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Titanium-Salan-Catalyzed Asymmetric Oxidation of Sulfides and Kinetic Resolution of Sulfoxides with H_2O_2 as the Oxidant

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Asymmetric oxidation of sufides to sulfoxides by aqueous hydrogen peroxide with catalysis by titanium-salan complexes is presented. Optically active sulfoxides have been obtained with good to high enantioselectivities (up to 97 % *ee*) by a tandem enantioselective oxidation and kinetic resolution procedure, the catalyst performing over 500 turnovers with no loss of enantioselectivity.

Introduction

Optically pure sulfoxides are valuable chiral auxiliaries in organic synthesis, the sulfinyl group being one of the most efficient and versatile chiral controllers in C–C and C–X bond formation.[1] Some sulfoxides are important bioactive ingredients in the pharmaceutical industry.[2] There are several possible approaches to enantiomerically pure organic compounds: (i) resolution of racemic mixtures, (ii) chemical modification of chiral objects available from the "chiral pool", and (iii) asymmetric synthesis. The most challenging is catalytic asymmetric synthesis, because one chiral catalyst molecule can (in principle) create millions of chiral product molecules. Asymmetric oxidations of prochiral sulfides to sulfoxides mediated either by biological (e.g., isolated enzymes or whole cells, or antibodies) or by chemical (both metal complexes and metal-free catalysts) agents are known in the literature.[2a,3]

Historically, the first systems used for the asymmetric oxidation of sulfides were those of Kagan[3a,3b] and Modena,[3c] who first applied the "Katsuki–Sharpless reagent" Ti(O*i*Pr$_4$)/diethyl tartrate/alkyl hydroperoxide, with appropriate modifications, to asymmetric oxidations of prochiral sulfides by alkyl hydroperoxides. Catalytic versions and modifications of the titanium tartrate systems were later developed (with up to 90% yields and 90% *ee* values for certain sulfides) and remain the most widely applied so far (including industrial applications; see, for example[3b,4d]). However, these systems have certain disadvantages, such as low turnover numbers (so that 4–16 mol-% of the catalyst is required), complexity, and expensiveness.

The importance of asymmetric sulfoxidations for the pharmaceutical chemistry has stimulated the search for other transition-metal-based catalytic systems. An ideal catalytic system is expected to be cheap, simple and robust, environmentally safe, efficient (in terms of turnover numbers), and highly enantioselective, and to use a readily available "green" oxidant. Accordingly, catalytic systems based on nontoxic metals such as titanium and using hydrogen peroxide as oxidant are of particular interest. Attempts to find appropriate ligand systems for titanium(IV)-catalyzed sulfoxidations with H_2O_2 date from 1986, when Pasini[5a] reported titanium(IV) salen complexes capable of oxidizing thioanisole with <20% *ee*. Fifteen years later, Katsuki examined a mononuclear "second-generation" titanium-salen complex (bearing additional elements of chirality in the 3,3′-positions of the salen ligand) as a sulfoxidation catalyst and found only poor enantioselectivity.[5b] Surprisingly, though, when this complex was converted into its di-μ-oxo binuclear titanium counterpart, this appeared to be a very active and enantioselective catalyst for oxidation of alkyl aryl sulfides with H_2O_2 or urea hydroperoxide (UHP; this gave better results) in methanolic solution (up to 92–99% *ee* values).[5b,5c] Soon after, this system was successfully applied to the asymmetric oxidation of cyclic dithioacetals (with *ee* values of the resulting monosulfoxides ranging from 39 to 99%).[5d] Later, Jackson and co-workers reported solid-supported titanium catalysts featuring a β-amino alcohol-derived chiral Schiff base as the chirality carrier, obtaining sulfoxidation enantioselectivities (for alkyl aryl sulfoxides) between 45 and 72% *ee*.[5e] Very recently, a family of titanium(IV) complexes with *N*-salicylidene-L-amino alcohol-derived Schiff bases capable of asymmetric oxidation of prochiral sulfides with H_2O_2 has been published.[5f] The sulfoxidation reactions proceeded with high

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selectivity and conversion levels, but with only moderate enantioselectivities (up to 65% *ee*).[5f,5g]

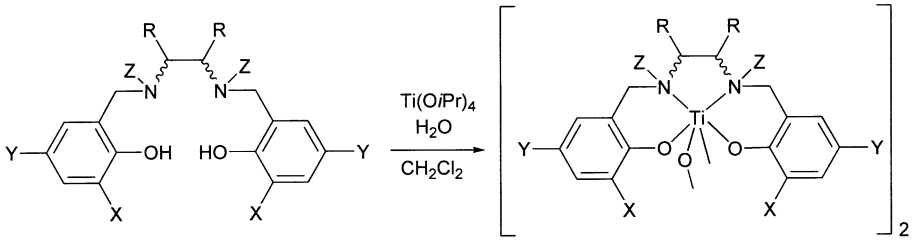
In recent years, salan [*N*,*N*′-bis(salicylamine)] and salalen (*N*-salicylamine-*N*′-salicylimine) complexes of different transition metals have been applied in asymmetric catalytic processes.[6] Iron(III)-salan complexes bearing additional centers of chirality in the aromatic rings, for example, were found to be capable of catalyzing efficient oxidation of alkyl aryl sulfides with H_2O_2 in aqueous media (in 81–96% *ee*).[6c] Al^{III}-salalen complexes with additional chiral centers, taking advantage of the synergistic combination of initial enantioselective oxidation and the subsequent oxidative kinetic resolution process, showed even more remarkable results in methanolic solutions: alkyl aryl sulfoxides were obtained in up to 94–99% *ee* values.[6d,6e] Notably, bis-μ-oxo-bridged binuclear Ti-salan catalysts have been found to catalyze enantioselective epoxidation of olefins with H_2O_2 as the oxidant, demonstrating moderate to high enantioselectivities (55–98% *ee* values).[6f,6g]

We have found that similar titanium-salan complexes are capable of catalyzing enantioselective oxidation of sulfides to sulfoxides with H_2O_2, with simultaneous kinetic resolution of the sulfoxides (which increases the optical yield). Here we report the preparation of a family of various salan ligands and their corresponding titanium(IV) complexes and their application as enantioselective sulfoxidation catalysts.

