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Isoinversion Behavior in the Enantioselective Oxidations of Pyridylmethylthiobenzimidazoles to Chiral Proton Pump Inhibitors on Titanium Salalen Complexes

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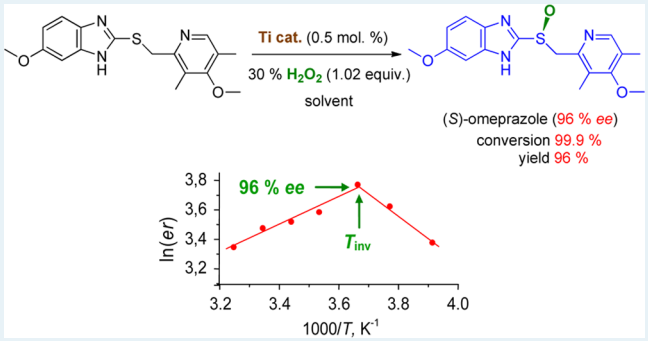
Supporting Information

ABSTRACT: The oxidation of two pyridylmethylthiobenzimidazoles to proton pump inhibitors (*S*)-omeprazole and (*R*)-lansoprazole, and to their enantiomers, with H_2O_2 is achieved by using chiral titanium salalen complexes as catalysts. The latter ensure high enantioselectivities (up to 96% ee) and efficiencies (TN 200−300), with high sulfoxide yields (up to >96%). The oxidation enantioselectivities vary with temperature in a nonmonotonic manner, demonstrating isoinversion behavior. Maximum enantioselectivity is attained at 273···283 K, which temperature region may be recommended for preparative oxidations. Kinetic peculiarities and the oxidation mechanism are discussed.



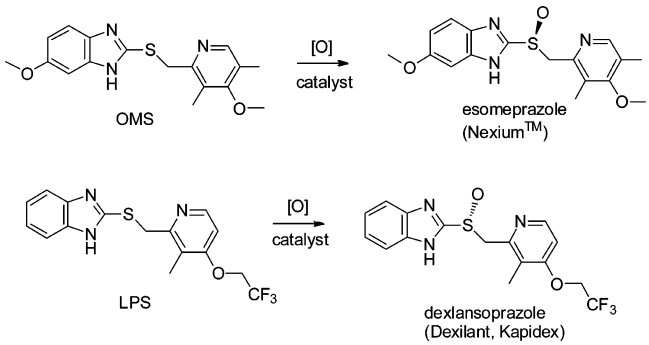
KEYWORDS: *asymmetric oxidation, hydrogen peroxide, esomeprazole, isoinversion, mechanism, titanium*

The oxidation of thioethers to enantiomerically enriched sulfoxides has been a matter of extensive studies in the last decades, with the design of catalyst systems relying on the practical and environmentally benign oxidants—hydrogen peroxide—representing the major recent trend.[1] Although nowadays this area may be considered a "mature field", none of the novel catalysts has so far been transferred from the laboratory into practice; the industry continues exploiting the Kagan−Modena type titanium-dialkyltartrate/alkylhydroperoxide catalyst systems.[2] The most likely reason for this is the lack of simple and stereoselective catalyst systems capable of asymmetric oxidation of thioethers with bulky substituents at the sulfur atom.[3] Scheme 1 illustrates the practically relevant chiral sulfoxides−proton pump inhibitors (PPIs) esomeprazole and dexlansoprazole, synthesized from the corresponding bulky sulfide precursors OMS ("omeprazole sulfide") and LPS ("lansoprazole sulfide").[4,5]

In the last years, we sought transition-metal-based catalysts for the asymmetric oxidation of bulky thioethers to sulfoxides.[3c−g] Herewith, we present a series of titanium(IV) salalen complexes, capable of catalyzing the oxidation of pyridylmethylthiobenzimidazole precursors to esomeprazole and dexlansoprazole by H_2O_2 with high chemo- and enantioselectivities, and we report on some intriguing peculiarities of the oxidation mechanism.

