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Asymmetric oxidation of sulfides with H_2O_2 catalyzed by titanium complexes with aminoalcohol derived Schiff bases

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Abstract

Sulfoxidation catalysts generated in situ from titanium(IV) isopropoxide and enantiopure Schiff bases promote the enantioselective oxidation of alkyl aryl sulfides to the corresponding sulfoxides at low catalyst loadings (<1 mol%), 30% aqueous hydrogen peroxide being the terminal oxidant. Upon screening of several ligands derived from β-aminoalcohols and salicylaldehydes, a catalyst affording sulfoxides with over 90% chemoselectivity and up to 60% ee was found, and the kinetics of the catalytic reaction was analyzed by ^{1}H NMR.

Keywords: Asymmetric catalysis; H_2O_2; Sulfoxides; Chiral Schiff bases; Titanium complexes

1. Introduction

In early 1980s chiral sulfoxides were discovered to be efficient chiral auxiliaries capable of bringing about important asymmetric transformations [1]. Nowadays, asymmetric sulfoxides are finding increasing use in pharmaceutical industry [2–9]. Transition metal catalyzed asymmetric oxidation is regarded as one of the most challenging approaches to chiral sulfoxides since the discoveries of Kagan [10] and Modena [11] who found that prochiral sulfides could be effectively oxidized by modified Sharpless catalytic systems based on Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET/*t*-BuOOH. Most methodologies for catalytic asymmetric sulfide oxygenation involve a transition metal (titanium, vanadium or manganese) and a chiral ligand such as bidentate diethyl tartrate [12], diol [13], BINOL [14], tetradentate Salen type ligands [15–19]. Bolm and coworkers first introduced chiral aminoalcohol derived tridentate Schiff bases in asymmetric sulfoxidations catalyzed by vanadium(V) [20–22] and iron(III) [23–24] complexes. Since 1995, several groups examined tridentate Schiff base ligands in vanadium catalyzed sulfoxidations by H_2O_2 [25–29].

Until how, modified Sharpless systems have been regarded as the most effective sulfoxidation systems. However, they suffer from low turnover numbers (10–20 mol% of the catalyst required), low chemoselectivity and the need in relatively expensive alkylhydroperoxides as oxidants [9–12]. In turn, vanadium(V) catalysts are not desirable from the environmental point of view. Thus, it is tempting to find such systems that would combine the high enantioselectivity of Ti-based systems with the simplicity and activity of vanadium systems. In the last decade, several works utilizing titanium-*N*-salicylidene β-aminoalcohols complexes in enantioselective trimethylsilylcyanation [30,31] and conjugate addition [28] were published. In this paper, we describe a novel efficient enantioselective sulfoxidation catalyzed by titanium(IV) complexes with similar tridentate Schiff base ligands derived from chiral aminoalcohols.

2. Experimental

2.1. General

$CDCl_3$, CCl_4 and CH_2Cl_2 (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. H_2O_2 was used as analytical grade 30% aqueous solution. 95% hydrogen peroxide was obtained by concentrating 30% aqueous H_2O_2 in vacuo at room temperature. Silica gel 40 (0.063–0.200 mm)

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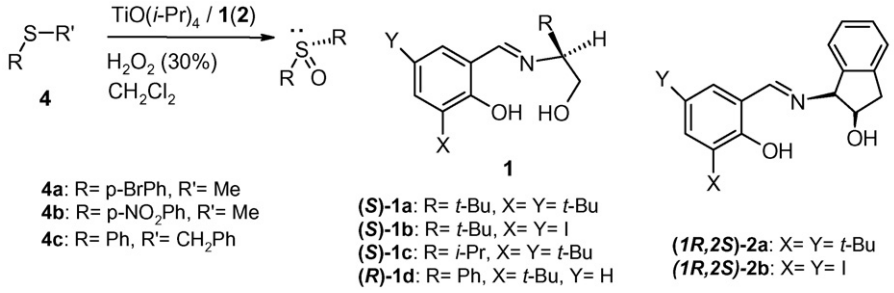


Scheme 1. Titanium catalyzed asymmetric oxidation of sulfides to sulfoxides.

for column chromatography was purchased from Merck. All other chemicals were Aldrich, Lancaster or Acros commercial reagents. (*R*)- and (*S*)-2-aminoalcohols were synthesized by reduction of the corresponding commercially available aminoacids as described [32]. *t*-BuOOH was synthesized as in Ref. [33].

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-250 spectrometer at 250.13 and 62.87 MHz, respectively, using 5 mm cylindrical tubes. Chemical shifts were referenced to CH_2Cl_2 solvent ($\delta(^1H) = 5.35$, $\delta(^{13}C) = 53.8$) or internal reference TMS, with positive values in the low-field direction. ^{1}H-decoupled ^{13}C NMR measurements: spectral widths, 25.000 Hz; spectrum accumulation frequency, 0.2 Hz; number of scans, 1000; 90°, radio-frequency pulse; duration, 6.2 μs.

2.2. Synthesis of Schiff bases

About 1 mmol of appropriate 2-aminoalcohol and 1 mmol of substituted salicylic aldehyde were dissolved in 10 ml of CH_2C1_2 and kept over 4 Å molecular sieves at slow stirring (100 rpm) overnight. Short column purification (hexane, then hexane/EtOAc) and drying in vacuo gave the pure products as yellow solids or syrups (Scheme 1).

