Asymmetric Oxidation of Dithioacetals and Dithioketals Catalyzed by a Chiral Vanadium Complex¹

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Abstract: Vanadium-catalyzed enantioselective oxidations of dithioacetals and dithioketals with 30% aqueous H_2O_2 give the corresponding monosulfoxides with enantioselectivities of up to 85% *ee*. The scope of this asymmetric catalysis has been investigated.

Sulfoxides have widely been used as chiral auxiliaries in asymmetric synthesis.² More recently, they have been introduced as ligands in enantioselective metal catalysis^{3,4} and as bioactive substances for drugs and plant protection.⁵ A number of methods are available for the synthesis of optically active sulfoxides.⁶ The most common ones are based on stereoselective transformations involving chiral auxiliaries⁷ and asymmetric oxidations of sulfides with a modified Sharpless reagent.^{8,9} In 1995, we introduced a chiral vanadium catalyst for enantioselective sulfide oxidations.¹⁰ A number of groups have since used this system for various asymmetric sulfur oxidations.¹¹ Interesting features of this system are: 1) the use of 30% aqueous H₂O₂ as terminal oxidant, 2) the simplicity of the reaction conditions, 3) its catalytic efficiency (0.01 - 1 mol% of catalyst), 4) the use of simple ligands derived from amino alcohols and salicylaldehydes, and 5) the ligand acceleration¹² of the catalysis. The oxidation of a variety of compounds was studied, and the highest enantioselectivities have been achieved with a combination of $[VO(acac)_2]$ and ligands (S)-3.



Whereas simple alkyl aryl sulfides were oxidized to the corresponding sulfoxides with enantioselectivities in the range of 50-76% *ee*, dithioacetal **1a** afforded *trans*-sulfoxide (*IR*,*2R*)-**2a** with 85% *ee*. This result is particularly noteworthy because the synthetic value of optically active oxides derived from dithioacetals and dithioketones has been described in a number of reports.^{13,14} In order to investigate whether this asymmetric vanadium catalysis could be generalized and with the intention to expand the scope of the process we decided to study sulfur oxidations of various substrates of type **1**.¹⁵

An early catalyst screening had revealed that ligand (S)-**3a** having a *tert*butyl substituent in the 4-position gave a higher asymmetric induction in the oxidation of **1a** than nitro-substituted (S)-**3b**. This behavior was in contrast to oxidations of most alkyl aryl sulfides where catalysts with (S)-**3b** as ligand gave higher *ee*-values. In further studies we therefore employed *in situ* catalysts prepared from 1 mol% of [VO(acac)₂] and 1.5 mol% of ligand (S)-**3a**. The reactions were performed at room temperature on a 1 mmol scale using 1.1 equiv. of 30% aqueous H_2O_2 in

a two-phase solvent system with CH_2Cl_2 as the organic component. Table 1 summarizes the most significant results.

| Table 1. Asymmetric oxidation of dithioacetals and dithioketals |
|-----------------------------------------------------------------|
| to give sulfoxides 2 catalyzed by 1 mol% of $[VO(acac)_2]$ |
| |

| and 1.5 mor/o of figand (5)-5a | | | | | | |
|--------------------------------|-----------------------------------------------------|-----------------|--------------|--------------------------|------------------------------------|--|
| Entry | R | R' | Yield [%] | ee [%] ^[b] | Optical rotation ^[c] | |
| 1 ^[a] | C ₆ H ₅ | Н | 77 | 76 | (-) | |
| 2 | C ₆ H ₅ | Н | 84 | 85 | (-) | |
| 3 | $p-CH_3-C_6H_4$ | Н | 79 | 77 | (-) | |
| 4 | p-Cl-C ₆ H ₄ | н | 87 | 64 | (-) | |
| 5 | p-CH ₃ O-C ₆ H ₄ | Н | 60 | 57 | (-) | |
| 6 | o-Br-C ₆ H ₄ | Н | 81 | 64 | (-) | |
| 7 | o-NO2-C6H4 | Н | 75 | 62 | (+) | |
| 8 | $(CH_3)_3C$ | Η | 67 | 46 | n. d. | |
| 9 | C(CH ₃) ₂ CH ₂ OH | Н | 62 | 47 | (+) | |
| 10 | C ₆ H ₅ | CH_3 | 44 (cis) | 68 | n. d. | |
| | | | 37 (trans) | 12 | (-) | |
| 11 | o-Br-C ₆ H ₄ | CH ₃ | 57 (cis) | ≈ 85 ^[d] | n. d. | |
| | 0 4 | 5 | 25 (trans) | 15 | n. d. | |

[a] (*S*)-**3b** was used as ligand in this run. [b] Determined by HPLC on chiral phase (entries 1 - 9, 11: Chiralcel OD; entry 10: Chiralcel OD-H; hexane/*iso*-propanol mixtures). [c] Sign of optical rotation (entries 1, 2, 6, 10 in acetone; 3 - 5, 7, 9 in CHCl₃; n. d. = not determined). [d] Not baseline separated

Various 1,3-dithianes were efficiently oxidized to give the corresponding monosulfoxides in good yields. The enantiomeric excesses were moderate to good depending on the substituents at the 2-position. 1,3-Dithianes prepared from aromatic aldehydes (entries 1-7) afforded products with higher asymmetric induction than those obtained from compounds with branched aliphatic substituents (entries 8 and 9). Only *trans* sulfoxides were formed from dithioacetals. Dithioketals (entries 10 and 11) gave *cis/trans* mixtures with the former as the major isomer.¹⁶ The enantiomeric excesses of the *cis* sulfoxides were significantly higher than those of the *trans* ones. Vanadium-catalyzed oxidation of 2-phenyl-1,3-dithiolane (**4**) resulted in the formation of the corresponding *trans* monosulfoxide (+)-**5** (acetone) in 81% yield with an enantioselectivity of 33% *ee*.



Previously, we had demonstrated that even catalyst loadings of 0.01 mol% of the vanadium complex catalyzed the formation of optically active sulfoxides.¹⁰ In a scale-up experiment we now oxidized 100 mmol of **1a** using one tenth of the usual catalyst amount. With 0.1 mol% of a catalyst prepared from (*S*)-**3a**, sulfoxide (1R,2R)-**2a** was obtained in 91% yield with an *ee* of 84%. Thus, compared to the 1 mmol test reaction (Table 1, entry 2) the chemical yield was increased without significantly lowering the enantiomeric excess (85 versus 84% *ee*).

Attempts to improve the enantioselectivity of the vanadium catalysis by modifying the oxidant remained unsuccessful.¹⁷ H_2O_2 is crucial for high catalyst activity and good asymmetric induction. These results together with those obtained from ⁵¹V-NMR investigations and asymmetric amplification studies¹⁰ let us assume that vanadium(V) species such as **6** having oxoperoxo groups could be involved in the catalysis.¹⁸ The two orientations of the oxo moiety with respect to the substituent R would then lead to diastereomeric arrangements **6a** and **6b**.¹⁹



Based on this hypothesis our current efforts are directed towards a refinement of the ligand structure to increase the enantioselectivity of the oxygen transfer. In addition, we investigate whether complexes bearing ligands of type **3** could also be used in other oxidations.²⁰

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