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Synthetic Methods

Titanium Salan Catalysts for the Asymmetric Epoxidation of Alkenes: Steric and Electronic Factors Governing the Activity and Enantioselectivity

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Abstract: A new insight into the highly enantioselective (up to >99.5% *ee*) epoxidation of olefins in the presence of chiral titanium(IV) salan complexes is reported. A series of 14 chiral ligands with varying steric and electronic properties have been designed, and it was found that electronic effects modulate the catalytic activity (without affecting the enantioselectivity), whereas the steric properties account for the enantioselectivity of the epoxidation. Competitive oxidations of *p*-substituted styrenes reveal the electrophilic nature of the oxygen-transferring active species, with a Hammett ρ value of −0.51; the enantioselectivity is unaffected by the electron-donating (or withdrawing) ability of the *p*-substituents. Mechanistic studies provide evidence in favor of a stepwise reaction mechanism: in the first (rate-determining) stage, olefin most probably coordinates to the active species, followed by intramolecular enantioselective oxygen transfer. The enantioselectivity increases with decreasing temperature. The modified Eyring plots for the epoxidation of styrene and (*Z*)-β-methylstyrene are linear, indicating a single, enthalpy-controlled mechanism of stereoselectivity, with $\Delta\Delta H^{\neq} = -6.6$ kJ mol^{-1} and −5.4 kJ mol^{-1}, respectively.

Introduction

Chiral epoxides containing one or two stereogenic centers are versatile and reactive yet stable intermediates that can be readily involved in further asymmetric transformations through, for example, asymmetric ring-opening reactions.[1] Since the milestone discoveries of organocatalyzed[2] and transition-metal-catalyzed[3,4] enantioselective epoxidations of olefinic substrates, catalytic approaches to the asymmetric synthesis of chiral epoxides have developed greatly and they are nowadays regarded as the most straightforward and reliable ways of the producing enantiopure epoxides. More recently, catalyst systems that rely on inexpensive and environmentally benign hydrogen peroxide as terminal oxidant are of increasing interest.

Titanium is one of the cheapest transition metals (7th most abundant metal on Earth), and the products of its hydrolysis are not toxic, which is in contrast to those of other available transition metals such as Cr, Ni, and V. Together with its relative inertness toward redox processes and with rich possibilities of tuning its activity and selectivity by rational ligand design, this makes titanium a welcome protagonist for various enantioselective catalytic transformations, including epoxidations.[5]

In 2005, Katsuki with co-workers introduced the first titanium-based family of salalen (dihydrosalen) catalysts that were capable of epoxidizing unfunctionalized conjugated olefins with H_2O_2 with high enantioselectivity.[6,7] Berkessel and co-workers developed alternative procedures for the syntheses of salalen ligands,[8,9] and demonstrated that titanium–salalen catalysts can also catalyze the epoxidation of nonconjugated, including terminal, olefins with high *ee* values.[10]

Alongside titanium–salalen,[11,12] more synthetically accessible titanium–salan complexes have been studied in recent years as catalysts for enantioselective epoxidations[13–18] and sulfoxidations[19–25] with H_2O_2. In spite of the large amount of reported catalytic data, to our knowledge, there have been no systematic studies of the influence of ligand structure on the catalytic activity and oxidation selectivity. This work was initiated with the aim of bridging this gap. Herewith, we report the effects of the ligand structure (salalen vs. salan), symmetry, steric bulk, and electronic properties on the epoxidation of conjugated olefins. These studies have allowed us to delineate the steric and electronic rules that govern the reaction outcome, so that catalytic properties of titanium–salan catalysts can be predicted for a particular combination of electron-donating (or withdrawing), and bulky substituents. In addition, some general conclusions on the mechanism of epoxidation can be drawn. In particular, the epoxidation proceeds in a stepwise rather than a concerted mechanism, with the process being most

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likely rate-limited by substrate coordination to the titanium active species.

