Selective Aerobic Oxidation of Sulfides Using a Novel Palladium Complex as the Catalyst Precursor

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The palladium complex $[Pd(PBu^t_2H)(\mu\text{-}PBu^t_2)]_2$, on exposure to oxygen in THF, generates an active catalytic system for the selective oxidation of sulfides to sulfoxides in 30–83% yields. The process is stereospecific in the case of (+)-biotin-sulfoxide 4-nitrophenyl ester.

The oxidation of sulfides has been studied extensively, resulting in the development of many synthetic routes[1] to sulfoxides or sulfones. Nevertheless, scrutiny of the existing methods suggests that there is a need to find new, exceptionally simple and mild processes for the selective oxidation of sulfides to sulfoxides without overoxidation to the corresponding sulfone.

Molecular oxygen is an inexpensive and easily available oxidant, and studies have been made for its use in reactions such as the one mentioned above. Transition metal compounds (oxides, salts, and complexes) can undergo facile reaction with oxygen.[2]

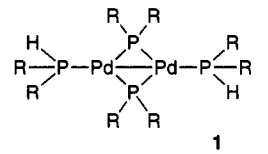
The oxidation of sulfides, catalyzed by halides, sulfates, acetates, acetyl acetonates, and other complexes of VO^{2+}, Cu, Co, Ni, Mn, Mo, Cr, Fe, and Rh takes place at a pressure of 5 MPa and 120 °C, the maximum yield being 20–30 mol % without solvent, or 40% and 70–80% selectivity toward sulfoxide in the presence of solvent. Chlorides of many transition metals (e.g. Cr, Mn, Co, Rh, Ni, Pd, Pt) in benzene or alcohol, at 50–250 °C and 1–10 MPa, are inactive for this kind of process, while Ir, Au, and Fe chloride catalysts afford sulfoxides in low yield (10–35 mol %) and in 47–100% selectivity.[2] Complexes of Ru halogenides with dimethyl sulfoxide in methanol or 2-propanol are completely selective toward sulfoxide or sulfone formation at 105 °C and 0.7 MPa.[3]

Sulfoxides were obtained from dialkyl sulfides, as well as thiacyclohexane and thiolane, in high selectivity using copper(II) compounds (e.g. chlorides, carboxylates) at elevated temperatures and pressures (80–150 °C and 2–8 MPa).[4] A catalytic system based on O_2–Zn–AcOH–Mn(TPP)Cl–1-MeIm (TPP = tetraphenylporphyrin, 1-MeIm = 1-methylimidazole) has been used for the selective oxidation of thioethers, and the highest yield was obtained in the preparation of *n*-butyl sulfoxide (68%).[5]

We now describe a new application of a catalytic system which previously was found to be effective for the oxidation, by molecular oxygen, of alkenes to ketones and of ethers to esters or lactones at 1 atm.[6] The catalytic system is based on the Pd dimer, $[Pd(PBu^t_2H)(\mu\text{-}PBu^t_2)]_2$, **1**, as a catalytic precursor, and the oxidation process takes place under very mild conditions with total selectivity for sulfoxide formation.

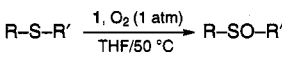
Results and Discussion

It was shown before[6] that complex **1**, although catalytically inactive itself, reacts with molecular oxygen, to form an active catalytic system for the oxidation of alkenes and ethers. We have now found that this system, generated by the use of 1–3 mol % **1** and O_2 in tetrahydrofuran, is capable of converting sulfides to sulfoxides, under gentle conditions (50 °C, 1 atm O_2) (eq 1). Other reaction solvents including 1,2-dimethoxyethane, methylene chloride, or methanol were not useful for this reaction.



R = Bu^t

1



(1)

A wide variety of sulfides (i.e. aliphatic, aromatic, allylic, benzylic, and heterocyclic) were subjected to oxidation, and the results are presented in Table 1. All reactions occur with complete selectivity for sulfoxide formation. Small amounts of γ-butyrolactone, resulting from the oxidation of THF,[6] were formed in some of these reactions. The amount of lactone increases, as anticipated, if the reaction time or volume of the solvent is increased.

An excellent result for the oxidation reaction was obtained using dibenzyl sulfide (entry 1, Table 1) which afforded the sulfoxide in 83% isolated yield. The replacement of the benzyl group, by an aliphatic or phenyl group, results in lower product yields (entries 2–4). Phenyl

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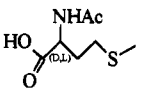
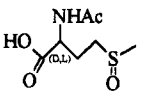
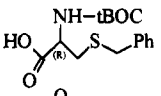
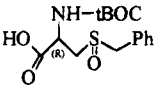
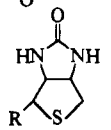
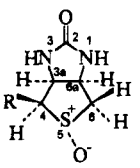
Table 1. Oxidation of Sulfides to Sulfoxides by Oxygen Using 1 as Catalyst Precursor[a]

Entry	Substrate	Rxn.time (h)	Product	Conversion(%)[b] (Isolated yield%)
1.	$PhCH_2SCH_2Ph$	36	$PhCH_2S(O)CH_2Ph$	100 (83)
2.	$PhCH_2SPh$	48	$PhCH_2S(O)Ph$	83(60)
3.	$PhCH_2SCH_3$	48	$PhCH_2S(O)CH_3$	75(50)
4.	$PhSCH(CH_3)_2$	24	$PhS(O)CH(CH_3)_2$	83(47)
5.	$PhSCH_2CH{=}CH_2$	48	$PhS(O)CH_2CH{=}CH_2$	82(43)
6.	$nC_4H_9\text{-}S\text{-}nC_4H_9$	60	$nC_4H_9\text{-}S(O)\text{-}nC_4H_9$	60(37)
7.	$(CH_2)_4S$	96	$(CH_2)_4S{=}O$	100(76)
8.	$(CH_2)_5S$	72	$(CH_2)_5S{=}O$	75(56)
9.		48		(50)
10.		50		(55)
11.		48		(30)