2.2.1. (S)-2-(N-3,5-Di-tert-butylsalicylidene)amino-3,3-dimethyl-1-butanol (**1a**)

Yellow solid, 65% yield. ^{1}H NMR, $\delta(CCl_4, 25\,^\circ C)$, 1.02 (9H, s, CHC(C$H_3$)$_3$), 1.31 (9H, s, C(C$H_3$)$_3$), 1.43 (9H, s, C(C$H_3$)$_3$), 2.84 (1H, dd, NCH), 3.67 (1H, dd, CH_2O), 3.86 (1H, dd, CH_2OH), 7.04 (1H, d, Ph), 7.30 (1H, d, Ph), 8.31 (1H, s, CH=N), 13.4 (1H, s, Ph–OH).

^{13}C NMR, $\delta(CH_2Cl_2, 25\,^\circ C)$, 26.8 (3C, C(*C*H$_3$)$_3$), 29.2 (3C, C(*C*H$_3$)$_3$), 31.2 (3C, C(*C*H$_3$)$_3$), 33.0 (1C, *C*(CH$_3$)$_3$), 34.0 (1C, *C*(CH$_3$)$_3$), 34.9 (1C, *C*(CH$_3$)$_3$), 62.4 (*C*H$_2$O), 81.4 (*C**H), 117.8, 126.2, 126.9, 136.5, 140.2, 158.1 (*C*(Ph)OH), 167.0 (*C*=N).

2.2.2. (S)-2-(N-3,5-Diodosalicylidene)amino-3,3-dimethyl-1-butanol (**1b**)

Yellow crystalline solid, 82% yield. ^{1}H NMR spectrum, $\delta(CCl_4, 25\,^\circ C)$, 1.01 (9H, s, CHC(C$H_3$)$_3$), 2.94 (1H, dd, NCH), 3.58 (1H, dd, CH_2OH), 3.87 (1H, dd, CH_2OH), 7.49 (1H, d, Ph), 7.94 (1H, d, Ph), 8.08 (1H, s, CH=N), 14.5 (1H, s, Ph–OH).

2.2.3. (S)-2-(N-3,5-Di-tert-butylsalicylidene)amino-3-methyl-1-butanol (**1c**)

Yellow solid, 81% yield. ^{1}H NMR, $\delta(CH_2Cl_2, 25\,^\circ C)$, 0.94 (6H, d, CH(C$H_3$)$_2$), 1.34 (9H, s, C(C$H_3$)$_3$), 1.46 (9H, s, C(C$H_3$)$_3$), 1.97 (1H, m, (CH$_3$)$_3$C*H*), 3.04 (1H, m, CH–N), 3.80 (2H, m, CH_2OH), 7.19 (1H, d, Ph), 7.42 (1H, d, Ph), 8.41 (1H, s, CH=N), 13.7 (1H, s, Ph–OH).

2.2.4. (R)-2-(N-3-tert-Butylsalicylidene)amino-2-phenyl-1-propanol (**1d**)

Yellow syrup, 71% yield. ^{1}H NMR, $\delta(CCl_4, 25\,^\circ C)$ 1.45 (9H, s, C(CH$_3$)$_3$), 3.91 (2H, m, CH_2OH), 4.47 (1H, m, N–CH), 6.76 (1H, t, Ph), 7.12 (1H, t, Ph), 7.26–7.42 (6H, m, Ph), 8.49 (1H, s, CH=N), 13.6 (1H, s, Ph–OH).

2.2.5. (1R,2S)-2-(N-3,5-Di-tert-butylsalicylidene)-cis-1-amino-2-indanol (**2a**)

Yellow syrup, 49% yield after two column purifications. ^{1}H NMR, $\delta(CCl_4, 25\,^\circ C)$ 1.32 (9H, s, C(CH$_3$)$_3$), 1.41 (9H, s, C(CH$_3$)$_3$), 3.13 (2H, md, CH$_2$), 4.59 (1H, m, C*H*OH), 4.73 (1H, d, C*H*–N), 7.0–7.3 (6H, Ph and Ind), 8.58 (1H, s, CH=N), 12.9 (1H, s, Ph–OH).

2.2.6. (1R,2S)-2-(N-3,5-Diiodosalicylidene)-cis-1-amino-2-indanol (**2b**)

Yellow crystalline solid, 75% yield. ^{1}H NMR, $\delta(CCl_4, 25\,^\circ C)$ 3.20 (2H, md, CH$_2$), 4.71 (1H, m, C*H*OH), 4.88 (1H, d, C*H*–N), 7.1–7.3 (4H, Ind), 7.59 (1H, d, Ph), 8.07 (1H, d, Ph), 8.33 (1H, s, CH=N), 14.3 (1H, s, Ph–OH).