Results and Discussion

In the course of our studies, a number of tetradentate salan ligands of the type **1** were synthesized (Scheme 1) by condensation of the corresponding substituted salicylaldehydes with optically pure 1,2-diamines and subsequent reduction of the resulting Schiff bases with $NaBH_4$ (see the Experimental Section). Preliminary screening of the titanium-salan catalysts generated in situ was performed, with use of a small excess of the oxidant (Table 1). In the oxidation experiments, sulfoxides and sulfones were found as the reaction products along with the starting sulfides. The ligands containing 3-*tert*-butyl substituents in the salicylidene rings (**1**, **2**) showed quite low enantioselectivities and required rather long times for the reactions to proceed to a significant extent (Table 1, Entries 1, 2). The introduction of 5-nitro substituents decreased the oxidation enantioselectivity, while similarly poor results were obtained with ligand **3**. However, the use of ligands **4** and **5**, bearing no substituents in their 3-positions, led to much higher *ee* values (Table 1, Entries 4, 5), thus allowing greater optimism about the prospects of the titanium-salan complexes in asymmetric sulfoxidation. The *ee* obtained with ligand **6**, with Ph substituents in the 3-positions of the salicylidene rings and in the chiral diamine moiety was not as high; however, the use of cyclohexane-1,2-diamine as the chirality carrier was more profitable. It was found that the sulfoxidation enantioselectivity attained its maximum at a ligand/titanium ratio of 1.0 (Table 1, Entries 7–9), thus indicating that the catalytically active sites include one salan ligand per titanium. When the catalytic system was tested in MeOH with UHP as the catalyst (by Katsuki's oxidation protocol[5b,5c]), the *ee* was much poorer (Entry 10). It was also found that other bulky substrates [e.g., 2-(methylthio)-naphthalene] were oxidized with much lower enantioselectivity with the **7**/Ti(O*i*Pr)$_4$ system (Table 1, Entry 11). In all cases, the absolute sulfoxide configuration was retained [i.e., use of the (*S*,*S*) ligand led to (*S*) sulfoxides]. Significant amounts of sulfone were found in the reaction products, thus suggesting that the second oxidation step might noticeably affect the *ee* of the sulfoxide, through kinetic resolution (see below).

For the most successful ligands, the corresponding di-μ-oxo titanium salan complexes were prepared (Scheme 1) and used as catalysts (Table 2). One can see that the gain in *ee* due to the replacement of the ligand/Ti(O*i*Pr)$_4$ by preliminarily prepared titanium complexes was about +9 to +24% *ee* at comparable oxidant-to-substrate ratios (cf. Table 1 and Table 2). Complexes Ti-**4** and Ti-**5** showed moderate to high enantioselectivities in the oxidation of the

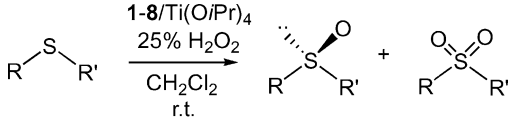


Z = H:
1 (*R*,*R*)-, R = -C_2H_4-, X = *t*Bu, Y = *t*Bu
2 (*R*,*R*)-, R = -C_2H_4-, X = *t*Bu, Y = NO_2
3 (*S*,*S*)-, R = -C_2H_4-, X = Adamantyl, Y = CH_3
4 (*R*,*R*)-, R = -C_2H_4-, X = H, Y = H
5 (*R*,*R*)-, R = -C_2H_4-, X = H, Y = Br
6 (*R*,*R*)-, R = Ph, X = Ph, Y = H
7 (*S*,*S*)-, R = -C_2H_4-, X = Ph, Y = H
8 (*R*,*R*)-, R = -C_2H_4-, X = Ph, Y = NO_2
Z = CH_3:
7' (*R*,*R*)-, R = -C_2H_4-, X = Ph, Y = H

⟹ Ti-**4**, Ti-**5**, Ti-**6**, Ti-**7**, Ti-**8**, Ti-**7'**

Scheme 1. Salan ligands considered and the synthesis of the corresponding di-μ-oxo titanium complexes.

Table 1. Enantioselective oxidation of sulfides with the system **1**–**8**/Ti(O*i*Pr)$_4$/H_2O_2.[a]

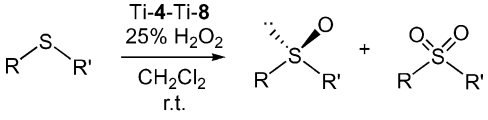


Entry	Ligand/Ti	R′	R	Reaction time [h]	Sulfoxide/sulfone yield [%][b]	Selectivity [%][b]	Sulfoxide *ee* [%][c]	Sulfoxide config.[d]
1	**1**/Ti = 1.25	Ph	CH_2Ph	24	41.5/8.5	83.0	13.0	*R*
2	**2**/Ti = 1.0	Ph	CH_2Ph	14	58.5/9.5	86.0	5.0	*R*
3	**3**/Ti = 1.0	Ph	CH_2Ph	1	32.5/7.0	82.5	2.0	*S*
4	**4**/Ti = 1.0	Ph	CH_2Ph	5	62.5/29.5	68.0	62.5	*R*
5	**5**/Ti = 1.0	Ph	CH_2Ph	5	64.5/26.5	70.5	62.0	*R*
6	**6**/Ti = 1.0	Ph	CH_2Ph	24	62.5/8.5	88.0	43.0	*R*
7	**7**/Ti = 0.85	Ph	CH_2Ph	24	67.5/20.0	77.0	59.0	*S*
8	**7**/Ti = 1.0	Ph	CH_2Ph	2.5	62.5/14.5	81.0	64.0	*S*
9	**7**/Ti = 1.25	Ph	CH_2Ph	15	68.8/17.0	80.0	60.0	*S*
10	**7**/Ti = 1.0[e]	Ph	CH_2Ph	15	60.0/3.0	95.0	14.0	*S*
11	**7**/Ti = 1.0	Me	2-Naph	1	72.0/16.0	82.0	22.0	*S*