We have focused on titanium(IV) salalen complexes, earlier established as efficient and highly enantioselective catalysts of asymmetric epoxidation of olefins.[6] Basically, four chiral Ti

Scheme 1. Enantioselective Synthesis of (*S*)-Omeprazole (Esomeprazole) and (*R*)-Lansoprazole (Dexlansoprazole) from Sulfide Precursors



complexes **Ti-1**...**Ti-4** featuring the previously successful 1,2-diaminocyclohexane and *o*-xenyl motifs[6,7] were obtained; to modulate their electronic properties, various 5,5′-substituents were introduced (Figure 1). All complexes were isolated in single crystalline form. In contrast to reported titanium(IV) salan complexes,[6i,7d] titanium salalen analogues exhibited two different types of dimeric structures in crystals: [LTi(OEt)(μ-O)Ti(OEt)L] (**A**) and [LTi(μ-O)$_2$TiL] (**B**).[8] Orange crystals

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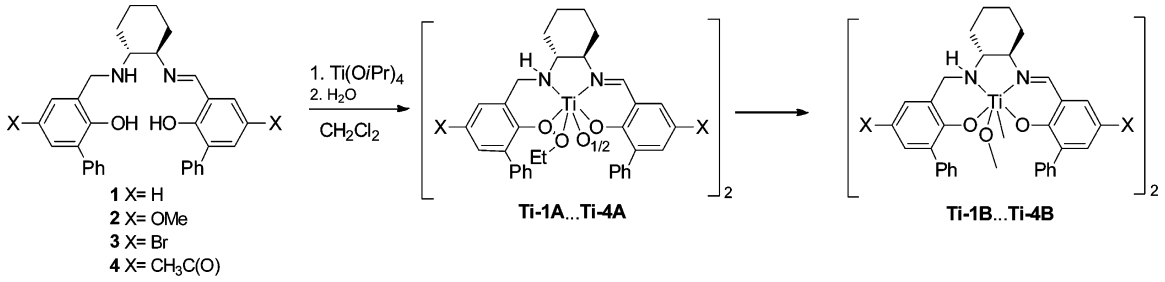

Figure 1. Titanium(IV) salalen catalysts studied in this work.

