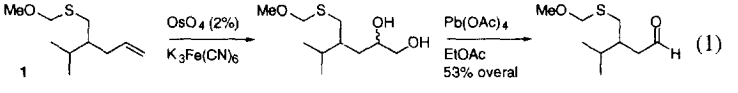
Abstract: The dihydroxylation of olefins using AD-mix or OsO_4 / $K_3Fe(CN)_6$ in the presence of sulfides has been examined as has the rate of oxidation of various classes of sulfides. The selectivity of olefin oxidation in preference to sulfur oxidation depends on the nature of the sulfur moiety, and can be problematic for certain classes of substrates. Copyright © 1996 Elsevier Science Ltd

This communication describes our studies of the dihydroxylation of olefins in the presence of sulfur functionalities. We recently had a need to perform an oxidative cleavage of an olefin in the presence of a protected thiol, and found that the most common methods (i.e., ozonolysis, Lemieux - Johnson oxidation, etc.) could not be employed due to oxidation of the protected thiol. We therefore decided to explore a two step process in which the olefin is first dihydroxylated, then cleaved with $Pb(OAc)_4$.[1] The mildest and most commonly used reagent for the dihydroxylation of olefins is OsO_4, and in stoichiometric quantities OsO_4 is known to be inert to reaction with sulfides.[2] Kaldor[3] and Priebe,[4] however, have shown that in the presence of tertiary amines OsO_4 efficiently oxidizes sulfides to sulfones, and that catalytic quantities of OsO_4 in the presence of stoichiometric amounts of trialkyl amine N-oxides will also accomplish this transformation. This precludes the use of this reagent combination for the dihydroxylation of olefins in the presence of sulfides; however, it occurred to us that milder cooxidants may be compatible with the catalytic procedure. We have therefore examined the use of ferricyanide based cooxidants[5] in this reaction, and report our results herein. While our work was in progress, Sharpless and coworkers reported the use of the Sharpless reagent AD-mix for the dihydroxylation of olefins in the presence of sulfides, disulfides, and dithianes.[6] Our work defines the scope of this transformation, and illustrates that the amount of sulfur oxidation can be highly substrate dependent.

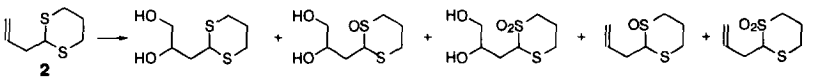
Our initial experiments were conducted with substrate **1** (eq 1). Dihydroxylation using the Yamamoto procedure (OsO_4, 0.02 equiv; $K_3Fe(CN)_6$, 3 equiv; K_2CO_3, 3 equiv; *t*-BuOH / water, 1:1) provided the corresponding diols as a 1:1 mixture of diastereomers which were subjected to oxidative cleavage by the action of $Pb(OAc)_4$ in ethyl acetate, providing the desired aldehyde in an overall yield of 53% after



(1)

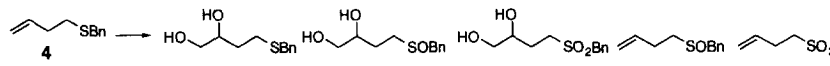
chromatography. With the success of this reaction, we decided to explore in greater detail the scope of the dihydroxylation in the presence of various sulfur functionalities. We prepared substrates **2** - **6** and subjected these to dihydroxylation using the Yamamoto procedure (2 - 3 equiv $K_3Fe(CN)_6$) and using AD-mix-β (1 equiv. of oxidant), and analyzed the products by GC (Table 1).[7,8] Our results show that the efficacy of the dihydroxylation varies significantly depending on the substrate. Attempted dihydroxylation of compounds **2** and **4** using either the Sharpless or the Yamamoto procedure resulted in low to moderate yields of the desired product due to competitive sulfur oxidation. Even at incomplete conversion, sulfur oxidation products comprise a significant percentage of the reaction mixture with the Yamamoto procedure. Dithianes seem to be especially susceptible to oxidation under these conditions with sulfoxides comprising the majority of the over-oxidized products.[9] This stands in contrast with simple sulfides in which the sulfone is the major product.[2,3,4] Dihydroxylation of compound **5** on the other hand proceeded without over-oxidation. Compounds **3** and **6** provided varying amounts of over-oxidized products, with better results being obtained with AD-mix.

These results indicate that there is a fine balance between olefin dihydroxylation and sulfur oxidation, and that factors which influence the rate of either reaction can effect the outcome with a particular substrate.