Results and Discussion

Taking into account the previous success of salalen and salan ligands[6–26] bearing 3,3′-aryl substituents, the framework of salan ligand **1** was chosen as the basis for further modifications. Several titanium(IV) salan and salalen complexes with ligands **1**–**14** (Figure 1) were prepared and tested as catalysts in

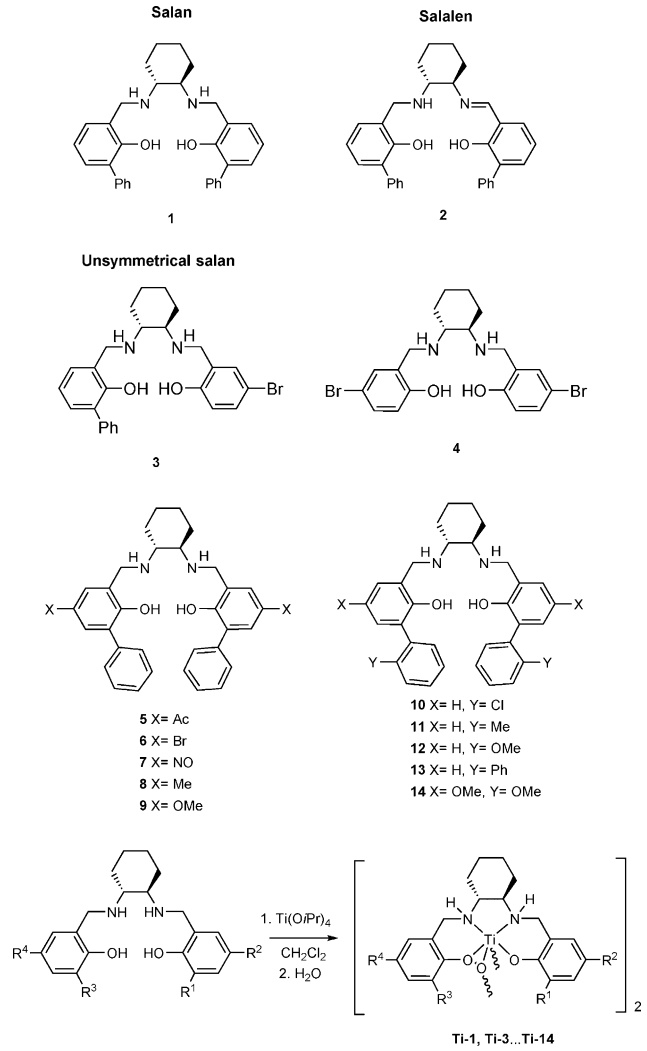
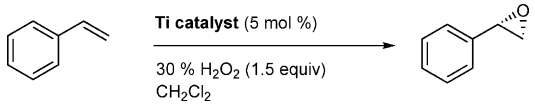


Figure 1. Structures of chiral ligands studied in this work, and the general method of synthesis of chiral titanium(IV) complexes.

the epoxidation of the same substrate (styrene) with H_2O_2 (Table 1). We note that virtually no reaction byproducts were found (in most cases no more than 0.2%), with the substrate converting exclusively into the corresponding epoxide.

First, the salan framework was identified as being preferred over that of the salalen, with catalyst Ti-**1** showing higher enantioselectivity than Ti-**2** (cf. Table 1, entries 1 and 2). The presence of 3,3′-Ph_2 substituents was critical for high enantioselectivity; for example, ligand **4**, lacking 3,3′-Ph_2, led to the catalyst Ti-**4** affording styrene epoxide with only 75% *ee* (entry 4). The introduction of one and two Ph moieties increased the enantioselectivity to 78 (entry 3) and 81.5% *ee* (entry 1), respectively. Indeed, it seems to be a general trend that reduction of symmetry from C_2 to C_1 is detrimental to the optical purity of the products.

Table 1. Enantioselective epoxidation of styrene with H_2O_2 in the presence of catalysts Ti-**1** through Ti-**14**.[a]



Entry	Ligand	Complex	Epoxide yield [%][b]	Epoxide *ee* [%][c]
1	**1**	Ti-**1**	60	81.5
2	**2**	Ti-**2**	61	75.5
3	**3**	Ti-**3**	44	78
4	**4**	Ti-**4**	28	75
5	**5**	Ti-**5**	19	79.5
6	**6**	Ti-**6**	24	79
7	**7**	Ti-**7**	8[d]	73
8	**8**	Ti-**8**	46	80.5
9	**9**	Ti-**9**	32	80
10	**10**	Ti-**10**	26	86
11	**11**	Ti-**11**	66	87.5
12	**12**	Ti-**12**	74	92
13	**13**	Ti-**13**	65	91.5
14	**14**	Ti-**14**	17	85.5