[a] [Oxidant]/[substrate]/[titanium] ratio was 56:50:1. Reaction was carried out at room temperature (25 °C) in CH_2Cl_2. The sulfide initial concentration was 0.05 M. The preparation of the catalyst systems in situ is described in the Experimental Section. [b] Determination based on ^{1}H NMR measurements of the sulfide, sulfoxide, and sulfone relative concentrations in the reaction products. [c] The enantiomeric excess values were measured by ^{1}H NMR with Eu(hfc)$_3$ chiral shift reagent in CCl_4. [d] The absolute configuration was determined as described in the Supporting Information of ref.[7] [e] Reaction was carried out in methanol, UHP was used as the oxidant.

selected sulfides (Table 2, Entries 1–8). As expected, poorer results were obtained with complex Ti-**6** (Entries 9, 10). Ti-**8** demonstrated unexpectedly low *ee* values and reactivities, thus demonstrating the particularly negative effect of the highly electron-withdrawing group in the 5-position[8] (see Entries 11, 12). In turn, complex Ti-**7**, although giving a very modest *ee* in the oxidation of *p*-BrPhSMe, showed rather high enantioselectivities with other substrates (Entries 13–15). Particularly high enantioselectivity was achieved for the oxidation of $PhSCH_2Ph$, a bulky substrate that can be regarded as a model for pyrmetazole, the prochiral precursor *S*-omeprazole, the efficient proton-pump inhibitor sulfoxide.[3b,4d] In all cases, however, the oxidation selectivity (and hence sulfoxide yield) was not very high (indicating pronounced overoxidation to the sulfones), so we attempted to increase the chemoselectivity by using a

Table 2. Enantioselective oxidation of sulfides with the Ti-**4** to Ti-**8**/H_2O_2 systems.[a]



Entry	Complex	[O]/[S] [mol/mol]	R′	R	Reaction time [h]	Sulfoxide/sulfone yield [%][b]	Selectivity [%][b]	Sulfoxide *ee* [%][c]	Configuration[d]
1	Ti-**4**	1.12	CH_3	Ph	2	77.5/12.0	87.0	45.0	*R*
2	Ti-**4**	1.12	CH_3	*p*-BrPh	2	70.5/10.5	87.0	42.0	*R*
3	Ti-**4**	1.28	*i*Pr	Ph	3	52.2/40.0	56.6	69.5	*R*
4	Ti-**4**	1.6	Ph	CH_2Ph	3	51.0/47.6	51.7	86.0	*R*
5	Ti-**5**	1.12	CH_3	Ph	2	76.0/16.5	82.0	46.7	*R*
6	Ti-**5**	1.12	CH_3	*p*-BrPh	2	68.3/10.7	86.5	39.0	*R*
7	Ti-**5**	1.28	*i*Pr	Ph	3	60.5/21.0	73.5	64.0	*R*
8	Ti-**5**	1.6	Ph	CH_2Ph	3	62.0/34.0	64.5	74.5	*R*
9	Ti-**6**	1.28	*i*Pr	Ph	5	55.5/19.5	74.5	42.5	*R*
10	Ti-**6**	1.12	Ph	CH_2Ph	5	67.5/11.0	86.0	52.0	*R*
11	Ti-**8**	1.28	*i*Pr	Ph	2.5	23.0/3.5	85.0	4.5	*R*
12	Ti-**8**	1.12	Ph	CH_2Ph	2.5	26.5/3.0	90.0	4.0	*R*
13	Ti-**7**	1.12	CH_3	*p*-BrPh	16	72.5/13.5	84.0	16.0	*S*
14	Ti-**7**	1.12	*i*Pr	Ph	16	47.5/27.0	63.5	69.0	*S*
15	Ti-**7**	1.12	Ph	CH_2Ph	2	75.0/19.0	80.0	88.0	*S*
16	Ti-**7**	0.64	Ph	CH_2Ph	16	48.0/4.0	92.5	82.0	*S*
17	Ti-**7′**	1.12	Ph	CH_2Ph	4.5	30.0/4.5	87.0	0	–

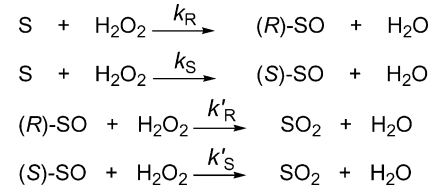
[a] [Substrate]/[titanium complex] ratio was 100:1 mol/mol unless otherwise stated. Reaction was carried out at room temperature (25 °C) in CH_2Cl_2. The sulfide initial concentration was 0.05 M. [b] Determination based on ^{1}H NMR measurements of the sulfide, sulfoxide, and sulfone relative concentrations in the reaction products. [c] The enantiomeric excess values were measured by ^{1}H NMR with Eu(hfc)$_3$ chiral shift reagent in CCl_4. [d] The absolute configuration was determined as described in the Supporting Information of ref.[7]

smaller quantity of the oxidant (Table 2, Entry 16). This resulted in higher selectivity but lower *ee*, indicating that the high enantioselectivity is attained both through the asymmetric oxidation and through the subsequent kinetic resolution.[9] Importantly, when **7′**, containing N–CH_3 functional groups, was used as the chiral ligand, the resulting titanium catalyst showed no oxidation enantioselectivity, together with reduced reactivity, thus confirming the proposed crucial role of the hydrogen bonding of the N–H hydrogen and the coordinated peroxo group.[6f]

