Asymmetric Catalysis

DOI: 10.1002/ange.200501318

Construction of Pseudo-Heterochiral and Homochiral Di-μ-oxotitanium(Schiff base) Dimers and Enantioselective Epoxidation Using Aqueous Hydrogen Peroxide

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Remarkable advances in asymmetric synthesis using optically active metal complexes as catalysts have been achieved in the last half century.[1] Monometallic complexes are used as the catalysts in most of the asymmetric reactions developed so far. Particularly in the last two decades, it has been revealed that chiral metallosalen complexes result in diverse and excellent asymmetric catalysis.[2] Chiral salen ligands can be synthesized in a single step from chiral diamine and chiral and/or appropriately substituted salicylaldehydes and form complexes with a variety of metal ions. Moreover, metallosalen complexes are conformationally flexible as a result of the presence of two methylene carbon atoms and they can adopt three different configurations (*trans*, *cis*-α, and *cis*-β). Metallosalen complexes usually adopt *trans* configurations, but they can be readily transformed in the presence of a bidentate ligand into the corresponding *cis*-β complexes.[2,3] Thus, various chiral metallosalen complexes have been synthesized and used as catalysts for a wide range of asymmetric reactions. Most of the metallosalen complexes used are monomeric, but for some reactions, depending on their mechanisms, dimeric or oligomeric metallosalen complexes have proven to be superior catalysts to the corresponding monomeric ones.[4] Nevertheless, the use of such dimeric or oligomeric metallosalen complexes as catalysts has been limited mainly because their synthesis involves laborious routes, except for metallosalen complexes prepared by self-assembly. Thus, di-μ-oxotitanium(salen) complexes that can be prepared spontaneously by treatment of monomeric [Ti(salen)] complexes with water,[5] attracted our attention.[6] Furthermore, in contrast to the usual monomeric [Ti(salen)] complexes that adopt *trans* configurations, each {Ti(salen)} unit of the di-μ-oxo complexes take a *cis*-β configuration. In contrast to the *trans* isomer, the *cis*-β isomer is chiral and exists in enantiomeric forms (Δ or Λ; Figure 1). Thus, there are six possible isomers for the di-μ-oxotitanium(salen) dimer

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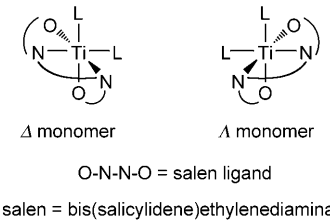


Figure 1. Enantiomeric isomers for the monomeric *cis*-β-titanium-(salen) complex.

(two enantiomeric pairs and two *meso* isomers).[5b] However, Belokon', North, et al. have reported that treatment of a *trans*-[$TiCl_2$(salen)] ([$TiCl_2$**A**]) complex with water in the presence of amine spontaneously gives homochiral dimer **1** as the sole product [(*RΔ*,*RΔ*)-*syn*-**1**] (Figure 2a).[5] This result indicated that the salen ligand **A** which included an (*R*,*R*)-cyclohexanediamine moiety as a constituent part forced the {Ti(salen)} unit to adopt the *Δ* configuration.