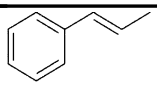
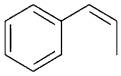
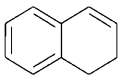
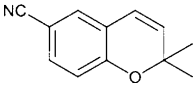
[a] At 290 K; $[H_2O_2]$/[substrate]/[catalyst] = 150:100:5 μmol, the oxidant was added in one portion and the mixture was stirred for 18 h. [b] Determined by ^{1}H NMR analysis. [c] (*S*)-Configuration; determined by chiral HPLC analysis. [d] The catalyst was poorly soluble in CH_2Cl_2, the mixture was inhomogeneous.

As the next step, the effect of electron-withdrawing and electron-donating groups on the catalytic properties of Ti complexes with ligands **5**–**9** was examined. Catalysts with ligands **5**–**9** (except the poorly soluble Ti-**7**) demonstrated virtually the same enantioselectivity (ca. 80% *ee*) as that of the parent Ti-**1**. At the same time, the introduction of either electron-donating or electron-withdrawing groups reduced the conversion and epoxide yield significantly (cf. Table 1, entries 1 and 5–9).

Replacement of 3,3′-Ph_2 substituents with *o*-substituted aryls led to a dramatic increase in the enantioselectivity (Table 1, entries 10–14). Apparently, the *o*-substituent in the 3,3′-Ph_2 groups leads to organization of the steric environment of the active sites in the transition state, resulting in higher enantioselectivity at the oxygen-transfer step. The size of the *o*-substituents is important: the enantioselectivity increases when passing from *o*-Cl to *o*-Me and then to *o*-OMe (entries 10, 11, and 12); further replacement of *o*-OMe with even bulkier *o*-Ph does not improve the optical purity but reduces the conversion and epoxide yield. The addition of electron-donating methoxy groups is detrimental to the catalytic performance (cf. Ti-**14** vs. Ti-**12**; Table 1, entries 14 and 12).

The results demonstrated by catalysts Ti-**12** (cf. Ref. [26]) and Ti-**13** were the most fruitful of the series. Furthermore, the enantioselectivities they showed (91.5–92% *ee*) are among the

Table 2. Enantioselective epoxidation of conjugated olefins with H_2O_2 in the presence of catalysts of the type [LTi(μ-O)$_2$TiL].[a]

Entry	Substrate	Catalyst	Epoxide yield [%][b]	Epoxide *ee* [%][c]
1		Ti-**1**	28	37
2		Ti-**12**	33	50
3		Ti-**13**	23	57
4		Ti-**1**	73	74.5
5		Ti-**12**	90	89.5
6		Ti-**13**	92	82
7		Ti-**1**	92	95 (1*S*,2*R*)
8		Ti-**9**	45	93 (1*S*,2*R*)
9		Ti-**12**	94	97 (1*S*,2*R*)
10		Ti-**13**	82	96 (1*S*,2*R*)
11		Ti-**1**	94	96 (1*S*,2*R*)
12		Ti-**9**	43	92 (1*S*,2*R*)
13		Ti-**12**	66.5[d]	98 (1*S*,2*R*)
14		Ti-**13**	86	96 (1*S*,2*R*)
15		Ti-**1**	76	99.5 (3*S*,4*S*)
16		Ti-**12**	80[e]	99.7 (3*S*,4*S*)
17		Ti-**13**	69	99.5 (3*S*,4*S*)

[a] At 290 K; [H_2O_2]/[substrate]/[catalyst] = 150:100:5 μmol, the oxidant was added in one portion and the mixture was stirred for 18 h. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis. [d] Conversion 79.3%, side product 13%. [e] Conversion 91.1%, side product 11%.

highest reported for titanium-catalyzed styrene epoxidations.[6,8,11,12]

The positive effect of *o*-substituents is higher for styrene (Table 1) and for (*E*)- and (*Z*)-β-methyl styrene, and somewhat lower for indene and dihydronapthalene (Table 2, entries 1–17). For 2,2-dimethyl-2*H*-chromene-6-carbonitrile (dbpcn), this effect nearly vanishes; catalysts Ti-**1**, Ti-**12**, and Ti-**13** convert the alkene into the corresponding epoxide with equally excellent enantioselectivities of 99.5% *ee* or more. We note the high yields and enantiomeric purities of indene epoxide and dbpcn epoxide, which are precursors of popular chiral drugs.[27–30]