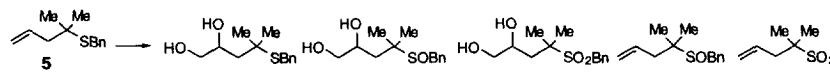


AD-mix-β	14%	37%	5%	5%	36%	2%
$K_3Fe(CN)_6$	31%	12%	11%	13%	28%	3%

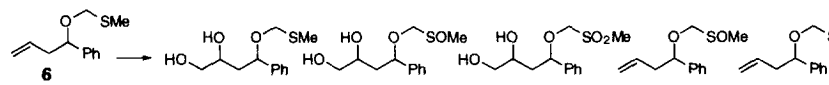
AD-mix-β	-	92%	4%	3%	-	-
$K_3Fe(CN)_6$	-	90%	4%	6%	-	-



AD-mix-β	1%	71%	12%	15%	-	-
$K_3Fe(CN)_6$	15%	47%	9%	22%	3%	3%



AD-mix-β	-	100%	-	-	-	-
$K_3Fe(CN)_6$	6%	94%	-	-	-	-



AD-mix-β[a]	0.3%	93%	-	7%	-	-
$K_3Fe(CN)_6$[a]	32%	55%	-	12%	-	-

Table 1: Conditions: AD-mix-β: 1 equiv oxidant, 1:1 *t*-BuOH / H_2O, RT, 24 h; $K_3Fe(CN)_6$: OsO_4 (0.02 to 0.04 eq), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv) , 1:1*t*-BuOH / H_2O, RT, 24 h. (a) Reaction was conducted at 5°C. The desired product was obtained as a 1:1 mixture of diastereomers

Though the rate of oxidation of various olefin classes is known due to the extensive work of Sharpless,[10] the rate of sulfur oxidation with these reagents has not been reported. We have therefore performed a series of competition experiments to determine the relative rates of oxidation of ethyl dithiane, benzyl methyl sulfide, thioanisole, the MOM-ether of benzyl mercaptan, and *tert*-butyl phenyl sulfide (Table 2). As expected from the results of Table 1, we found that the most reactive substrates are the dithiane (k_{rel} = 11 vs thioanisole using AD-mix), and benzyl methyl sulfide (k_{rel} = 10 vs thioanisole using AD-mix). The least reactive is the bulky *tert*-butyl phenyl sulfide (k_{rel} = <0.01 vs thioanisole using AD-mix) while thioanisole and the MOM-ether of benzyl mercaptan, show similar reactivity. This trend indicates that electron withdrawing substituents (including phenyl groups) retard the rate of oxidation as does steric hindrance in the vicinity of the sulfur atom. These results suggest that in the dihydroxylation of olefins bearing thiols, either bulky, such

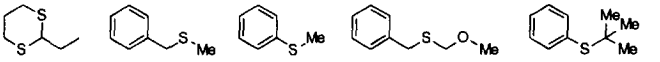


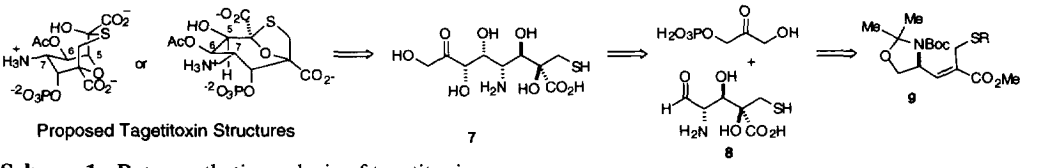
Table 2

k_{rel} (AD-mix-β)	11	10	1	0.32	<0.01
k_{rel} ($K_3Fe(CN)_6$)	10	10	1	0.25	0.02

as a *tert*-butyl thioether, or electron withdrawing, such as a thioacetal, sulfur protecting groups should be employed in order to minimize the amount of over-oxidized product.

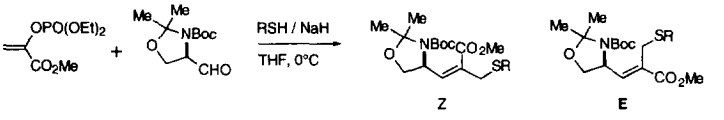
This point is illustrated in the synthesis of the RNA polymerase inhibitor tagetitoxin.[11] In our retrosynthetic analysis of this molecule, we envisioned an enzymatic coupling of dihydroxy acetone phosphate with aldehyde **8** to form the fully functionalized tagetitoxin precursor **7**. This precursor could then be cyclized to form either of the two proposed structures for tagetitoxin (Scheme 1).[12] Aldehyde **8** can be

prepared from oxazolidine olefin **9** by dihydroxylation followed by hydrolysis of the oxazolidine and oxidation of the primary alcohol to the aldehyde. We therefore prepared alkenes **9a-e** and examined the effect of protecting groups on the ratio of dihydroxylation to sulfur oxidation.



Scheme 1: Retrosynthetic analysis of tagetitoxin

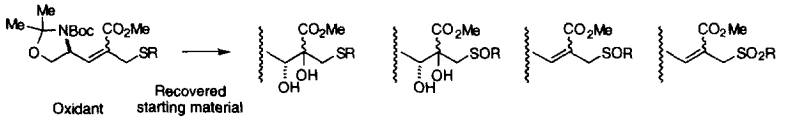
Alkenes **9a-e** are readily prepared in a one pot synthesis by generation of the phosphonate *in situ* followed by condensation with the oxazolidine aldehyde.[13] Using this method we can vary the thiolate anions to produce a series of oxazolidine alkenes bearing protected thiols of different steric and electronic properties (Table 3). Our results show that while these α,β-unsaturated esters are much less reactive than the



R	Ethyl	*i*-Propyl	*t*-Butyl	Phenyl	Benzyl
Z:E	60:40	70:30	100:0	20:80	30:70

Table 3: One step procedure for generation of oxazolidine alkenes with varying sulfur protecting groups.