To probe the kinetic resolution process in more detail, we performed an oxidation of $PhSOCH_2Ph$ under the same conditions as in Table 2, Entry 16. Complex Ti-**7** was chosen because of the optimum selectivity/enantioselectivity combination. The reaction mixture contained 62% of the sulfone and 38% of the sulfoxide in 77% *ee* (*S* configuration), revealing a stereoselectivity factor[9,10] of 6.25. Thus, one could expect that an excess of the oxidant could be exploited to improve the *ee* of the sulfoxide (at the expense of the sulfoxide yield). To illustrate this, PhSO*i*Pr and $PhSOCH_2Ph$ were obtained in up to 82.5 and 97.0% *ee* values, respectively, with a 1.6-fold excess of the oxidant. The dependences of the sulfoxide and sulfone overall yields, together with the sulfoxide *ee* values vs. the oxidant/substrate ratio, are shown in Figure 1. From these data, the kinetic parameters of the sulfoxidation/kinetic resolution tandem process could be evaluated. Indeed, the analysis of the model reaction scheme (see the scheme for Table 3, in which S, SO, and SO_2 stand for the sulfide, sulfoxide, and sulfone, respectively; see Supporting Information for details) gave the following ratios of the apparent rate constants (Table 3). The lower stereoselectivity of the sulfoxidation stage (k_S/k_R) along with the relatively fast second oxidation stage (k'_R/k_R) explain the lower sulfoxide yield and *ee* for the oxidation of PhS*i*Pr (in relation to the case of $PhSCH_2Ph$).

Further, the effects of solvent, temperature, and substrate/catalyst ratio on the sulfoxidation were probed. Several reactions were performed in different solvents (Table 4, Entries 1–4; Table 1, Entry 10), demonstrating the advantage of CH_2Cl_2 as solvent over others. A decrease in the catalyst loading down to 0.2 mol% did not cause any deterioration in enantioselectivity, thus demonstrating the high efficiency of the catalytic system studied. However, further reduction of the catalyst concentration (to [S]/[Cat] = 1000 and 2000) led to lower conversions and enantioselectivities after 24 and 48 h, respectively. Apparently, the catalyst turnover limit lies between the [S]/[Cat] ratios of 500 and 1000. A reduction in the reaction temperature to 0 °C resulted in somewhat better chemo- and enantioselectivities (Table 4, Entries 8–10). Indeed, with complex Ti-**7**, $PhSOSCH_2Ph$ was obtained in 77.5% yield and 92.5% *ee* (cf. 75.0% yield and 88.0% *ee* at room temperature, Table 2, Entry 15) at the same oxidant/substrate ratio. Ti-**4**- and Ti-**5**-catalyzed sulfoxidations gave essentially the same *ee* values as at room temperature, but rather higher yields (cf. Table 4, Entries 8–9 and Table 2, Entries 4 and 8). This result is not surprising, because for the room-temperature oxidations we had to use higher excesses of H_2O_2 to achieve similar *ee* levels, so the systems demonstrate potential for oxidation procedure improvement by use of lower oxidation

Table 3. The ratios of the apparent rate constants for the model kinetics scheme of the titanium-catalyzed tandem sulfoxidation/kinetic resolution process.[a]



Entry	Complex	Sulfide	k_S/k_R	k'_R/k'_S	k'_R/k_R
1	(*S*,*S*)-Ti-**7**	PhS*i*Pr	4.1	1.8	7.0
2	(*S*,*S*)-Ti-**7**	$PhSCH_2Ph$	8.1	6.25[b]	4.0

[a] Determination based on the experimental data shown in Figure 1. [b] Determination based on the results of a separate kinetic resolution experiment (see the text).

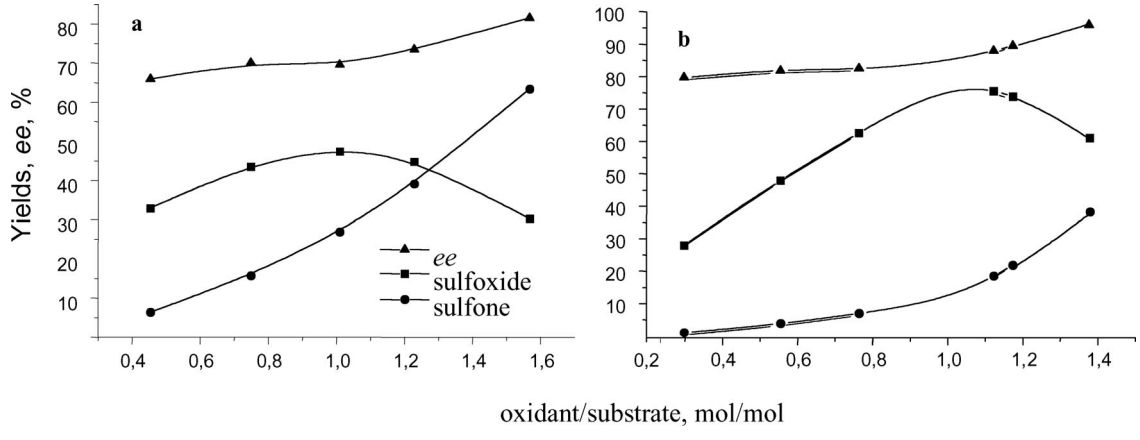


Figure 1. Sulfoxide and sulfone yields and the sulfoxide enantioselectivities vs. oxidant/substrate ratio in the oxidation of PhS*i*Pr (a) and $PhSCH_2Ph$ (b). Catalyst: Ti-**7**, CH_2Cl_2, 25 °C, sulfide/Ti-**7** = 100:1.