2.3. Preparation of samples for NMR

2.3.1. Interaction of the Schiff base ligands with Ti(Oi-Pr)$_4$

About 26.3 μmol of Ti(O*i*-Pr)$_4$ was dissolved in 0.6 ml of CH_2Cl_2, and 1 equiv. of the ligand was added at room temperature, and ^{1}H NMR spectrum of the resulting yellow solution was measured. Then calculated quantities of the ligand were added stepwise to obtain the desired ligand/Ti ratios of 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, and ^{1}H NMR spectra were run for each step. If necessary, ^{1}H-decoupled ^{13}C NMR spectra were recorded at room temperature.

Species **3a** (**3a**/Ti(O*i*-Pr)$_4$ = 1.25:1). ^{1}H NMR, $\delta(CH_2Cl_2, 25\,^\circ C)$, 1.00 (9H, s, C(CH$_3$)$_3$), 1.34 (9H, s, C(CH$_3$)$_3$), 1.50, (9H, s, C(CH$_3$)$_3$), 3.66 (1H, d, CH–N), 4.43 (1H, d, CH$_2$O),

4.58 (1H, dd, CH_2O), 7.23 (1H, d, Ph), 7.57 (1H, d, Ph), 8.43 (1H, s, CH=N).

Species **3a** (**3a**/Ti(O*i*-Pr)$_4$ = 1.25:1). ^{13}C NMR, δ(CH_2Cl_2, 25 °C), 25.7 (TiOCH(CH_3)$_2$), 27.2 (3C, C(CH_3)$_3$), 29.4 (3C, C(CH_3)$_3$), 31.2 (3C, C(CH_3)$_3$), 34.1 (1C, C(CH_3)$_3$), 35.2 (1C, C(CH_3)$_3$), 35.4 (1C, C(CH_3)$_3$), 70.5 (CH_2O), 77.6 (TiOCH(CH_3)$_2$), 84.9 (C*H), 120.3, 127.5, 130.4, 138.1, 139.7, 162.0 (C(Ph)OH), 167.5 (C=N).

Species **3a** (**3a**/Ti(O*i*-Pr)$_4$ = 1.25:1). ^{13}C NMR, δ(CH_2Cl_2, −60 °C), 25.1 (TiOCH(CH_3)$_2$), 25.2 (TiOCH(CH_3)$_2$), 26.4 (3C, C(CH_3)$_3$), 28.4 (3C, C(CH_3)$_3$), 30.4 (3C, C(CH_3)$_3$), 33.4 (1C, C(CH_3)$_3$), 34.5 (1C, C(CH_3)$_3$), 34.6 (1C, C(CH_3)$_3$), 69.1 (CH_2O), 76.8 (TiOCH(CH_3)$_2$), 77.1 (TiOCH(CH_3)$_2$), 83.8 (C*H), 119.3, 127.0, 130.0, 136.8, 138.9, 160.6 (C(Ph)OH), 166.9 (C=N).

Species **3c** (**1c**/Ti(O*i*-Pr)$_4$ = 1:1). ^{1}H NMR, δ(CH_2Cl_2, 25 °C), 0.85 (6H, d, CH(CH_3)$_2$), 1.30 (9H, s, C(CH_3)$_3$), 1.45, (9H, s, C(CH_3)$_3$), 2.38 (1H, m, CH(CH_3)$_2$), 3.38 (1H, dd, CH–N), 4.29 (1H, d, CH_2O), 4.61 (1H, dd, CH_2O), 7.18 (1H, d, Ph), 7.51 (1H, d, Ph), 8.32 (1H, s, CH=N).

2.3.2. Kinetics of sulfoxidation by the system *1c/Ti(Oi-Pr)$_4$/H_2O_2*

The catalyst **3c** was prepared by combining **1c** and Ti(O*i*-Pr)$_4$ (**1c**:Ti(O*i*-Pr)$_4$ = 1:1) in CH_2Cl_2. About 95% H_2O_2 was diluted by CD_3CN (1:40–8:20 μl/μl), and 10 μl aliquots were taken to add to the pre-cooled (−30 to −40 °C) NMR sample containing **3c** (6.3×10^{-4} or 3.5×10^{-4} M) and *p*-BrPhSMe (1.64×10^{-2} M) in CH_2Cl_2. The resulting concentrations of H_2O_2 were within the range of 1.84×10^{-2} to 3.5×10^{-1} M. The sample was vigorously shaken and then placed in the probe head of the NMR spectrometer cooled to −20 °C. The initial reaction rates were measured by monitoring the concentrations of *p*-BrPhSMe, *p*-BrPhSOMe and *p*-BrPhSO$_2$Me versus time at the early stage of the reaction.

2.4. Oxidation procedure

Sulfide (0.1 mmol) was added to a magnetically stirred (100 rpm) solution of Ti(O*i*-Pr)$_4$ and Shiff base (**1a**–**1d** or **2a**–**2b**) in 1 ml of CH_2Cl_2. The amounts of Ti(O*i*-Pr)$_4$ and Schiff bases varied; see footnotes for Tables 1 and 2. The resulting solution was cooled below room temperature, and 0.11 mmol of 30% hydrogen peroxide was added in one portion. Stirring was continued at room temperature for 1 h–1 day, the reaction being monitored by TLC (eluent: EtOAc). For 0 °C experiments, the reaction flask was cooled with ice; for lower temperature runs, the flask was placed in a freezer (−10 °C), and H_2O_2 added in one portion. After short column purification (silica gel, hexane/EtOAc), an aliquot containing 0.01–0.02 mmol of the sulfoxide was taken. Volatiles were removed in vacuo, and solid residue was dissolved in 0.6 ml of CCl_4 for ^{1}H NMR analysis. The enantiomeric excess values (ee) were measured by ^{1}H NMR with Eu(hfc)$_3$ chiral shift reagent in CCl_4. The absolute configuration was determined by comparing Eu(hfc)$_3$-shifted NMR patterns of sulfoxides with those of the sulfoxides with known absolute configuration (for details see Ref. [34], supporting material).