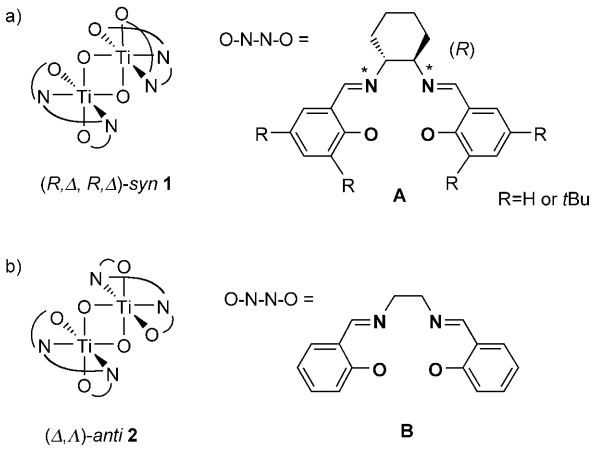
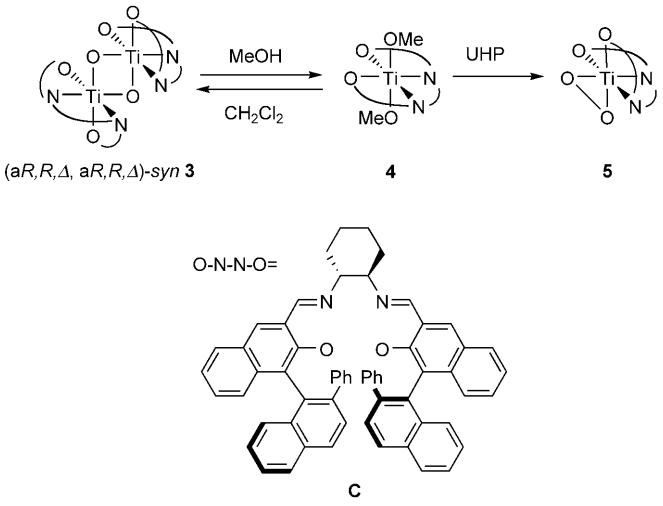


Figure 2. a) Structure of **1**. b) Structure of **2**.

In contrast to the report by Belokon', North, et al., Tsuchimoto has recently reported that di-μ-oxo dimer **2** bearing achiral ligand **B** is heterochiral: each {Ti(salen)} unit has opposite chirality (Figure 2b) and X-ray diffraction analysis has shown **2** to have a (*Δ*,*Λ*)-*anti* configuration.[7] This structure indicates that the interaction between the *Δ* and the *Λ* ligands is more favorable than the interaction between two *Δ* (or two *Λ*) ligands. This situation is reminiscent of asymmetric amplification (positive nonlinear effect) observed in asymmetric addition of diethylzinc to aldehydes using a chiral amino alcohol as the chiral auxiliary: the enantiomeric excess of the chiral auxiliary correlates nonlinearly with the enantioselectivity of the reaction, that is, carrying out the reaction even with a chiral auxiliary of low enantiomeric excess results in enantioselectivity similar to that obtained with the enantiopure auxiliary.[8] This unusual phenomenon has been rationally explained by self-recognition of the chirality of the complex upon its dimerization: the equilibrium between enantiomeric monomers, as well as homochiral and heterochiral dimers is weighted heavily towards the heterochiral dimer as a consequence of a favorable interaction between the enantiomeric monomers.

We also found that, in analogy with di-μ-oxo dimer **1**, complex **3** that was prepared from [$TiCl_2$**C**] also adopted a homochiral *aR*,*R*,*Δ*, a*R*,*R*,*Δ* configuration (Scheme 1) and it



Scheme 1. Structural change of di-μ-oxotitanium(salen) complex **3** bearing chiral salen ligand **C** as a result of the solvent or reagent.

served as an excellent catalyst for asymmetric sulfoxidation in the presence of urea·hydrogen peroxide (UHP).[9] However, complex **3** did not catalyze epoxidation. On the other hand, it was found that the asymmetric sulfoxidation with **3** showed a strong positive nonlinear effect and that di-μ-oxo-**3** and monomeric *trans*-**4** were readily interconverted by changing the solvent. This result indicated that the mixing of a*R*,*R*,*Δ* and the a*S*,*S*,*Λ* isomers made a heterochiral (a*R*,*R*,*Δ*, a*S*,*S*,*Λ*) dimer preferentially.[10] Taking into account Tuchimoto's and our own results, we expected that the pseudo-heterochiral (*aR*,*R*,*Δ*, a*R*,*R*,*Λ*)-**6**, in which each titanium ion carries the same but conformationally enantiomeric ligand, would be formed if the salen ligand became more flexible and if the a*R*,*R*,*Λ* configuration that is otherwise unstable is sufficiently stabilized by the interaction with the a*R*,*R*,*Δ* ligand. Furthermore, the unprecedented pseudo-heterochiral dimer might show unique asymmetric catalysis. Herein, we describe the construction of stable dimeric titanium/tetradentate Schiff base complexes that provide unique reaction sites as shown by in situ intramolecular Meerwein–Ponndorf–Verley (MPV) reduction in combination with self-assembly of the resulting titanium/tetradentate Schiff base complexes. We also describe their use as catalysts in the presence of hydrogen peroxide for asymmetric epoxidation.