Mechanism of Ti–salan catalyzed epoxidation reactions

There have been several reports addressing the nature of chemical transformations occurring in the course of Ti–salalen and Ti–salan catalyzed epoxidation of olefins. In particular, Katsuki and co-workers isolated and characterized by X-ray crystallography a dinuclear μ-oxo-μ-peroxo titanium–salan complex, formed in the reaction of the starting, also dinuclear, catalyst with H_2O_2: the authors suggested that the μ-oxo-μ-peroxo dimer was a possible precursor of the elusive active epoxidizing species.[26] In contrast, Berkessel and co-workers identified (by HRMS) the titanium—salalen complexes formed in situ from the salalen ligand and Ti(O*i*Pr)$_4$ as mononuclear species.[8] On the basis of kinetic and mass spectrometric studies, they predicted that the active epoxidizing species could also be mononuclear peroxotitanium(IV) salalen complexes.[9] Titanium–salan complexes were also studied as catalysts of asymmetric oxidation of sulfides; it is reasonable to assume that structurally similar intermediates may operate in both types of oxidation processes. For instance, a peroxotitanium(IV) reactive intermediate was predicted by DFT calculations in a titanium–salan based catalyst system for (nonstereoselective) sulfoxidation, and its formation was corroborated by atmospheric-pressure chemical ionization mass spectrometry studies.[31] Talsi and Bryliakov studied the kinetics of parallel oxidation of various sulfides on titanium–salan catalysts and concluded that, under those reaction conditions (−10 °C, $C_{Ti} = 10^{-4}$ M), the reaction is rate-limited by the reaction of H_2O_2 with the chiral Ti complex to form the active oxidant.[21] The latter rapidly reacts further with the sulfide. The oxidation of sulfide by the electrophilic active species (with Hammett ρ values of −1.35 to −1.40) was concluded to proceed through an oxygen-transfer mechanism.[21]

In this work, the nature of the active epoxidizing species was assessed in competitive epoxidations of various *p*-substituted styrenes (Figure 2). The reactive species was found to be

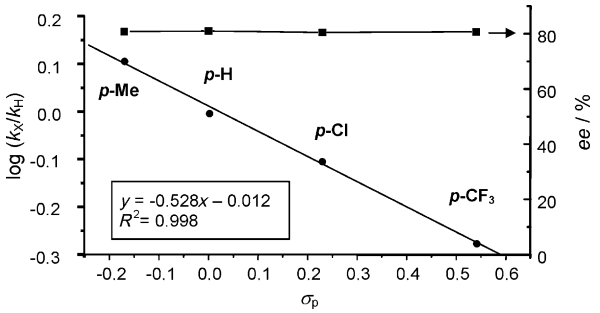


Figure 2. Hammett plot of log(k_X/k_H) (circles) and enantiomeric excess (squares) versus σ_p for the epoxidation of *p*-substituted styrenes with the Ti-**1**/H_2O_2 system.

moderately electrophilic, with a ρ value of -0.53 ± 0.02, which falls within the typical range (−0.38 to −1.4) reported for the oxidations by d^0-transition metal peroxo complexes such as V, Mo, W, and Re.[32–41] Correlation with σ^+_p rather than σ_p was poor, thus suggesting the absence of significant charge separation in the transition state of the rate-determining step.

Rather unexpectedly, the enantioselectivity of the epoxidation was not affected by the nature of the *p*-substituent, with the enantiomeric excess of the products remaining in the range 80.5–81.5% *ee* (Figure 2). This finding clearly suggests that the overall reaction rate and the enantioselectivity of the epoxidation are governed by different stages of a multistage reaction mechanism. In principle, it is not surprising that the overall reaction can be rate-limited by the olefin coordination to the electron-deficient titanium(IV) center. In particular, such a situation has been widely accepted for olefin polymerizations over Ziegler–Natta titanium catalysts.[42] It seems to be very likely that in this case we also deal with a similar situation, with the rate-limiting coordination of olefinic substrate to the titanium active site.