Conversion and selectivity were calculated based on ^{1}H NMR measurements of the sulfide, sulfoxide and sulfone relative concentrations. Selected ^{1}H NMR data for the compounds involved, δ(CCl_4, 20 °C), in $CDCl_3$, *p*-NO_2PhSCH_3 2.55, *p*-NO_2PhSOCH_3 2.77, *p*-NO_2PhSO$_2$CH_3 3.08; *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.

2.5. Kinetic resolution procedure

p-BrPhSMe (0.1 mmol) was added to a magnetically stirred (100 rpm) solution of Ti(O*i*-Pr)$_4$ and **1c** ([titanium]:[ligand] = 1:1.5, [oxidant]:[substrate]:[titanium] = 19:38:1) in 1 ml of CH_2Cl_2. The resulting solution was cooled below room

Table 1
Catalytic oxidation of benzyl phenyl sulfide (**4c**) at differing temperatures and ligand/titanium ratios

No.	Catalyst	Temperature (°C)	Conversion (%)	Selectivity (%)	ee (%)	Configuration
1	**1c**/Ti(O*i*-Pr)$_4$ = 1:1	−10[a]	27	92	46	*S*
2	**1c**/Ti(O*i*-Pr)$_4$ = 1:1	0[b]	71	88	43	*S*
3	**1c**/Ti(O*i*-Pr)$_4$ = 1:1	20[b]	72	81	46	*S*
4	**1c**/Ti(O*i*-Pr)$_4$ = 1.25:1	20[b]	85	91	46	*S*
5	**1c**/Ti(O*i*-Pr)$_4$ = 1.5:1	20[b]	89	89	53	*S*
6	**1c**/Ti(O*i*-Pr)$_4$ = 2:1	20[b]	64	91	36	*S*
7	**1c**/Ti(O*i*-Pr)$_4$ = 3:1	20[b]	45	93	30	*S*
8	**1c**/Ti(O*i*-Pr)$_4$ = 1.25:1[c]	20	34	97	20	*S*
9	**1c**/Ti(O*i*-Pr)$_4$ = 1.5:1[d]	20	96	90	60	*S*
10	**1c**/Ti(O*i*-Pr)$_4$ = 1.5:1[e]	20	78	88	13	*S*
11	**1c**/VO(acac)$_4$ = 1.5:1[f]	20	79	89	44	*S*

[Oxidant]:[substrate]:[titanium] ratio was 125:114:1 unless otherwise stated.
[a] Stored in a freezer without stirring for 24 h.
[b] Stirred for 1 h.
[c] [Oxidant]:[substrate]:[titanium] ratio was 1250:1140:1, stirred for 24 h.
[d] [Oxidant]:[substrate]:[titanium] = 21:19:1.
[e] 1.1 equiv. of urea hydroperoxide as oxidant, stirred for 3.5 h.
[f] [Oxidant]:[substrate]:[vanadium] ratio was 60:50:1, stirred overnight.

Table 2
Catalytic oxidation of sulfides **4a**–**4c** with different catalysts

No.	Catalyst	Substrate	Reaction time	Conversion (%)	Selectivity (%)	ee (%)	Configuration
1	**1c**/Ti(O*i*-Pr)$_4$ = 1.5:1[a]	**4a**	2 h	96	85	42	*S*
2	**1c**/Ti(O*i*-Pr)$_4$ = 1.5:1[a]	**4b**	2 h	54	90	30	*S*
3	**1a**/Ti(O*i*-Pr)$_4$ = 1.5:1[a]	**4c**	2 h	33	89	3	*S*
4	**1a**/Ti(O*i*-Pr)$_4$ = 1.5:1[b]	**4c**	3 h	93	89	32	*S*
5	**1a**/Ti(O*i*-Pr)$_4$ = 1.5:1[c]	**4a**	Overnight	81	45	29	*S*
6	**1a**/Ti(O*i*-Pr)$_4$ = 1.5:1[c]	**4b**	7 h	76	71	15	*S*
7	**1a**/Ti(O*i*-Pr)$_4$ = 2:1[c]	**4b**	Overnight	55	78	15	*S*
8	**1a**/VO(acac)$_4$ = 1.5:1[d]	**4c**	Overnight	84	85	43	*S*
9	**1d**/Ti(O*i*-Pr)$_4$ = 1.5:1[a]	**4a**	1 h	77	72	4	*R*
10	**2a**/Ti(O*i*-Pr)$_4$ = 1.25:1[a]	**4b**	1 day	70	80	37	*R*
11	**2a**/Ti(O*i*-Pr)$_4$ = 1.25:1[c]	**4c**	1.5 h	97	85	43	*R*
12	**1b**/Ti(O*i*-Pr)$_4$ = 1.25:1[a]	**4b**	2.5 h	43	86	0	–
13	**2b**/Ti(O*i*-Pr)$_4$ = 1.25:1[a]	**4c**	Overnight	67	91	17	*R*
14	Ti(O*i*-Pr)$_4$[e]	**4c**	1 day	19	92	–	–