Table 4. Effect of solvent, temperature, and the substrate/catalyst ratio on the $PhSCH_2Ph$ asymmetric oxidation by the systems Ti-**4**, Ti-**5**, and Ti-**7**/H_2O_2.[a]

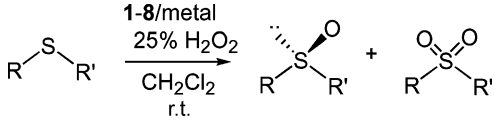
Entry	Cat.	Temp. [°C]	Solvent	[O]/[S] [mol/mol]	[S]/[Cat] [mol/mol]	Reaction time [h]	Sulfoxide/sulfone yield [%][b]	Select. [%][b]	Sulfoxide *ee* [%][c]	Config.[d]
1	Ti-**7**	25	$CHCl_3$	1.6	100	4	58.0/27.5	68.0	88.0	*S*
2	Ti-**7**	25	CCl_4	1.6	100	4	8.0/7.0	53.0	57.5	*S*
3	Ti-**7**	25	toluene	1.6	100	4	23.0/26.0	47.0	66.5	*S*
4	Ti-**7**	25	CH_2Cl_2	1.6	100	4	65.0/34.5	65.5	97.0	*S*
5	Ti-**7**	25	CH_2Cl_2	1.6	500	4	63.5/35.5	64.0	97.0	*S*
6	Ti-**7**	25	CH_2Cl_2	1.6	1000	24	49.5/14.5	77.5	77.0	*S*
7	Ti-**7**	25	CH_2Cl_2	1.6	2000[e]	48	34.0/3.0	91.5	60.0	*S*
8	Ti-**4**	0	CH_2Cl_2	1.12	100	5	71.0/15.5	82.0	81.0	*R*
9	Ti-**5**	0	CH_2Cl_2	1.12	100	5	67.5/10.0	87.0	75.5	*R*
10	Ti-**7**	0	CH_2Cl_2	1.12	100	5	77.5/13.0	85.5	92.5	*S*
11	Ti-**4**	0[f]	CH_2Cl_2	1.28	100	6	60.5/31.0	66.0	72.5	*R*
12	Ti-**4**	0[g]	CH_2Cl_2	1.28	100	6	85.5/14.0	85.5	59.0	*R*

[a] [Substrate]/[titanium complex] ratio was 100:1 mol/mol and sulfide initial concentration was 0.05 M unless otherwise stated. Reaction was carried out in CH_2Cl_2. [b] Determination based on ^1H NMR measurements of the sulfide, sulfoxide, and sulfone relative concentrations in the reaction products. [c] The enantiomeric excess values were measured by ^1H NMR with $Eu(hfc)_3$ chiral shift reagent in CCl_4. [d] The absolute configuration was determined as described in the Supporting Information of ref.[7] [e] Sulfide initial concentration was 0.1 M. [f] PhS*i*Pr was used as the substrate. [g] 2-NaphSMe was used as the substrate.

temperatures. The fair to high *ee* values obtained for the oxidation of other substrates at 0 °C (Table 4, Entries 11, 12) support this conclusion. Importantly, cumyl hydroperoxide used as the oxidant resulted in no conversion of the substrate ($PhSCH_2Ph$, catalyst: Ti-**4**).

Inspired by the findings of Zhu,[6b,6i] who applied salan-type ligands to vanadium- and tungsten-catalyzed sulfoxidations, we also examined our salan ligands in vanadium- and molybdenum-catalyzed reactions. The catalysts were prepared in situ by mixing the metal precursors with the ligands. Interestingly, unlike in the case of the Ti-salan systems, reversal of the sulfoxide absolute configuration was generally observed with the Mo- and V-salan counterparts. However, the enantioselectivities observed were not as encouraging as for the Ti-catalyzed sulfoxidations (Table 5). Zhu and co-workers proposed an oxovanadium(IV) salan complex as the reactive intermediate.[6b] Our experience in vanadium-catalyzed oxidations with hydroperoxides points in favor of formation of the vanadium(V) reactive intermediates upon interaction of the vanadium(IV) precursors with the terminal oxidants.[11] We have shown that vanadium-salan-catalyzed oxidations can also be performed starting with vanadium(V) precursors [e.g., $VO(OnBu)_3$; see Table 5, Entries 6–11], indicating that vanadium(V) rather than vanadium(IV) intermediates are the true oxidizing species.

Table 5. Enantioselective oxidation of sulfides with the **1**–**7**/metal/H_2O_2 system.[a]



Entry	Ligand/Metal	Metal source	Sulfide	Reaction time [h]	Sulfoxide/sulfone yield [%][b]	Sulfoxide *ee* [%][c]	Sulfoxide config.[d]
1	**7**/Mo = 1.0	$MoO_2(acac)_2$	$PhSCH_2Ph$	24	79.5/12.0	8.5	*R*
2	**7**/Mo = 1.0	$MoO_2(acac)_2$	$PhSCH_3$	24	82.0/10.5	0	–
3	**1**/Mo = 1.5	$MoO_2(acac)_2$	*p*-CH_3PhSCH_3	24	57.0/3.0	2.5	*S*
4	**7**/V = 1.5	$VO(acac)_2$	$PhSCH_2Ph$	15	86.0/10.5	8.5	*R*
5	**1**/V = 1.5	$VO(acac)_2$	*p*-CH_3PhSCH_3	4	85.8/5.5	10.0	*R*
6	**7**/Ti = 1.5	$VO(OnBu)_3$	*p*-$BrPhSCH_3$	14	89.5/6.0	2.0	*R*
7	**2**/Ti = 1.5	$VO(OnBu)_3$	*p*-CH_3PhSCH_3	14	51.5/6.5	6.0	*S*
8	**4**/Ti = 1.5[e]	$VO(OnBu)_3$	*p*-$BrPhSCH_3$	20	32.0/4.5	37.5	*R*
9	**4**/Ti = 1.5	$VO(OnBu)_3$	*p*-CH_3PhSCH_3	14	82.0/12.5	19.5	*R*
10	**5**/Ti = 1.0	$VO(OnBu)_3$	*p*-CH_3PhSCH_3	15	85.5/14.0	17.0	*R*
11	**5**/Ti = 1.0	$VO(OnBu)_3$	*p*-$BrPhSCH_3$	15	78.0/13.5	13.5	*R*

[a] [Oxidant]/[substrate]/[titanium] ratio was 56:50:1. Reaction was carried out at room temperature (25 °C) in CH_2Cl_2. The sulfide initial concentration was 0.05 M. [b] Determination based on ^1H NMR measurements of the sulfide, sulfoxide, and sulfone relative concentrations in the reaction products. [c] The enantiomeric excess values were measured by ^1H NMR with $Eu(hfc)_3$ chiral shift reagent in CCl_4. [d] The absolute configuration was determined as described in the Supporting Information of ref.[7] [e] Reaction carried out in $CHCl_3$ at –12 °C without stirring.