To gain further insight into the catalytic reaction mechanism, a series of UV/Vis experiments were conducted, with the aim of monitoring the catalyst transformations with time. One can see that the interaction of catalyst Ti-**1** with an excess of H_2O_2 in CH_2Cl_2 in the presence of nonabsorbing substrate (1-octene)

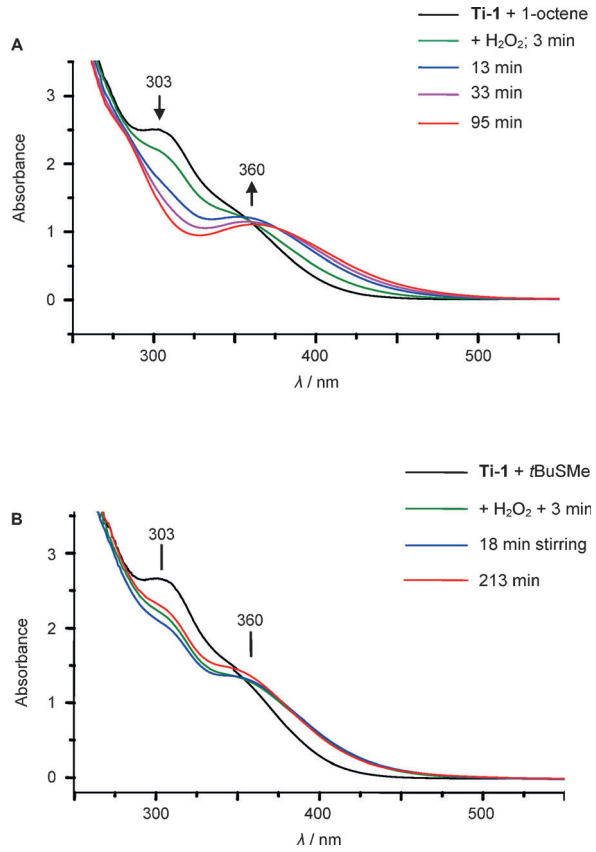
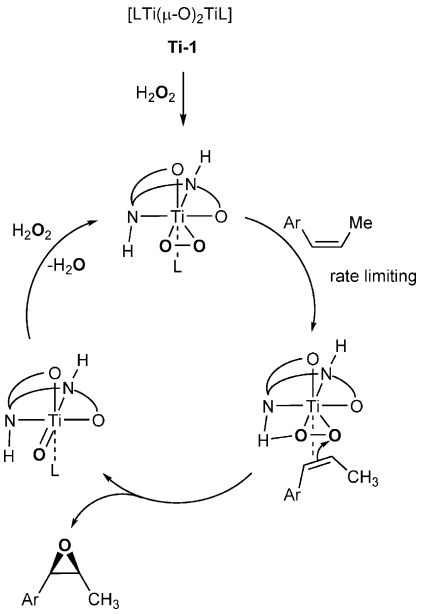


Figure 3. Transformations of Ti-**1** (6×10^{-5} M in CH_2Cl_2) upon the reaction with H_2O_2 (3×10^{-3} M) in the presence of A) 1.3×10^{-2} M 1-octene and B) 1.6×10^{-2} M *t*BuSMe at 20 °C.



Scheme 1. Proposed mechanism of titanium–salan-catalyzed epoxidations with H_2O_2. L stands for either vacant coordination sites or labile axial ligands (e.g., H_2O). Oxygen atoms originating from H_2O_2 are represented in bold.

occurs completely within approximately 1.5 h, as monitored by the drop of the characteristic band of Ti-**1** at $\lambda_{max}=303$ nm, and by the concomitant isosbestic formation of a new chromophore with $\lambda_{max}=360$ nm (Figure 3 A). This picture persists for hours, indicating the presence of the dominant portion of titanium in the form of the new, active (presumably (η^2-peroxo)-titanium) species.[43] The latter reacts with the substrate relatively slowly.