At 20 °C unless otherwise stated.
[a] [Oxidant]:[substrate]:[titanium] ratio was 125:114:1.
[b] [Oxidant]:[substrate]:[titanium] = 21:19:1.
[c] [Oxidant]:[substrate]:[titanium] = 42:38:1.
[d] [Oxidant]:[substrate]:[titanium] = 55:50:1.
[e] [Oxidant]:[substrate]:[titanium] = 86:78:1.

temperature, and 30% hydrogen peroxide was added in one portion. Stirring was continued at room temperature for 18 h. After short column purification (silica gel, hexane/EtOAc), an aliquot containing 0.01 mmol of the sulfoxide was taken. Volatiles were removed in vacuo, and solid residue was dissolved in 0.6 ml of CCl_4 for ^{1}H NMR analysis.

Conversion (44%) was calculated as [sulfone]/(1/2) ([sulfone] + [sulfoxide]). The enantiomeric excess value (2% ee) of the remaining sulfoxide was measured as described in Section 2.4.

3. Results and discussion

3.1. NMR study of the interaction of the ligands with Ti(Oi-Pr)$_4$

Schiff base ligands of the type **1, 2** were found to bind tightly to the titanium center. These interactions were monitored by ^{1}H and ^{13}C NMR in CH_2Cl_2. In Fig. 1, one can see the spectra of Ti(O*i*-Pr)$_4$/**1c** in CH_2Cl_2. At 1:1 ligand/Ti ratio, one molecule of the ligand substituted two molecules of *i*-PrOH to give presumably complexes of the type **3** (Scheme 2). Excess ligand added (ligand/Ti > 1) lead to the formation of multiple titanium-Schiff base species, the proportion of the initial **3** decreasing and the concentration of liberated *i*-PrOH increasing. At **1c**/Ti ratio of 2.0, no resonances of Ti(O*i*-Pr) groups could be detected, two types of coordinated ligand (types I and II) along with free ligand (L) being observed in ca. 2:1:1 ratio. This can be explained by further coordination of the chiral ligand to substitute *i*-PrOH, so that 2.0–2.25 ligands could be coordinated to one titanium center.

However, these titanium species containing more than one ligand per titanium can hardly be responsible for enantioselective oxidations. Catalytic experiments (see below) showed that increasing of ligand/titanium ratio (over 1.25–1.5) lead to lower conversions and ees. It seems reasonable that species of the type **3** are the true enantioselective oxidation catalysts precursors. For better characterization of the active sites **3**, ^{13}C NMR spectra of the system Ti(O*i*-Pr)$_4$/**1a** in CH_2Cl_2 (ligand/Ti = 1.25:1) were measured. Tridentate coordination of the ligand is apparent, as soon as *C*H$_2$O, *C***t*-Bu and *C*(Ph)–O carbons display the highest

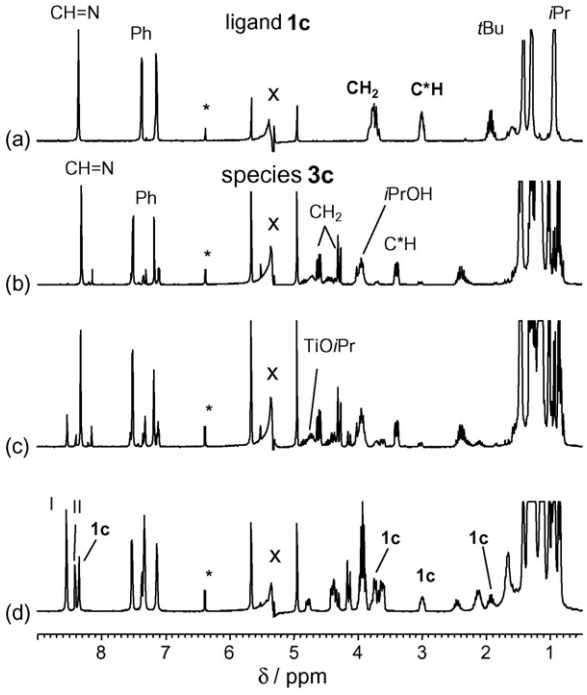
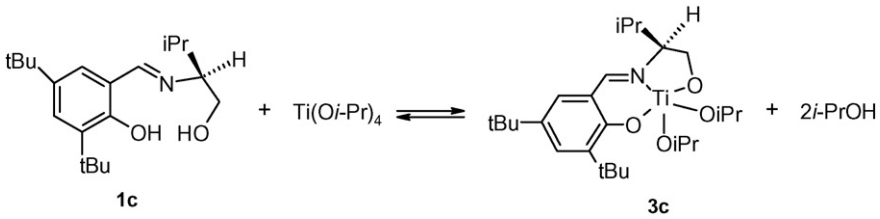


Fig. 1. ^{1}H NMR spectrum (CH_2Cl_2, 20 °C) of **1c**, [**1c**] = 0.1 M (a). ^{1}H NMR spectra (CH_2Cl_2, 20 °C) of the system **1c** + Ti(O*i*-Pr)$_4$ ([Ti] = 0.044 M) at differing ligand-to-titanium ratios: **1c**/Ti(O*i*-Pr)$_4$ = 1:1 (b); 1.25:1 (c); 2:1 (d). Asterisk mark an admixture in CH_2Cl_2 of trichloroethylene. The signal of solvent ("x") was suppressed by pre-saturation.