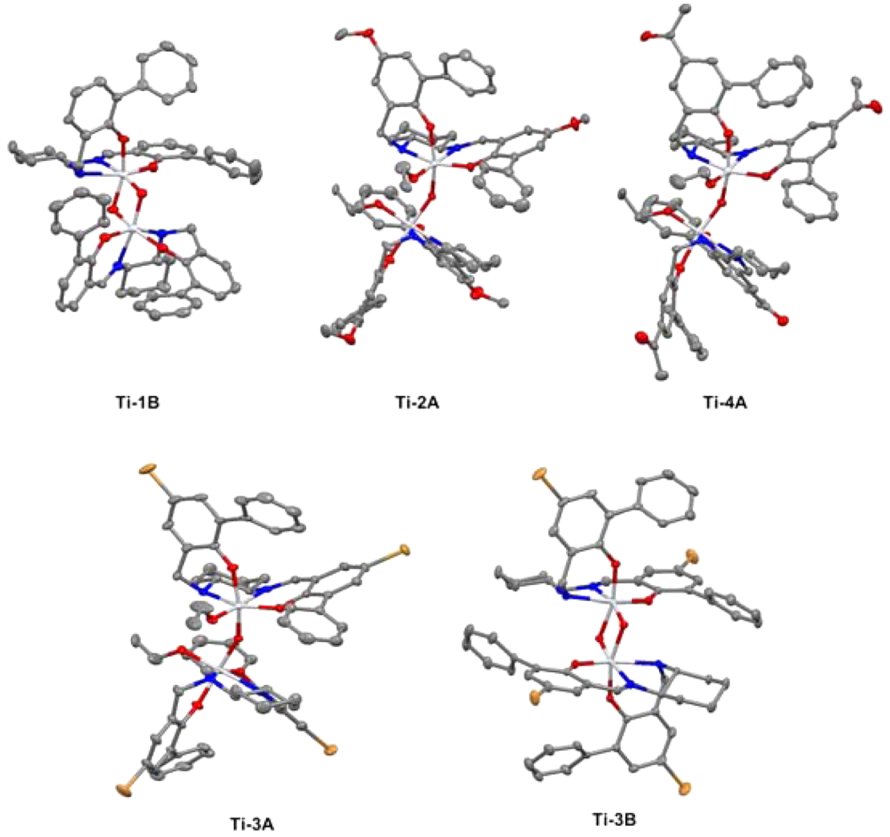

Figure 2. Molecular structures of complexes (Λ,*R*,*R*,S_N - Λ,*R*,*R*,S_N)-**Ti-1B**, (*R*,*R*,S_N - *R*,*R*,S_N)-**Ti-2A**, (*R*,*R*,S_N - *R*,*R*,S_N)-**Ti-4A**, (*R*,*R*,S_N - *R*,*R*,S_N)-**Ti-3A**, (Λ,*R*,*R*,S_N - Λ,*R*,*R*,S_N)-**Ti-3B**.[8] Thermal ellipsoids are drawn at 30% probability level. Hydrogen atoms and solvent molecules are omitted for clarity.

of complexes of the type **A** were readily obtained from CH_2Cl_2 (or $CHCl_3$) solutions layered with hexane. Complexes of the type **A**, when redissolved in CH_2Cl_2 or $CHCl_3$, were unstable and gradually converted to bis-μ-oxo structures of the type **B** (SI, Figures S2, S3). Complexes of the type **B** were typically obtained as yellow crystalline solids. Eventually, single crystals of **Ti-1** was only isolated as **Ti-1B**, whereas **Ti-2** and **Ti-4** afforded only **Ti-2A** and **Ti-4A**, respectively.[8] For complex **Ti-3**, single crystals of both **Ti-3A** and **Ti-3B** were collected (Figure 2 and SI). Sulfoxidation experiments (Table 1) predictably confirmed identical catalytic performances of **Ti-3A** and **Ti-3B**, thus witnessing that the same active sites are likely to originate from both precatalysts (apparently via dissociation of the dinuclear structures, followed by reaction with H_2O_2).

Complexes of the type **A** feature hydrogen bonding between the amine hydrogen of the ligand at one Ti atom and the oxygen atom of the OEt group at the other Ti atom (**Ti-2A**: 1.99 Å; **Ti-3A**: 2.06 Å; **Ti-4A**: 2.09 and 1.95 Å, Table S6). There are also intramolecular π-stacking interactions in both ligands of **Ti-4A** between the salicyl ring and the 3′-phenyl ring of the same ligand (distances between centers of rings 3.99 and 4.00 Å, SI).

Synthesized Ti complexes were tested as catalysts in the enantioselective oxidations of sulfide precursors of omeprazole and lansoprazole. Table 1 illustrates the catalytic performance of **Ti-1**...**Ti-4** at the same temperature (0 °C). Two-phase systems organic solvent/aqueous 30% H_2O_2) were used in all experiments.

Several common aprotic solvents were screened. Ethyl acetate was one of the best ones (Table 1, entries 3 and 6). Remarkably, the use of CH_2Cl_2 further improved the yield and enantioselectivity up to 96% ee (cf. entries 3, 12, and 8, 13). Further experimentation, however, was mostly conducted in EtOAc.[9] Complex **Ti-1** was most stereoselective for the oxidation of OMS and LPS (in EtOAc: 94.5 and 93.5% ee,