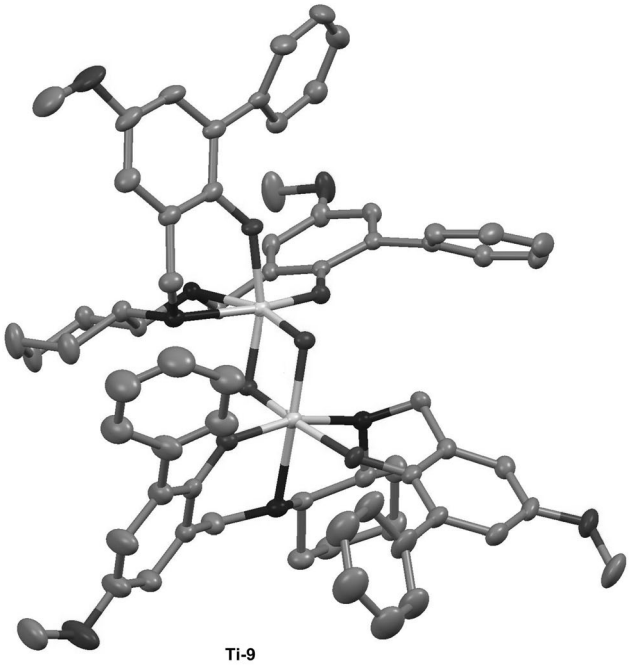
By contrast, when a more readily oxidizing sulfide substrate, *t*BuSMe, was taken instead of 1-octene, only partial disappearance of the 303 nm feature (to convert into the λ_{max} 360 nm active species) was documented; furthermore, the concentration of the λ_{max} 303 nm active species approached a minimum value within approximately 18 min and subsequently began to recover slowly (Figure 3 B). This behavior is characteristic of a quasi-steady-state situation when the active intermediate species (formed through a relatively slow reaction between Ti-**1** and H_2O_2[21]) rapidly oxidizes the sulfide substrate, to leave a relatively small concentration of the active species.

Combining the above considerations, the following epoxidation mechanism can be proposed (Scheme 1), which takes into account that the overall reaction rate is most likely limited by the olefin coordination to the titanium center, whereas the asymmetric induction is solely determined by the relative orientation of the coordinated olefin and peroxide group within the [LTi(η^2-O_2)(olefin)] intermediate.

The mechanism depicted in Scheme 1 assumes that H_2O_2 is the only source of oxygen atoms that become incorporated into the epoxide.[44–47] To check this hypothesis, a catalytic experiment on styrene epoxidation in the presence of an excess of ^{18}O-labeled water (see the Supporting Information) was carried out, which established the absence of ^{18}O in the resulting styrene epoxide.

The structure and reactivity of the initially formed [LTi(η^2-O_2)] active species are of major interest and should be briefly commented on. In the case of titanium–salan catalysts, there may be two distinct coordination sites available for the coordination of the peroxide. Indeed, our own experience and previously reported data[13,26] bear evidence that titanium–salan catalysts, when crystallized out as dinuclear complexes, feature *cis*-β-coordination topology (Figure 4). In the course of the catalytic reaction (Scheme 1), dissociation of the dimers should lead to two nonequivalent labile coordination sites at the titanium center, each one being accessible for the coordination of either a peroxide moiety or an olefin molecule. However, it appears that it is only the peroxide coordination to one of the coordination sites that leads to an active species; in particular, coordination that ensures close contact between the N–H hydrogen and the peroxide (Scheme 1).[13,19,23,25]

Taking into account the preceding discussion (Scheme 1), one could predict that the introduction of electron acceptors into the catalyst structure could facilitate olefin coordination to the active site and hence increase the catalyst reactivity. We have attempted to check this by following the kinetics of styrene epoxidation in the presence of titanium catalysts with ligands **1**, **5**, **6**, **8**, and **9**, featuring various *p*-substituents in the salicylidene moieties of the salan ligands. It was found that after an initial induction period (cf. Ref. [26]), the epoxidation acquires a pseudo-first-order kinetics, which persists for hun-