Conclusions

For the first time, catalytic asymmetric oxidation of prochiral sulfides with aqueous H_2O_2 has been performed in the presence of a novel titanium-salan-based catalytic system. Optically active sulfoxides have been obtained with good to high enantioselectivities (up to 97% *ee*). The system is particularly suitable for bulky thioethers, which could be regarded as models for the syntheses of bioactive compounds. The high asymmetric induction levels are attained in a tandem enantioselective oxidation/kinetic resolution procedure. The catalysts demonstrate high efficiency, being capable of performing over 500 turnovers with no loss of enantioselectivity. The catalytic system studied employs chiral ligands prepared from readily available precursors, a non-toxic metal, and a "green" oxidant; the reaction solvent – dichloromethane – is a volatile liquid and can be easily separated from the reaction mixture by distillation and recycled. The chemo- and enantioselectivities of the sulfoxidation can be increased by lowering the reaction temperature. Detailed studies of the temperature effect on both the oxidation and kinetic resolution stages and the detailed reaction mechanism are currently underway and will be reported in future publications.

Experimental Section

General Remarks: $CDCl_3$ and CCl_4 (analytical grade) were stored under molecular sieves and used without further purification. Ethyl acetate and hexane (reagent grade) were used for column chromatography without purification. For oxidation procedures, reagent grade CH_2Cl_2 (99.85%) was used. Toluene for synthesis was degassed in vacuo and dried with molecular sieves. H_2O_2 was used as analytical grade 30% aqueous solution. Silica gel 40 (0.063–0.200 mm) for column chromatography was purchased from Merck. All other chemicals were Aldrich, AlfaAesar, or Acros commercial reagents. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 250 spectrometer at 250.13 and 62.87 MHz, respectively, in 5 mm cylindrical tubes. Chemical shifts were referenced to internal reference TMS, with positive values in the low-field direction. ^1H-decoupled ^{13}C NMR measurements: spectral widths, 25000 Hz; spectrum accumulation frequency, 0.2 Hz; number of scans, 1000; 90° radio-frequency pulse; duration, 6.2 μs.

Synthesis of the Salan Ligands: Chiral salan ligands were synthesized as shown in Scheme 2, starting from substituted phenols or salicylaldehydes.

General Method for the Preparation of Substituted Salicylaldehydes from the Corresponding Phenols (adopted from ref.[12a], with modifications): The substituted phenol (10 mmol) was placed in a flask with dry toluene (20 mL) and a magnetic stirrer under argon, and $SnCl_4$ (1 mmol) was then added with stirring, followed by Et_3N (4 mmol). After the mixture had been stirred for 60 min at room temperature, paraformaldehyde (33 mmol) was added, and the flask was heated to 100 °C for 8–12 h. The resulting mixture was cooled to room temperature, poured into water (50 mL), acidified to pH 2, and extracted with diethyl ether (2 × 50 mL). The extract was washed with aqueous NaCl and dried with $CaSO_4$, and the solvent was removed. The crude product was, if necessary, purified by column chromatography on SiO_2 (eluent: hexane/ethyl acetate) and recrystallized from hexane.

3-Adamantyl-2-hydroxy-5-methylbenzaldehyde: ^1H NMR (250 MHz, CCl_4, 20 °C): δ = 11.67 (1 H, OH), 9.79 (1 H, CHO), 7.25 (1 H, Ar-H), 7.17 (1 H, Ar-H), 2.32 (3 H, Ar-CH_3), 2.12, 2.09 (9 H, -CH_2-, -CH-), 1.78 (6 H, -CH_2-) ppm.

2-Hydroxy-3-phenylbenzaldehyde: ^1H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 11.54 (1 H, OH), 9.97 (1 H, CHO), 7.59–7.01 (8 H, Ar-H) ppm.

Some of the synthesized aldehydes were subjected to nitration according to ref.[12b]

2-Hydroxy-5-nitro-3-phenylbenzaldehyde: ^1H NMR (250 MHz, CCl_4, 20 °C): δ = 12.06 (1 H, OH), 10.00 (1 H, CHO), 8.44 (2 H, Ar-H), 7.53–7.33 (5 H, Ph) ppm.

3-*tert*-Butyl-2-hydroxy-5-nitrobenzaldehyde: ^1H NMR (250 MHz, CCl_4, 20 °C): δ = 12.47 (1 H, OH), 9.99 (1 H, CHO), 8.37 (2 H, Ar-H), 1.49 (9 H, *t*Bu) ppm.

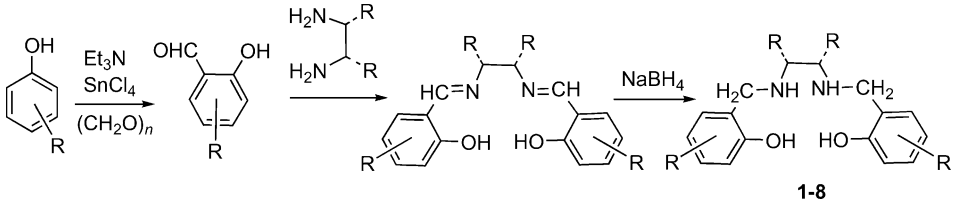
General Method for the Preparation of Salen Precursors of the Salan Ligands by Schiff Condensation of the Corresponding Salicylaldehydes with Chiral Diamines: The substituted salicylaldehyde (4.5 mmol) and the chiral diamine (2 mmol) were heated at reflux in EtOH (10–20 mL) for 3 h (if necessary, 10 vol.-% of $CHCl_3$ was added for better solubility). The mixture was cooled to room temperature. If precipitation of the Schiff base was observed, the solid was filtered off, washed with hexane, and dried in vacuo. Otherwise, the reaction mixture was evaporated in a flow of air and the tetradentate Schiff base was separated and purified by column chromatography on SiO_2 (eluent: hexane/ethyl acetate).