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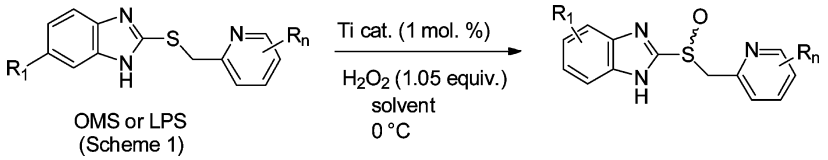
Table 1. Enantioselective Oxidation of OMS and LPS with 30% Aqueous H_2O_2 in the Presence of Titanium Salalen Complexes[a]



entry	catalyst	solvent (dielectric constant)	sulfide	conversion/yield [%]	ee [%] (config.)
1	**Ti-1B**	toluene (2.38)	OMS	89.5/80.0	35.0 (R)
2	**Ti-1B**	$CHCl_3$ (4.81)	OMS	78.0/72.5	79.0 (R)
3	**Ti-1B**	EtOAc (6.02)	OMS	97.0/94.5	94.5 (R)
4	**Ti-1B**	HC(O)OMe (8.50)	OMS	99.5/96.5	93.5 (R)
5	**Ti-1B**	$C_2H_4Cl_2$ (10.36)	OMS	98.7/94.0	91.5 (R)
6	**Ti-1B**	EtOAc	LPS	99.9/96.3	93.5 (R)
7	**Ti-2A**	EtOAc	OMS	98.0/94.0	94.5 (R)
8	**Ti-2A**	EtOAc	LPS	98.5/93.0	92.5 (R)
9	**Ti-3A**	EtOAc	OMS	44.0/42.5[b]	75.5 (R)
10	**Ti-3B**	EtOAc	OMS	44.5/42.5[b]	75.0 (R)
11	**Ti-4A**	EtOAc	OMS	14.0/13.6[b]	50.0 (R)
12	**Ti-1B**	CH_2Cl_2 (9.08)	OMS	99.9/96.0	96.0 (R)
13	**Ti-2A**	CH_2Cl_2	LPS	96.0/94.0[c]	95.0 (R)

[a]At 0 °C; $[H_2O_2]$/[substrate]/[catalyst] = 105:100:1, the oxidant was added in one portion, and the mixture was stirred for 14 h. Sulfoxide yield and ee were determined by chiral HPLC (SI). OMS − omeprazole sulfide (or pyrmetazole), LPS − lansoprazole sulfide. [b]Reaction time of 24 h. [c]Reaction time of 4 h.

respectively, entries 3, 6), while **Ti-2** demonstrated comparable results with OMS but somewhat lower enantioselectivity for LPS (entries 7, 8). A 2-fold alteration (either increase or reduction) of the catalyst (**Ti-1**) loading did not noticeably alter the sulfoxide yields and enantioselectivities. Complexes bearing electron-withdrawing 5,5′-substituents (**Ti-3**, **Ti-4**) showed much lower activity and enantioselectivity (entries 9−11).

Given the high conversions and enantioselectivities exhibited by catalysts **Ti-1** and **Ti-2**, they were chosen for conducting catalytic oxidations of OMS and LPS at differing temperatures. Intriguingly, the sulfoxidation enantioselectivities demonstrated a nonlinear behavior as the temperature was varied.[10a] The corresponding modified Eyring plots indicated either a maximum or a kink between 273−283 K (Figure 3A,B). Such behavior has been observed in various stereoselective processes,[11a] including asymmetric oxidation of olefins.[11b] The origin of such nonlinearity was debated controversially[11a,12] and was generally taken as evidence for a complex mechanism with at least two stereoselectivity-determining steps in the reaction.[12a,b] Alternatively, solvation was invoked as a potential reason for nonlinear stereoselectivity behavior.[12e] Previously, a maximum on enantioselectivity versus temperature dependence was reported by Kagan with co-workers for the oxidation of methyl *p*-tolyl sulfide by the Ti(O*i*Pr)$_4$/diethyltartrate/*t*BuOOH system, which was tentatively attributed to a changeover of the oxidation mechanism.[10b]

In any event, the Eyring plots as above indicate a changeover in the mechanism of stereoselectivity, switching the modes of stereodiscrimination on passing from low to high temperatures via the "inversion temperature" T_{inv}. Two sets of activation parameters ($\Delta\Delta H_1^{\neq}$, $\Delta\Delta S_1^{\neq}$, $T > T_{inv}$, and $\Delta\Delta H_2^{\neq}$, $\Delta\Delta S_2^{\neq}$, $T < T_{inv}$) are available that correspond to enthalpy and entropy in each of the partial selectivity steps.[11a] Subtraction of the activation parameters yields the $\delta\Delta\Delta H^{\neq}$ and $\delta\Delta\Delta S^{\neq}$ (Supporting Information). The latter values, when calculated and plotted on an enthalpy/entropy diagram, displayed a linear correlation passing through origin (Figure 3C). This behavior has previously been referred to as *isoinversion relationship*,[11] the slope corresponding to inversion temperature $T_{inv} \approx 274 \pm 7$ K (Figure 3C and SI).