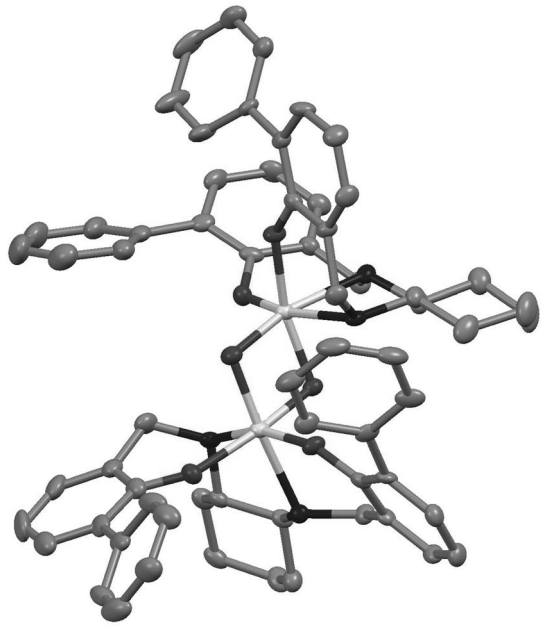


Figure 4. Crystal structures of complexes (Λ,*R*,*R*,S_N,S_N-Λ,*R*,*R*,S_N,S_N)-Ti-**9** (top) and (Δ,*S*,*S*,R_N,R_N-Δ,*S*,*S*,R_N,R_N)-Ti-**1**[20] (bottom). Thermal ellipsoids are drawn at 50% probability level. Hydrogen atoms and solvent molecules omitted for clarity.

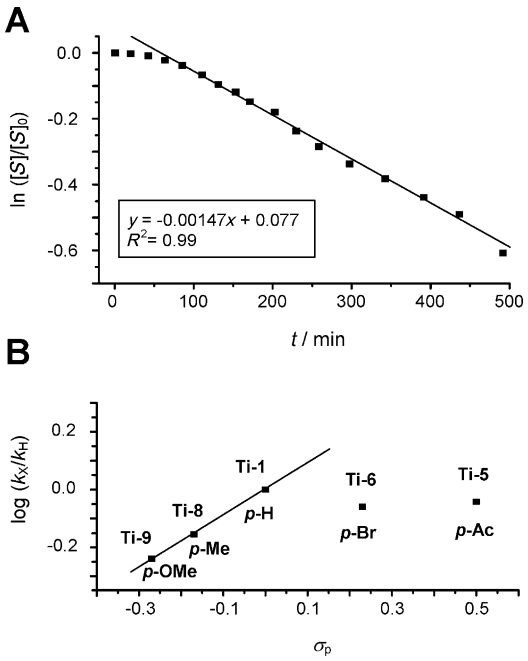


Figure 5. A) Kinetics of styrene epoxidation (CH_2Cl_2, 290 K) by catalyst system Ti-**1**/H_2O_2 and its linear fit, with the exception of first four points. B) Hammett plot of log(k_X/k_H) for styrene epoxidations with H_2O_2 in the presence of various titanium catalysts, and its linear fit performed for catalysts Ti-**9**, Ti-**8** and Ti-**1**.

dreds of minutes (Figure 5 A), thus making possible the evaluation of rate constants.

It was found that the observed first-order rate constants correlate well with the Hammett σ_p parameter for catalysts Ti-**9**, Ti-**8**, and Ti-**1**, demonstrating increasing reactivity in the order Ti-**9** < Ti-**8** < Ti-**1**, in line with increasing electrophilicity of the active sites (Figure 5 B). The observed rate constants for catalysts Ti-**6** and Ti-**5** did not show linear dependence. Apparently, because of the lower stability of active sites in the latter catalyst systems, the epoxidation kinetics was highly nonstationary, with rapid reaction deceleration, leading to understated estimates of k_{obs}. Faster catalyst degradation is also the most likely reason for low styrene epoxide yields obtained by the use of catalysts Ti-**6** and Ti-**5** (Table 1, entries 5 and 6).

Whereas the rate-limiting step can be reliably identified and characterized by kinetic studies, the reaction step determining the enantioselectivity (when it is relatively fast) is more difficult to access. In some cases, however, analysis of the temperature dependence of reaction enantioselectivity provides valuable information in this respect. We have found that the enantioselectivities of epoxidations in the presence of complex Ti-**1** increase as the temperature is decreased. The corresponding modified Eyring plots for the epoxidation of styrene and (*Z*)-β-methyl styrene (Figure 6) are linear within the accessible temperature range of −10 to +30 °C, without any deviation from linearity, suggesting that the mechanism of stereoselectivity is not varied and that the epoxidation proceeds through the same transition state.[48–50] In the linear fits, the slopes and intercepts are the differences in the activation enthalpy and entropy, for the formation of the major and the minor diastereomer, described by Equation (1).[50]

$$R\ln(er) = -\frac{\Delta\Delta H^{\neq}}{RT} + \frac{\Delta\Delta S^{\neq}}{R} \qquad (1)$$