We tried reducing one of the two imine bonds of a salen ligand to make it more flexible without losing its high asymmetry-inducing ability. Since titanium isopropoxide is known to undergo MPV reduction, we expected that the [Ti(salen)(O*i*Pr)$_2$] complex might undergo intramolecular MPV reduction of one or two of the imine bonds. Unfortunately, no reaction was observed for [Ti**A**(O*i*Pr)$_2$] (R = *t*Bu) that was prepared in situ and then left to stand. However, the

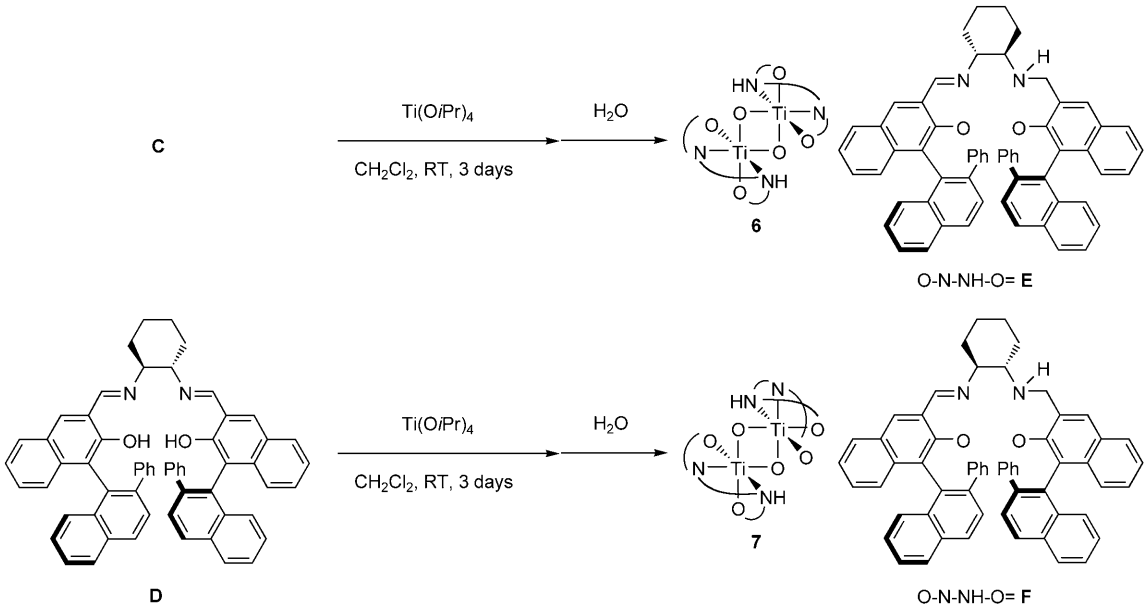
corresponding [Ti**C**(O*i*Pr)$_2$] complex prepared in situ from ligand **C** and Ti(O*i*Pr)$_4$ in dichloromethane was found to undergo the desired MPV reduction at room temperature, and the subsequent water treatment gave a new di-μ-oxo complex **6** that could be crystallized from heptane and dichloromethane (Scheme 2). X-ray diffraction analysis unambiguously demonstrated that the configuration of **6** was pseudo-heterochiral [(a*R*,*R*,*Δ*,a*R*,*R*,*Λ*)-*anti*].[11] Furthermore, the C–N bond lengths indicated that one of the two imine bonds of each salen ligand **C** was reduced to a single bond and the phenolic oxygen atom *ortho* to the reduced imine group occupied the apical position.[12] Encouraged by this result, we also synthesized the (a*RS*,a*RS*)-di-μ-oxotitanium complex **7**, bearing the corresponding half-reduced salen ligand **F**, according to the method described for the preparation of **6**. It is, however, noteworthy that complex **7** was found to adopt a homochiral configuration (a*R*,*S*,-*Δ*,a*R*,*S*,*Δ*) by X-ray diffraction analysis (Scheme 2).[11] These results suggested that the configuration of a di-μ-oxotitanium complex bearing a half-reduced salen ligand is determined by equilibrium involving ligand chirality, its structural flexibility, and weak intra- and interligand interactions such as CH–π interactions. To our delight, complexes **6** and **7** were much more stable than complex **3**: although complex **3** immediately dissociated into the corresponding monomeric {Ti(salen)} species **4** in methanol at room temperature (Scheme 1), complex **6** was stable in [D_4]MeOH for at least 5 h and complex **7** was stable even under aqueous epoxidation conditions for at least 24 h. On the basis of these findings, we examined epoxidation using hydrogen peroxide in the presence of complex **6** or **7**.[13]