The detailed understanding of the mechanistic changeover resulting in nonlinear Eyring plots is challenging. In principle, the latter may stem from the occurrence of at least two separate reaction pathways, each generating two diastereomeric transition states but in varying ratios (Supporting Information).[12b] It is characteristic that T_{inv}, irrespective of the catalyst (**Ti-1** or **Ti-2**), substrate (OMS or LPS), and solvent (EtOAc or CH_2Cl_2), remains nearby the melting point of water, suggesting that H_2O may be involved in the formation of the catalytically active sites. To check this possibility, we conducted a series of oxidations using $(NH_2)_2CO{\cdot}H_2O_2$ instead of 30% hydrogen peroxide. In all cases, the values of ee dropped when using $(NH_2)_2CO{\cdot}H_2O_2$ vs 30% H_2O_2 (Table S1), thus confirming the crucial role of the amount of water for the stereoselective oxidation. Our hypothesis is that water may occupy the axial position of the Ti center in the active species, thus attenuating the electron deficiency of the Ti center and eventually the overall electrophilicity of the active sites. In effect, the transition state becomes more product-like, resulting in a better stereoselection (Scheme 2). Lowering the temperature below 273 K freezes out water, thus reducing its concentration in the EtOAc solution and favoring the formation of the less stereoselective, water-free intermediate.

Interestingly, the amount of water seems to be a crucial but not the only factor affecting the stereoselection. Indeed, the inspection of oxidation reaction at differing substrate concentrations revealed an increase of ee with decreasing OMS concentration (Figure S4). This suggests possible presence of two competitive oxidation pathways, being different orders in the substrate concentration (i.e., first and second order). The resulting term for the enantiomeric ratio (expression (1)) reflects the dependence of the ee on the

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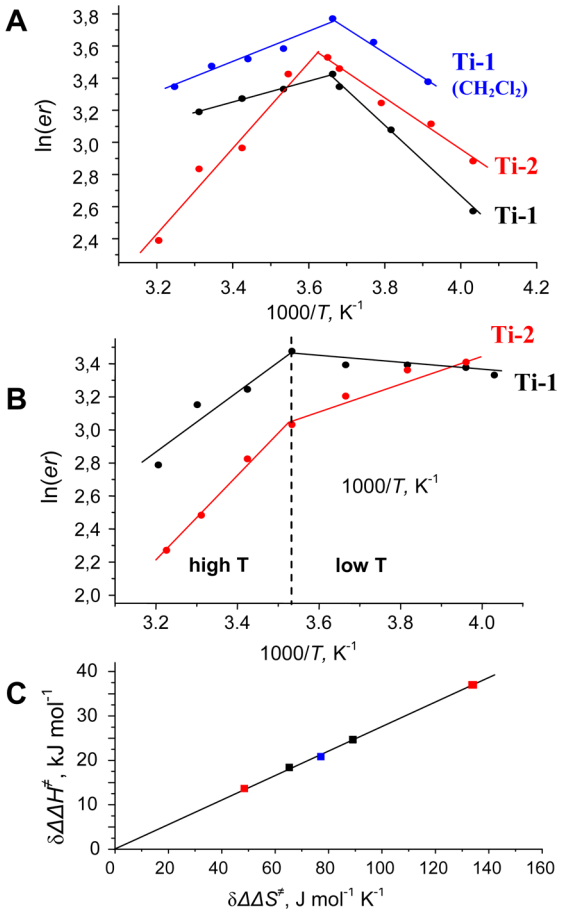