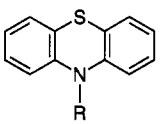
R=4-$NO_2C_6H_4COO(CH_2)_4$

[a] Reaction conditions: sulfide (1 mmol), **1** (0.01 mmol (entries 1–9), 0.02 mmol (entry 10), 0.03 mmol (entry 11)); THF (10 mL); O_2 (1 atm); 50 °C. [b] Determined by GC using an internal standard or from the amount of unreacted sulfide.

vinyl sulfide, in which two sp^2 carbons are directly bound to the sulfur atom, did not undergo oxidation. When phenyl allyl sulfide was used as substrate, the double bond remained unaffected in the oxidation process and the corresponding sulfoxide was obtained selectively but in 43% yield (entry 5). A simple dialkyl sulfide, di-*n*-butyl sulfide, was oxidized to the sulfoxide in 37% yield (entry 6). When cyclic aliphatic sulfides (i.e. tetrahydrothiophene, tetrahydrothiopyran) are used as reactants, the yield of the oxidation product varied from fair (pentamethylene sulfoxide) to good (tetramethylene sulfoxide) (entries 7, 8).

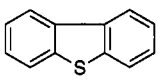
Interesting results were obtained in the case of derivatives of the amino acids, methionine and cysteine. In these cases, the presence of amide and carboxylic groups does not interfere with the oxidation process at sulfur (entries 9, 10). *N*-Acetyl-D,L-methionine and *N*-t-BOC-*S*-benzyl-L-cysteine give a 1:1 mixture of the two diastereoisomers.[7]

Comparison of the ^1H- and ^{13}C-NMR spectra of the product obtained from (+)-biotin 4-nitrophenyl ester (entry 11) with literature data,[7,8] showed that (+)-biotin sulfoxide 4-nitrophenyl ester was formed, with an equatorial sulfur–oxygen bond, the reaction being chemoselective and stereospecific. The formation of the (+)-sulfoxide is confirmed by the presence of a doublet of doublets for H-6(β) which has a smaller geminal coupling constant (J_{gem} = 13.2 Hz) compared to that for the (−)-stereoisomer (reported as a doublet with J_{gem} = 15.1 Hz). In addition the C_{3a} and C_{6a} carbons are more shielded (54.04/56.99 ppm) compared to those in the (−)-sulfoxide (reported higher than 60 ppm) in accordance with the antiperiplanar effect of sulfoxide oxygen on carbons γ to the oxygen atom.[8] Attempts to oxidize phenothiazines **2** (R = $(CH_2)_3N(CH_3)_2$; $CH(CH_3)N(CH_3)_2$; $COCH_3$) and dibenzothiophene **3** were unsuccessful.



R = $(CH_2)_3N(CH_3)_2$; $CH_2CH(CH_3)N(CH_3)_2$; $COCH_3$

2



3

The possibility of asymmetric synthesis of sulfoxides was investigated using **1**, O_2, and three different chiral ligands: (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), (2*S*,4*S*)- (−)-1-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine (BPPM), and (−)-dimethyl 2,3-*O*-benzylidene-L-tartrate. No asymmetric induction occurred in these cases, when benzyl methyl sulfide was employed as the reactant. However, it should be noted that use of BPPM as the chiral ligand for the oxidation of $PhCH_2SCH_3$ (eq 2), resulted in a more facile oxidation reaction, and

$$PhCH_2SCh_3 \xrightarrow[\text{BPPM (2 mol \%), THF, 50 °C, 48 h}]{\text{1(2 mol \%), } O_2\text{ (1 atm)}} PhCH_2\text{—}S(O)\text{—}CH_3 + PhCH_2\text{—}S(O)_2\text{—}CH_3 \quad (2)$$

sulfone is formed as well as sulfoxide (sulfone/sulfoxide = 2.4/1).

In conclusion, aliphatic, aromatic, allylic, benzylic, and heterocyclic sulfides can be selectively oxidized to sulfoxides by molecular oxygen, using a catalyst formed by the reaction of the palladium dimer **1** and oxygen. The reaction proceeds under very mild conditions (50 °C, 1 atm O_2), and is simple in execution and workup. Furthemore, the reaction can tolerate amide, carboxylic acid, imide, and nitro substituents. Finally, the process is stereospecific, as demonstrated in the case of (+)-biotin 4-nitrophenyl ester.

Experimental Section

General procedure for the oxidation of sulfides: A mixture of **1** (8 mg, 0.01 mmol)[9] and THF (10 mL) was stirred under oxygen for 1–2 h at 50 °C, until a clear, yellow-orange, solution was formed. The sulfide (1 mmol) was added at this time, and the reaction was stirred for 24–96 h (monitored by GC or TLC). The solvent was removed by rotary evaporation, and pure products were isolated by column chromatography on silica gel, using various ratios of ethyl acetate/hexane as eluant. If necessary Kugelrohr distillation was applied before column chromatography in order to remove the more volatile byproducts. The products were identified by comparison of spectral data with literature results and/or with authentic samples.

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