Scheme 2. Proposed interaction of Ti(O*i*-Pr)$_4$ with the chiral Schiff base ligands.

ligand induced shifts (see Section 2). Species **3a** was found to contain two O*i*-Pr ligands that are in fast exchange at room temperature. Lowering the temperature to −60 °C freezes this exchange, and the ^{13}C NMR peaks of these two non-equivalent O*i*-Pr ligands decoalesce (Section 2.3.1).

It is important to find appropriate L/Ti ratio when species **3** is the predominant one. For ligand **1c**, species **3c** strictly predominates at **1c**/Ti = 1.0–1.25 (Fig. 1). However, for **1a** even at **1a**/Ti = 1.5–1.75 species **3a** is the major one in solution. Thus, one can expect that in practical catalytic oxidations, the best results would be achieved at **1c**/Ti = 1.25 and **1a**/Ti = 1.75. The effect of differing L/Ti ratios on the oxidation products for the ligands **1a** and **1c** is presented in Section 3.3.

3.2. ^{1}H NMR monitoring of sulfoxidation kinetics and planning the catalytic experiment

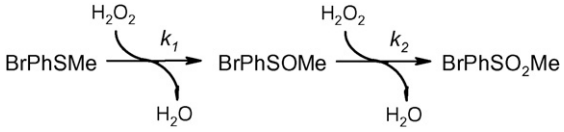
It was found that addition of H_2O_2 or H_2O to the samples containing species of the type **3** results in dramatic line broadening even at low temperatures (−10, . . ., −80 °C), so that the spectra of the expected reactive titanium(IV) peroxo species become low informative.

However, we managed to estimate the rate constants for sulfoxidation by the system **1c**/Ti(O*i*-Pr)$_4$/H_2O_2. In a typical experiment, to the solution of **3c** and *p*-BrPhSMe cooled to −20 °C, 95% H_2O_2 dissolved in CD_3CN was added. It was found that under the applied conditions ([H_2O_2] > [substrate] ≫ [Ti]) at the initial stage of the reaction, the concentrations of *p*-BrPhSMe and *p*-BrPhSOMe are well represented by exponential functions, thus reflecting the pseudo-first-order kinetic regime. The model reaction scheme was that in Scheme 3.

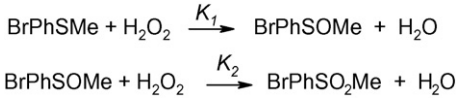
Some kinetic curves are presented in Fig. 2a and b. The solution of Scheme 3 was fit to the experimental data points:

$$\frac{C_S(t)}{C_S^0} = \exp(-k_1 t),$$

$$\frac{C_{SO}(t)}{C_S^0} = k_1(k_1 - k_2)^{-1}(\exp(-k_2 t) - \exp(-k_1 t)) \quad (1)$$



Scheme 3. The model kinetic scheme for *p*-BrPhSMe oxidation. k_1 and k_2 are regarded as pseudo-first-order constants.



Scheme 4. The model kinetic scheme for *p*-BrPhSMe oxidation. Here K_1 and K_2 are regarded as second-order rate constants: $k_1 = K_1[H_2O_2]$ and $k_2 = K_2[H_2O_2]$.

where C_S^0 and $C_S(t)$ are the initial and actual sulfide and $C_{SO}(t)$ is the actual sulfoxide concentration. The observed pseudo-first-order rate constants were found to depend on the concentration of H_2O_2 (Fig. 2c and d). These dependencies demonstrate saturation behavior and likely reflect the Michaelis–Menten type mechanism, when H_2O_2 binds to the catalyst to give the active intermediate (presumably peroxotitanium species like those recently reported in Refs. [35,36] for polyoxotitanates). The data obtained display mediocre reproducibility and considerable deviations and thus can only be regarded as an estimate.

The experimentally obtained k_1/k_2 ratios adopted the value of 6–8. Apparently, this ratio would affect the oxidation chemoselectivity. As an attempt to predict the latter, a more complex kinetic Scheme 4 was analyzed.

Analytical solution revealed that the yield of the sulfoxide and selectivity in this reaction scheme (assuming that $C_S^0 = 0.1$ M, all oxidant is consumed and no side reactions are the case) are governed by two parameters: (1) excess of the oxidant and (2) $m = K_1/K_2 = k_1/k_2$ ratio [37]. In Fig. 3, corresponding diagrams are presented for m = 4–20. One can see that for a wide range of m values, maximum sulfoxide concentration (Fig. 3a) is attained when one uses 4 to 10 mol% excess of H_2O_2. Obviously, the selectivity (Fig. 3b) monotonically decreases, thus making it undesirable to use high excess of oxidant. Thus, for practical catalytic oxidations we chose 10 mol% excess of H_2O_2.