Figure 3. Modified Eyring plots representing the temperature dependence of stereoselectivity for the oxidation of OMS (A) and LPS (B) on complexes **Ti-1** (black circles) and **Ti-2** (red circles) in EtOAc, and for the oxidation of OMS on **Ti-1** in CH_2Cl_2 (blue circles), with the corresponding linear fits. $\delta\Delta\Delta H^{\neq}/\delta\Delta\Delta S^{\neq}$ diagram (*isoinversion relationship*) for the above oxidations (C). er – enantiomeric ratio; er = (100 + ee)/(100 − ee).

sulfide concentration, as well as the ee variation in the course of the oxidation (see below).

$$\ln\frac{W_{major}}{W_{minor}} = \ln(\mathrm{er}) = \ln\frac{k_{major}[RSR'] + k_{major}[RSR']^2}{k_{minor}[RSR'] + k_{minor}[RSR']^2} \quad (1)$$

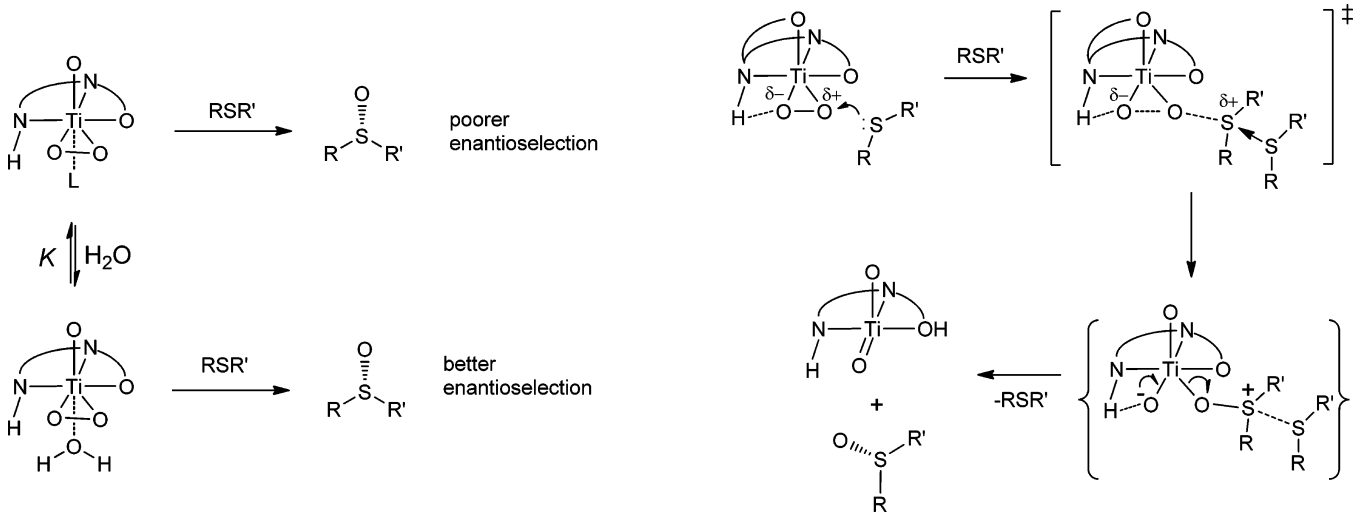
What is the rational for the predicted difference in the reaction orders for the competitive oxidation pathways? Given that a substantial charge separation is expected to occur in the course of the oxidation of OMS or LPS with a titanium(IV) peroxo complex,[13] the role of the second molecule of the nucleophilic sulfide may be to increase the stabilization of the charge separation and weakening of the O−O bond (Scheme 2).

One can expect that more polar solvents may have stabilizing effect on the charge-separated transition state, thus eliminating the need in the second substrate molecule and preventing the enantiomeric depletion via the substrate-assisted pathway. This may be the case for EtOAc and CH_2Cl_2, the solvents that ensured the highest enantioselectivities (Table 1). On the other hand, at low sulfide concentrations, the contribution of the substrate-assisted pathway becomes negligible according to expression (1), which also results in higher er (Figure S4).