The catalytic activities of **6** and **7** for epoxidation were examined with 1,2-dihydronaphthalene (**8**) as the test material (Table 1, entries 1–8). Epoxidation using **6** as the catalyst in the presence of the urea·hydrogen peroxide adduct proceeded with good enantioselectivity, but was slow and the turnover number (TON) of **6** was modest (TON = 14) (entry 1).[14] Epoxidation using **7** was performed in the presence of 1.01 equivalents of aqueous (30%) hydrogen peroxide at room temperature[15,16] and it was found that the epoxidation proceeded with excellent enantioselectivity as well as high yield (entry 2). The turnover number of **7** was 4600 when hydrogen peroxide was added slowly over a period of 8 h (entry 4).

Epoxidation of other conjugated olefins also proceeded smoothly with high enantioselectivity (entries 9–13). It is noteworthy that epoxidation of (*Z*)-5-phenylpent-2-en-3-yne (**11**) was stereospecific and gave the corresponding *cis*-epoxide as a single product, albeit with a slightly inferior enantioselectivity of 88% *ee* (entry 11). This result suggested that oxygen transfer proceeds in a concerted rather than a stepwise manner. This proposal was also supported by the fact that epoxidation of styrene (**12**) was highly enantioselective (entry 12). Moreover, the epoxidation of the nonconjugated olefin 1-octene (**14**) proceeded with slightly reduced but good enantioselectivity, albeit somewhat slowly (entry 14).

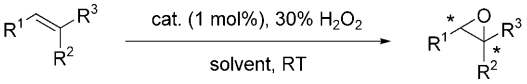
Although the reaction mechanism of the present epoxidation is unclear, a peroxotitanium species **15** or **16** is considered to act as the active species because the epoxidation is stereospecific (Figure 3).[17] Furthermore, we speculate that the peroxotitanium species may be activated by an intramolecular hydrogen bond with the amine proton. This speculation might explain why complex **3** that does not possess such an NH group cannot catalyze the epoxidation.

The oxidation of methyl phenyl sulfide was also examined in dichloromethane with **6** as the catalyst in the presence of UHP. The reaction smoothly proceeded but the enantioselectivity was moderate (67% *ee*), although the oxidation with **3** under the same conditions showed a high enantioselectivity of 95% *ee*. It is, however, noteworthy that the sense of asymmetric induction by **6** was opposite to that by **3**, thus suggesting that the structure of the active species derived from **6** was different from **5**.



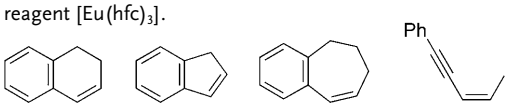
Scheme 2. Syntheses of di-μ-oxotitanium complexes **6** and **7**.