simpler systems examined above they display similar trends. The use of conventional methods of dihydroxylation using either stoichiometric or catalytic amounts of OsO_4 provided only sulfur oxidized products, prompting us to examine the use of ferricyanide cooxidants.[5,6] With these substrates AD-mix-β gave poorer results overall, probably because the bulky osmium-ligand complex is sterically demanding and reacts slowly with our electron deficient and sterically hindered alkenes.[14] Attempted dihydroxylations of **9a**, **9b**, and **9e** gave little of the desired product utilizing either procedure. Over-oxidation was observed, again with the sulfoxide being the major product in contrast to the expected sulfone.[2,3,4] The phenyl sulfide **9d** follows the expected trend and produces less sulfur oxidized products. The bulky *t*-butyl thiol substrate **9c**, is the only substrate that produces any dihydroxylation with AD-mix-β. The most synthetically useful



R	Oxidant	Recovered starting material				
Et (**9a**)	AD-mix-β	54	–	–	46	–
	$K_3Fe(CN)_6$	30	–	–	70	–
i-Pr (**9b**)	AD-mix-β	56	6	–	28	–
	$K_3Fe(CN)_6$	39	15	–	44	–
t-Bu (**9c**)	AD-mix-β	86	14	–	–	–
	$K_3Fe(CN)_6$	32	55	–	11	–
Ph (**9d**)	AD-mix-β	99	–	–	<1	–
	$K_3Fe(CN)_6$	34	27	–	–	39
Bn (**9e**)	AD-mix-β	82	–	–	10	–
	$K_3Fe(CN)_6$	22	6	–	72	–

Table 4: Conditions: AD mix-β: 1.5 g/mmol alkene in 30 mL of 1:1 *t*-butanol-water, RT 72h;
$K_3Fe(CN)_6$: 3 eq.$K_3Fe(CN)_6$ and K_2CO_3, 10. eq OsO_4 in 30 mL of 1:1*t* -butanol-water, RT 72h.

reaction is that of substrate **9c** with the ferricyanide based oxidation. This reaction provides isolated yields in the range of 50-63%. The osmylation occurs with a diastereomeric ratio of 25:1 (major isomer is desired for

the synthesis of tagetitoxin as shown in Table 4) as determined by isolated product weights. The structure of the major isomer is consistent with approach of the osmium away from the BOC group in the minimum energy conformation of the molecule (as dictated by $A^{1,3}$ strain). We are utilizing this reaction for the synthesis of the tagetitoxin aldehyde.

These results illustrate that a judicious choice of protecting group can greatly influence the outcome of dihydroxylations of olefins bearing sulfur functionalities.

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1 $Pb(OAc)_4$ is known to cleave diols in the presence of sulfides. For a recent example, see: Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 7001.

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4 Priebe, W.; Grynkiewcz, G. *Tetrahedron Lett.* **1991**, *32*, 7353.

5 Ferricyanide was first reported as a cooxidant for osmium tetroxide catalyzed dihydroxylations by Yamamoto and coworkers. See: Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766. We chose to use the protocol described in this paper without added amines since the Sharpless AD procedure, which we have also examined, contains amines, and since Kaldor has shown that sulfide oxidation is accelarated by amines (see ref 3). Warren has reported an achiral ligand accelerated dihydroxylation using quinuclidine which is similar to the Yamamoto procedure. See: Eames, J.; Mitchell, H. J,; Nelson, A.; O'Brien, P.; Warren, S.; Wyatt, P. *Tetrahedron Lett.*, **1995**, *36*, 1719.

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7 In all cases, authentic samples of products were prepared and used as standards.

8 Representative experimental procedures: **$K_3Fe(CN)_6$:** $K_3Fe(CN)_6$ (8.2g, 25 mmol, 3 equiv) and K_2CO_3 (3.4g, 25 mmol, 3 equiv) were added to a solution of **3** (1.24g, 8.3 mmol, 1 equiv) in 120 ml of 1:1 *t*-butanol / water and the heterogeneous solution was allowed to stir for 24 h at room temperature. The reaction was quenched by the addition of solid Na_2SO_3 and saturated $NaHSO_3$, and extracted with three portions of ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. Flash chromatography on Silica gel (5:1 hexanes / ethyl acetate, then ethyl acetate, then 10:1 ethyl acetate / methanol) provided the desired diol (994 mg, 65%). **AD-Mix-β**: AD-Mix-β (363 mg,) was added to a solution of **5** (50 mg, 0.24 mmol) in 3 ml of 1:1 *t*-butanol / water and allowed to stir for 24 h at room temperature. The reaction was quenched by the addition of solid Na_2SO_3 and saturated $NaHSO_3$, and extracted with three portions of ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated and purified by flash chromatography (hexanes, then 1:1 hexanes / ethyl acetate, then ethyl acetate) to provide the desired diol (46 mg,, 80%).

9 We could not detect any bis-sulfoxides from the dithiane reactions. We suspect that oxidation to the mono-sulfoxide deactivates the remaining sulfide towards further oxidation.

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