The above discussion assumes that the catalytically active, oxygen-transferring species is titanium(IV) peroxo complex. Previously, mass-spectrometric, kinetic, spectroscopic, and structural data were reported in favor of key role of salalen titanium(IV) peroxo species in catalytic epoxidation reactions.[6c,d,i,7d,14] However, the mechanistic landscape of the sulfoxidation reaction requires a separate discussion.

First of all, competitive sulfoxidations of *p*-substituted thioanisoles were conducted. The Hammett−Brown treatment (Figure 4A) showed a linear correlation (with the exception of *p*-Br-PhSMe),[15] indicative of electron-demanding transition state with positive charge buildup at the substrate, giving a ρ^+ value of −0.70 ± 0.03. The slope value falls within a typical range (−0.38 to −1.4) reported for oxidations by d^0-transition metal peroxo complexes such as V, Mo, W, Re (see ref 6i and references therein). The log(er) vs σ_p^+ correlation was also linear (Figure 4B). One can conclude that the enantioselective oxygen transfer most likely occurs via concerted rather than

Scheme 2. Proposed Reaction Schemes for the Water-Assisted Pathway (Left) and Substrate-Assisted Pathway (Right)[a]



[a]L is solvent or vacancy.

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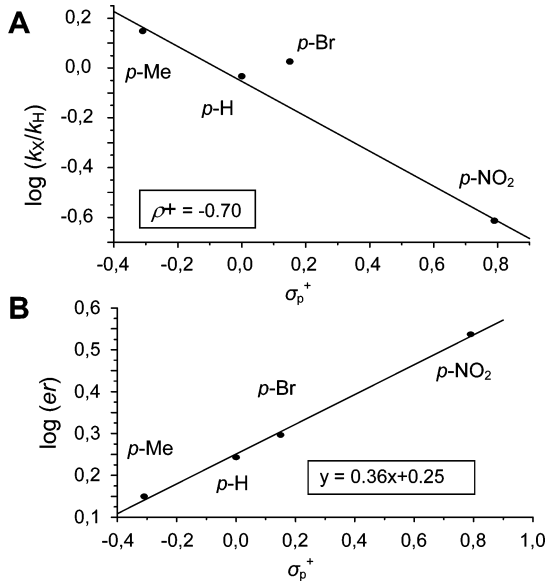

Figure 4. Hammett plots of $\log(k_X/k_H)$ vs σ_p^+ (A) and log(er) vs σ_p^+ (B) for the oxidation of *p*-substututed thioanisoles with **Ti-1**/H_2O_2 system (CH_2Cl_2, −10 °C).

stepwise mechanism:[16] in the latter case, the enantioselectivity would very likely be independent of nature of the *p*-substituents.[6i]

The observed decline of enantioselectivity in the order **Ti-2** ≈ **Ti-1** > **Ti-3** > **Ti-4** (Table 1, entries 3, 7, 9−11) may be explained on the basis of the Hammond−Leffler postulate. The active species bearing electron acceptors are more electrophilic, and the transition state for them should be more reactant-like, with weaker oxidant-substrate interactions, thus resulting in a poorer stereocontrol (SI, Figure S5).

To identify the rate-limiting step, the kinetics of oxidation of OMS and LPS on catalyst **Ti-1** was monitored. After an initial induction period of ca. 1.5−2 h,[17] the sulfide concentration decreased with a constant rate within the next couple of hours, followed by reaction deceleration in the completion phase (Figure 5). Under the steady-state regime, the apparent oxidation rates were close (4.4×10^{-5} M min^{-1} for OMS and 4.8×10^{-5} M min^{-1} for LPS), the difference in fact falling within experimental uncertainty and thus hinting that the steady-state reaction rate may be independent of the sulfide concentration. Such situation may be the case when the oxidation is rate-limited by the reaction of the catalyst with