3.3. Sulfide oxidation catalyzed by the systems ***1a–1d*/Ti(Oi-Pr)$_4$ and *2a–2b*/Ti(Oi-Pr)$_4$**

To investigate the titanium catalyzed sulfoxidation chemo- and enantioselectivity, three substrates **4a–c** have been selected. First of all, the influence of temperature on the enantioselectivity was probed. Surprisingly, temperature variations did not affect the ee significantly (Table 1, entries 1–3), thus all further experiments were carried out at room temperature (20 °C). Then, the experiments at differing ligand/titanium ratios revealed that the ratio of 1.5:1 (but not 1.25:1, as we expected in Section 3.1) was the most profitable for the system **1c**/Ti(O*i*-Pr)$_4$ (Table 1, entries 4–7). Increasing the **1c**/Ti ratio resulted in lower conver-

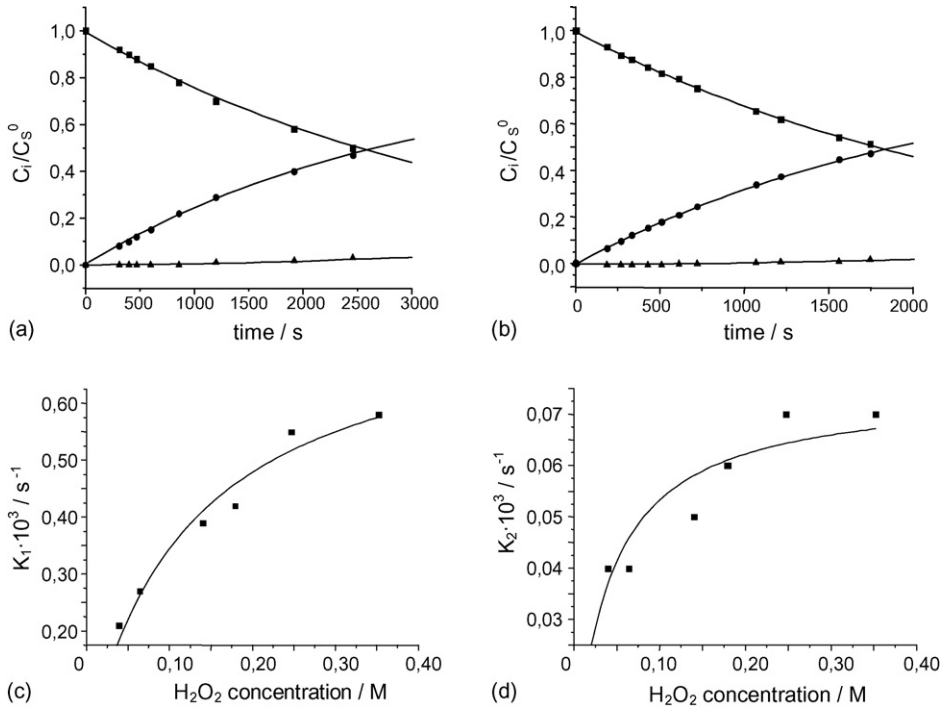


Fig. 2. Kinetic plots of the sulfide (■), sulfoxide (●) and sulfone (▲) concentrations vs. time: $[H_2O_2] = 0.064$ M (a); $[H_2O_2] = 0.14$ M (b). Lines represent the fits of the solutions of Scheme 3 to the experimental data. Experimental pseudo-first-order rate constants vs. H_2O_2 concentrations k_1 (c) and k_2 (d) and their two-parameter fit to $k_i = A[H_2O_2]/(B + [H_2O_2])$.

sions and ees. An attempt to decrease the catalyst concentration gave lower conversion (and ee) (Table 1, entry 8) even after 24 h stirring, probably due to the ligand deactivation after 300–350 catalytic cycles. When the catalyst loading was increased to 5 mol% (Table 1, entry 9), benzyl phenyl sulfoxide was obtained with 60% ee. This catalyst was found to demonstrate worse results with urea hydroperoxide (Table 1, entry 10) which was reported as a good terminal oxidant for Ti(salen) catalyzed sulfoxidations [19]. Unlike some other recent chiral titanium catalysts [4,38,39], **1c**/Ti(O*i*-Pr)$_4$ gave nearly racemic *p*-BrPhSOMe with cumyl hydroperoxide as oxidant. For comparison, the result of **1c**/VO(acac)$_2$ catalyzed oxidation is presented in entry 11.

We found surprisingly that unlike the vanadium(V) systems [20–22], substitution of *i*-Pr by *t*-Bu at the asymmetric center resulted in lower ees, conversion and selectivity, ligand **1a** requiring longer reaction times to reach similar conversions (Table 2). This is the case with different substrates. Even using relatively high [titanium]:[substrate] ratio (entry 4), ligand **1a** did not demonstrate as good results as ligand **1c**. For **1a**, increasing the ligand/Ti ratio did not improve the ee (entries 6 and 7). Vanadium catalyzed oxidation of **4c** is presented for comparison (entry 8). Ligand **1d** demonstrated very poor results (e.g. entry 9). Also, Schiff base ligand derived from 1-amino-2-indanol was tested (proposed in Ref. [40] for chromium catalyzed hetero-Diels–Alder reactions) and showed moderate enantioselectivities (entries 10 and 11).