For styrene epoxidation, $\Delta\Delta H^{\neq} = -6.6(\pm 0.9)$ kJ mol^{-1} and $\Delta\Delta S^{\neq} = -3.7(\pm 3.0)$ kJ mol^{-1} J^{-1}, and for (*Z*)-β-Me-styrene, $\Delta\Delta H^{\neq} = -5.4(\pm 0.5)$ kJ mol^{-1} and $\Delta\Delta S^{\neq} =$

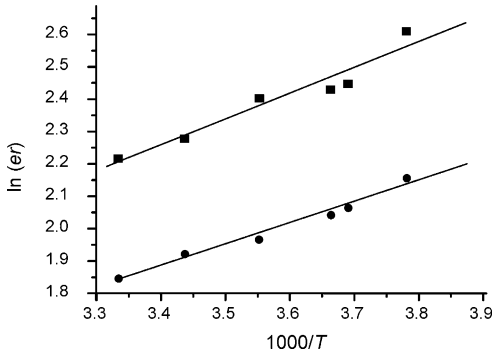


Figure 6. Modified Eyring plots for the epoxidation of styrene (squares) and (*Z*)-β-Me-styrene (circles) on catalyst Ti-**1**. e.r. = enantiomeric ratio, (100+*ee*)/(100−*ee*).

$-2.8(\pm 1.4)$ kJ mol^{-1} J^{-1}, which is indicative of predominant enthalpy control. Although the enantioselectivity steadily increases with decreasing temperature, the choice of an appropriate epoxidation temperature should be a balance between the high enantioselectivity and practically acceptable reaction time.

Conclusion

The effect of steric bulk and electronic properties of the chiral ligands on the enantioselectivity of olefin epoxidation with H_2O_2 in the presence of a series of titanium(IV) salan complexes has been examined. It has been found that the electronic properties influence the catalytic activity (without affecting the enantioselectivity), whereas the steric bulk (varied by the *o*-aryl substituents) determine the epoxidation enantioselectivity. With a suitable design of ligand structure, very high enantiomeric purities (up to $>99.5\%$ *ee*) may be achieved for some chiral epoxides, including the precursors to biologically active compounds and pharmaceuticals. Competitive oxidations of *p*-substituted styrenes reveal the electrophilic nature of the (presumably titanium(η^2-peroxo)) active species, with a Hammett ρ value of -0.51. The enantioselectivity is unaffected by the electron-donating (or withdrawing) ability of the *p*-substituents of styrenes. Mechanistic studies provide evidence in favor of a stepwise reaction mechanism: most likely, in the first (rate-limiting) step, olefin coordinates to the active species, followed by intramolecular enantioselective oxygen transfer. The overall epoxidation rate can be enhanced, without any effect on enantioselectivity, by increasing the electrophilicity of the titanium(IV) centers; this apparently occurs by facilitating coordination of the nucleophilic olefin to titanium. The enantioselectivities increase with decreasing temperature, and the modified Eyring plots for the epoxidation of styrene and (*Z*)-β-methylstyrene are linear, indicating a single, enthalpy controlled mechanism of stereoselectivity.

Experimental Section

Full experimental details, as well as spectral and X-ray data are provided as Supporting Information.

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Keywords: asymmetric catalysis · epoxidation · green chemistry · peroxides · reaction mechanisms

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FULL PAPER

Synthetic Methods

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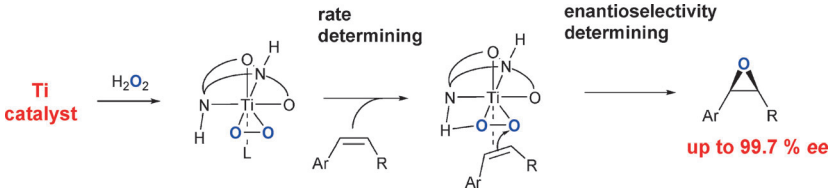
Titanium Salan Catalysts for the Asymmetric Epoxidation of Alkenes: Steric and Electronic Factors Governing the Activity and Enantioselectivity



Bigger is better: Electronic effects only govern the rate of asymmetric olefin epoxidation with H_2O_2 on titanium–salan complexes, whereas the steric bulk of the substituents alone determines the enantioselectivity of epoxidation (see scheme).