^1H NMR spectroscopic data for the Schiff base precursors of ligands **1**–**3**, **5**, and **7** can be found in ref.[12c] (Supporting Information).

(*R*,*R*)-*N*,*N*′-Bis(3-phenylsalicylidene)-1,2-diphenylethylenediamine: ^1H NMR (250 MHz, CCl_4, 20 °C): δ = 13.62 (2 H, OH), 8.38 (2 H, CH=N), 7.56, 7.12 (26 H, Ar-H), 4.65 (2 H, C*H) ppm.

(*R*,*R*)-*N*,*N*′-Bis(5-nitro-3-phenylsalicylidene)cyclohexane-1,2-diamine and (*R*,*R*)-*N*,*N*′-Bis(salicylidene)cyclohexane-1,2-diamine were used in imine moiety reduction without separation.

General Method for the Reduction of Salens to Salans (adopted from ref.[12d]): Solid $NaBH_4$ was added portionwise at 0 °C over a period of 30 min to a solution of the corresponding salen precursor (1 mmol) in MeOH/THF solution (3:5, 16 mL). After the addition,



1-8

Scheme 2. Preparation of salan ligands **1**–**8**.

the mixture was stirred at room temperature overnight (with a change of the solution color from yellow to colorless, except in the cases of ligands **2** and **8**) and poured into H_2O (30 mL). The resulting mixture was extracted with CH_2Cl_2 (2 × 30 mL), and the extract was dried with $CaSO_4$, diluted with hexane, and allowed to evaporate slowly to yield solid **1**–**8**.

(*R*,*R*)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicyl)cyclohexane-1,2-diamine (1): ^{1}H NMR (250 MHz, CCl_4, 20 °C): δ = 10.17 (s, 2 H, OH), 7.24 (s, 2 H, Ar-H), 6.71 (s, 2 H, Ar-H), 3.98 (d, 2 H, N-CH*H*-), 3.90 (d, 2 H, N-C*H*H), 2.44 (2 H, C*H), 2.18, 1.72, 1.62, (6 H, *c*Hex), 1.33, (s, 18 H, *t*Bu), 1.26 (s, 18 H, *t*Bu) ppm; two cyclohexane protons are masked by *t*Bu peaks.

(*R*,*R*)-*N*,*N*′-Bis(5-*tert*-butyl-3-nitrosalicyl)cyclohexane-1,2-diamine (2): ^{1}H NMR (250 MHz, CCl_4, 20 °C): δ = 11.7 (2 H, OH), 8.02 (d, 2 H, Ar-H), 7.72 (d, 2 H, Ar-H), 4.10 (d, 2 H, N-CH*H*-), 4.04 (d, 2 H, N-C*H*H-), 2.53 (2 H, C*H), 2.26 (2 H, *c*Hex), 1.39 (s, 18 H, *t*Bu) ppm; some peaks are masked by *t*Bu signals and traces of THF.

(*S*,*S*)-*N*,*N*′-Bis(3-adamantyl-5-methylsalicyl)cyclohexane-1,2-diamine (3): ^{1}H NMR (250 MHz, CCl_4, 20 °C): δ = 6.78 (2 H, Ar-H), 6.53 (2 H, Ar-H), 3.97 (d, 2 H, N-CH*H*-), 3.83 (d, 2 H, N-C*H*H-), 2.39 (2 H, C*H), 2.19 (6 H, Ar-CH_3), 2.04 (12 H, Ada-CH_2), 2.00 (6 H, Ada-CH), 1.74 (12 H, Ada-CH_2) ppm. Some peaks masked by intense signals in the range 2.2–2.0 ppm.

(*R*,*R*)-*N*,*N*′-Bis(salicyl)cyclohexane-1,2-diamine (4): ^{1}H NMR (250 MHz, CCl_4, 20 °C): δ = 7.17 (t, 2 H, Ar-H), 6.94 (d, 2 H, Ar-H), 6.77 (m, 4 H, Ar-H), 4.06 (d, 2 H, N-CH*H*-), 3.93 (d, 2 H, N-C*H*H-), 2.44 (2 H, C*H), 2.20 (2 H, *c*Hex), 1.73 (2 H, *c*Hex), 1.3–1.1 (4 H, *c*Hex) ppm.

(*R*,*R*)-*N*,*N*′-Bis(5-bromosalicyl)cyclohexane-1,2-diamine (5): ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 7.24 (dd, 2 H, Ar-H), 7.06 (d, 2 H, Ar-H), 6.68 (d, 2 H, Ar-H), 4.03 (d, 2 H, N-CH*H*-), 3.90 (d, 2 H, N-C*H*H-), 2.41 (2 H, C*H), 2.17 (2 H, *c*Hex), 1.45 (2 H, *c*Hex), 1.3–1.1 (4 H, *c*Hex) ppm.

(*R*,*R*)-*N*,*N*′-Bis(3-phenylsalicyl)-1,2-diphenylethylenediamine (6): ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 7.47–6.93 (26 H, Ar-H), 3.91 (d, 2 H, N-CH*H*-), 3.90 (s, 2 H, C*H), 3.60 (d, 2 H, N-C*H*H-) ppm.