For both vanadium(V)- and iron(III)-Schiff base catalysts, introduction of electron withdrawing substituents in the aromatic ring resulted in higher enantioselectivity [20,23]. We also prepared two 3,5-diiodo substituted ligands and tested them in catalysis. Unlike iron and vanadium systems, these ligands demonstrated decreased conversions and ees with titanium (Table 2, entries 12 and 13).

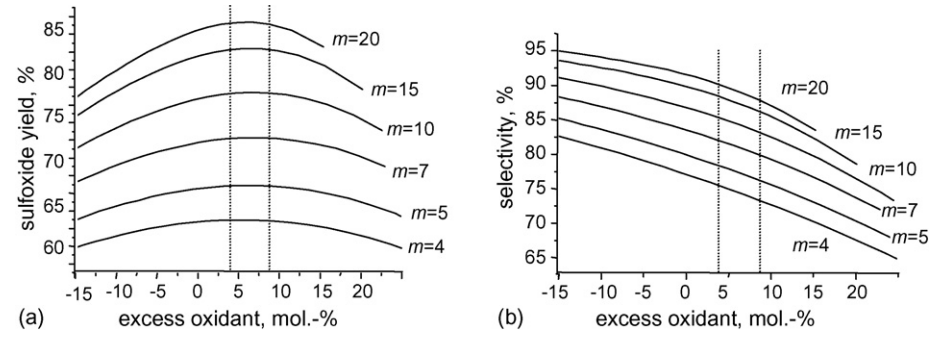


Fig. 3. Diagrams sulfoxide yield vs. excess of H_2O_2 (a) and sulfoxidation selectivity vs. excess of H_2O_2 (b) originating from the solution of Scheme 4 [37]. $m = K_1/K_2$.

It is not straightforward why the ligands **1a**, **1b**, **2a**, **2b** at the same time show both lower activity and enantioselectivity if compared with **1c**. Possible explanation might be the existence of the second oxidizing agent. In the reaction mixture some uncoordinated titanium isopropoxide may be present in equilibrium along with the free ligand (Scheme 2), and the former one may catalyze stereorandom sulfoxidations. Apparently, the lower the catalytic activity, the higher is the contribution of non-stereoselective oxidation pathway associated with Ti(O*i*-Pr)$_4$ catalyzed oxidation. An experiment with no ligand (Table 2, entry 14) showed that Ti(O*i*-Pr)$_4$ itself can perform up to 15 catalytic cycles and thus can partially affect the oxidation results under the experimental conditions used (depending on the equilibrium concentration of Ti(O*i*-Pr)$_4$).

In recent works, kinetic resolution of the sulfoxides accompanying asymmetric sulfoxidations has been reported [41–44]. Therefore, the system proposed was examined in kinetic resolution of racemic *p*-BrPhSOMe in the presence of Ti(O*i*-Pr)$_4$/**1c** (for details see Section 2). At the titanium concentration used ([oxidant]:[substrate]:[vanadium] = 42:38:1), only 44% conversion of the sulfoxide was observed, the process being nearly racemoselective (ee of the remaining sulfoxide only 2%, implying 1.10 stereoselection factor [45]; (*S*)-configuration). Thus, it is apparent that under practical sulfoxidation conditions (i.e. those providing high yield of the sulfoxide and low yield of the sulfone), the contribution of the kinetic resolution on the yield and ee of the target sulfoxides is negligible.

4. Conclusions

In conclusion, we have propose a new catalytic system for asymmetric oxidation of sulfides by 30% aqueous H_2O_2. The catalysts are generated in situ from titanium(IV) isopropoxide and enantiopure Schiff bases and promote the enantioselective oxidation of alkyl arylsulfides to the corresponding sulfoxides at low catalyst loadings (<1 mol%) with over 90% chemoselectivity and 60% ee. The precursor of the reactive species contains one chiral ligand per titanium center. The optimized catalytic conditions (i.e. oxidant:ligand:Ti ratios) have been formulated based on the examination of ligand interaction with titanium(IV) isopropoxide and following the oxidation kinetics by NMR. Several chiral ligands were tested in catalytic oxidations. The reactivity pattern of the presented Ti–Schiff base catalyst is different from that of similar V and Fe systems. The titanium system is more active: oxidations are performed within hours at catalyst and substrate concentrations one order of magnitude lower than in Fe and V systems. As distinct from vanadium(V) systems, the replacement of the *i*-Pr substituent at the asymmetric center by *t*-Bu leads to lower ees. Unlike iron(III) catalysts, introduction of iodine atoms in the aromatic ring instead of *t*-Bu results in lower ees. Chiral Schiff base ligand derived from 1-amino-2-indanol have been tested and display moderate ee. A more detailed mechanistic investigation of the presented titanium systems as well as broad catalytic studies are planned in our laboratory.

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the actual sulfide, sulfoxide, sulfone concentrations and C_S^0 is the initial sulfide concentration.

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