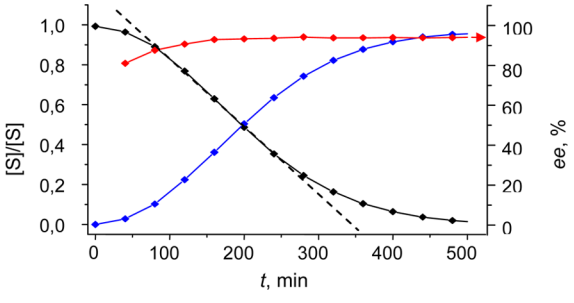

Figure 5. Kinetic plots for the oxidation of LPS on catalyst **Ti-1** (EtOAc, 0 °C, $[S]_0 = 1.49 \times 10^{-2}$ M, $[S]_0$:[cat] = 80.7): concentrations of LPS − (black) and lansoprazole (sum of (*R*)- and (*S*)-enantiomers) − blue. Lansoprazole enantioselectivity − red. Linear fit for the steady-state regime − dash line.

H_2O_2, which stage being followed by a relatively fast enantioselective oxygen transfer to the sulfide (cf. ref 3c). This model offers an explanation for the low activity of catalysts **Ti-3** and **Ti-4** (compared to **Ti-1** and **Ti-2**): these complexes, bearing electron-acceptors, must generate more electrophilic metal peroxo active species, which requires higher activation barrier for their formation (SI, Figure S5).

Note that the oxidation enantioselectivity increases at the early stage of the reaction (Figure 5 and S1),[18] which increase further slows down; at >50% conversions, the values of ee are virtually constant (93.5−94.5% ee for reaction points measured at t > 200 min). Such behavior unambiguously rules out the hypothesis of kinetic resolution of the resulting sulfoxide.[19] The gradual enantioselectivity increase to a nearly constant value may be due to degressing sulfide concentration, which affects the observed er as defined by expression (1).

From a practical perspective, the temperature range of 273···283 K is recommended for preparative use. Two examples of this kind (0.5 g-scale oxidations of OMS to esomeprazole in EtOAc) at 273 K are provided with the SI. After workup, 73−87% (*S*)-omeprazole sodium isolated yields were achieved, with HPLC purity of up to 99.7% and up to 99.9% ee. These preparations of (*S*)-omeprazole are among the best in terms of sulfoxide yield and ee, as well as catalyst efficiency (TN 200) and atom economy.[3e,20]

In summary, the enantioselective sulfoxidation of pyridylmethylthiobenzimidazoles with H_2O_2 in the presence of chiral titanium(IV) salalen complexes is reported. Two thioethers have been converted to the biologically active chiral sulfoxides (antiulcer drugs of the PPI family) with up to >96% yield and 96% ee. The reaction requires 0.5−1.0 mol % catalyst loading. Hammett correlations reflect the electrophilic nature of the active oxidant, the oxygen transfer to sulfide occurring in a concerted way. The overall reaction is rate-limited by the generation of the active (peroxotitanium) species, which stage is followed by oxygen transfer to the sulfide. The presence of electron-withdrawing substituents in the chiral ligand reduces both the reaction rate and the sulfoxidation enantioselectivity, which is rationally explained in terms of the Hammond−Leffler principle. For the first time, isoinversion behavior is documented for the asymmetric sulfoxidation reactions, with T_{inv} of 273···283 K, in which temperature range maximum enantioselectivities are achieved. Such behavior may be due to interference of (1) effect of amount of water and (2) existence of competitive reaction pathways, one of those likely being substrate-assisted. A plausible reaction mechanism is discussed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01212.

Materials and methods, synthetic procedures, procedures for the asymmetric sulfoxidations oxidations, kinetic measurements, NMR data, and consideration of the isoinversion scheme (PDF)

For X-ray data, see files below and note in ref 8.

X-ray data (CIF)

X-ray data (CIF)

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Notes

The authors declare no competing financial interest.

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(19) Kinetic resolution leads to an evident jump of enantiomeric excess at high conversion (>90%), accompanied by a pronounced decline in the sulfoxide yield owing to overoxidation to sulfone (ref 3c).

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