(*S*,*S*)-*N*,*N*′-Bis(3-phenylsalicyl)cyclohexane-1,2-diamine (7): ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 7.54, 7.39, 7.25, 6.95, 6.83 (16 H, Ar-H), 4.10 (d, 2 H, N-CH*H*-), 3.96 (d, 2 H, N-C*H*H-), 2.50 (2 H, C*H), 2.20 (2 H, *c*Hex), 1.72 (2 H, *c*Hex), 1.25 (4 H, *c*Hex) ppm.

(*R*,*R*)-*N*,*N*′-Bis(5-nitro-3-phenylsalicyl)cyclohexane-1,2-diamine (8): ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 8.15 (d, 2 H, Ar-H), 7.88 (d, 2 H, Ar-H), 7.48, 7.36 (10 H, Ar-H), 4.20 (d, 2 H, N-CH*H*-), 4.04 (d, 2 H, N-C*H*H-), 2.45 (2 H, C*H), 2.23 (2 H, *c*Hex), 1.78 (2 H, *c*Hex), 1.26 (4 H, *c*Hex) ppm.

(*R*,*R*)-*N*,*N*′-Bis(3-phenylsalicylmethyl)cyclohexane-1,2-diamine (7′): This compound was prepared by Mannich condensation of (*R*,*R*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine with biphenyl-2-ol (2 equiv.) and purified by column chromatography on SiO_2 (eluent: hexane/ethyl acetate).[12e] ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 7.5–6.8 (16 H, Ar-H), 3.90 (d, 2 H, N-CH*H*-), 3.64 (d, 2 H, N-C*H*H-), 2.72 (2 H, C*H), 2.27 (6 H, N-CH_3), 1.8 (2 H, *c*Hex) ppm. Some signals not found (masked by admixtures of ethyl acetate and butyl acetate).

Preparation of Bis(μ-oxo) Binuclear Ti-Salan Complexes: Ti-salan complexes Ti-**4** to Ti-**8** were prepared by a procedure described in ref.[6d] and were recrystallized from CH_2Cl_2/hexane at +4 °C. The Ti-salan complexes show poorly informative ^{1}H NMR spectra (broad signals).

General Oxidation Procedure

A: Catalysts Prepared in Situ: The appropriate salan ligand (1.68–3.0 μmol) and the metal source [Ti(O*i*Pr)$_4$ or VO(acac)$_2$ or MoO_2(acac)$_2$, 2.0 μmol] were combined in CH_2Cl_2 (2 mL) and stirred for 30 min. Sulfide (0.1 mmol) was added to the resulting solution, followed by an appropriate amount of aqueous hydrogen peroxide (25%), added in one portion. Stirring was continued at room temperature for 1 h–48 h, the reaction progress being monitored by TLC (eluent: EtOAc/hexane).

B: Preliminarily Prepared Ti Catalysts: The sulfide (0.1 mmol) was added at the desired temperature to the appropriate Ti-salan catalyst (1 μmol) dissolved in CH_2Cl_2 (2 mL). The appropriate amount of aqueous hydrogen peroxide (25%) was then added to the resulting solution in one portion. Stirring was continued at the desired temperature for 1 h–48 h, the reaction progress being monitored by TLC (eluent: EtOAc/hexane). For 0 °C experiments, the reaction flask was cooled with an ice bath.

To stop the reaction, the mixture was diluted with water (1 mL). The organic phase was separated, and volatiles were removed quickly (in 1–2 min) in a flow of air. The residue was extracted with CCl_4 (8 mL), and the extract was dried with $CaSO_4$ and analyzed by ^{1}H NMR. The enantiomeric excess values were measured by ^{1}H NMR with Eu(hfc)$_3$ chiral shift reagent in CCl_4 or CCl_4/$CDCl_3$. The absolute configurations were determined by comparison of Eu(hfc)$_3$-shifted NMR patterns of sulfoxides with those of the sulfoxides of known absolute configuration (for details see ref.[7], Supporting Information). The *ee* measurement uncertainty was ≤1% (in the range of 10–80% *ee*) and not higher than 0.5% for >80% *ee*. Conversion and selectivity were calculated from ^{1}H NMR measurements of the sulfide, sulfoxide, and sulfone relative concentrations. Selected ^{1}H NMR spectroscopic data for the compounds involved, (250 MHz, CCl_4, 20 °C): δ = *p*-BrPhSCH_3 2.45, *p*-BrPhSOCH_3 2.62, *p*-BrPhSO$_2$CH_3 2.94, PhSCH_2Ph 4.05, PhSOCH_2Ph 3.90 (m), PhSO$_2$CH_2Ph 4.15, *p*-CH$_3$PhSCH_3 2.42, *p*-CH_3PhSCH$_3$ 2.31, *p*-CH$_3$PhSOCH_3 2.57, *p*-CH_3PhSOCH$_3$ 2.42, *p*-CH$_3$PhSO$_2$CH_3 2.90, *p*-CH_3PhSO$_2$CH$_3$ 2.46, PhSCH_3 2.35, PhSOCH_3 2.61, PhSO$_2$CH_3 2.92; PhSCH(CH$_3$)$_2$ 3.32, PhSOCH(CH$_3$)$_2$ 2.64, PhSO$_2$CH(CH$_3$)$_2$ 2.92, 2-Naph-SCH_3 2.55, 2-Naph-SOCH_3 2.68, 2-Naph-SO$_2$CH_3 2.99 .

Kinetic Resolution Procedure: PhSOCH$_2$Ph (0.1 mmol) was added at room temperature to the Ti-**7** catalyst (1 μmol) dissolved in CH_2Cl_2 (2 mL). Aqueous hydrogen peroxide (25%, 64 μmol) was added in one portion to the resulting solution. Stirring was continued at the desired temperature for 16 h. The reaction products were separated as described for the general oxidation procedure and were analyzed by ^{1}H NMR spectroscopy.

Supporting Information (see also the footnote on the first page of this article) includes the mathematical treatment of the model kinetic scheme for the tandem sulfoxidation/kinetic resolution process.

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