Table 1: Asymmetric epoxidation using aqueous hydrogen peroxide as the terminal oxidant.[a]

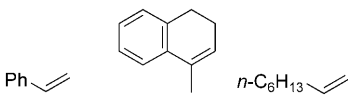


Entry	Substrate	Solvent	*t*	Yield [%][b]	*ee* [%]	Config.[c]
1	**8**	CH_2Cl_2	24	14	83[d,e]	1*S*,2*R*
2	**8**	CH_2Cl_2	12	>99	>99[d]	1*R*,2*S*
3	**8**	CH_2Cl_2	72	>99	>99[d,f]	1*R*,2*S*
4	**8**	CH_2Cl_2	48	92	>99[d,g]	1*R*,2*S*
5	**8**	toluene	18	>99	>99[d]	1*R*,2*S*
6	**8**	ethyl acetate	18	>99	>99[d]	1*R*,2*S*
7	**8**	THF	85	97	97[d]	1*R*,2*S*
8	**8**	MeOH	NR			
9	**9**	ethyl acetate	24	87	99	1*R*,2*S*
10	**10**	ethyl acetate	24	85	98[h]	5*R*,6*S*
11	**11**	ethyl acetate	24	64	88[i]	2*S*,3*R*
12	**12**	CH_2Cl_2	24	90	93[j]	*R*
13	**13**	CH_2Cl_2	24	75	95[k]	1*S*,2*R*
14	**14**	CH_2Cl_2	48	70	82[l,m]	*S*

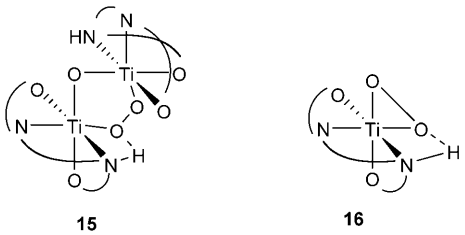
[a] Reactions were carried out at room temperature with a molar ratio of substrate/catalyst **7**/aq H_2O_2 = 1:0.01:1.01, unless otherwise stated. [b] Determined by ^{1}H NMR (400 MHz) spectroscopic analysis. [c] Determined by comparison of the elution order with that of the authentic sample in HPLC analysis and/or comparison of the chiroptical data with the literature value. [d] Determined by HPLC analysis on a chiral stationary phase (Daicel Chiralcel OB-H; hexane/*i*PrOH 99:1). [e] Reactions were carried out at room temperature with a molar ratio of substrate/catalyst **6**/UHP = 1:0.01:1. [f] 0.1 mol% of **7** was used. [g] 0.02 mol% of **7** was used and hydrogen peroxide was added over the period of 8 h. [h] Determined by HPLC analysis on a chiral stationary phase (Daicel Chiralpak AS-H; hexane/*i*PrOH 99.9:0.1). [i] Determined by HPLC analysis on a chiral stationary phase (Daicel Chiralcel OD-H; hexane/*i*PrOH = 99:1). [j] Determined by HPLC analysis on a chiral stationary phase (Daicel Chiralcel OD-H; hexane:*i*PrOH 99.9:0.1). [k] Determined by HPLC analysis on a chiral stationary phase (Daicel Chiralcel OB-H; hexane/*i*PrOH = 99:1). [l] 3 mol% of **7** was used. [m] Determined by ^{1}H NMR spectroscopic analysis using a chiral shift reagent [Eu(hfc)$_3$].



8 **9** **10** **11**



12 **13** **14**



15 **16**

Figure 3. Possible peroxo intermediates for the epoxidation.

In conclusion, we were able to synthesize stable di-μ-oxo dimers—not only a homochiral **7** but also an unprecedented pseudo-heterochiral di-μ-oxo dimer **6**—by using an in situ intramolecular Meerwein–Ponndorf–Verley reduction in combination with self-assembly of the resulting titanium/tetradentate Schiff base complexes. Furthermore, we were able to show that these stable di-μ-oxo dimers (**6** and **7**) catalyzed epoxidation with hydrogen peroxide; in particular, complex **7** efficiently catalyzed a highly enantioselective epoxidation using aqueous (30%) hydrogen peroxide as the oxidant. Other applications of the current oxidation are under investigation.

Experimental Section

7: Ti(O*i*Pr)$_4$ (2 equiv) was added to a solution of salen ligand **D** (1 equiv) in dry dichloromethane in a nitrogen atmosphere and the resultant solution was stirred at room temperature. After 3 days, water (4 equiv) was added and the reaction mixture was stirred for 2 h. The resulting yellow precipitate was collected by filtration and recrystallized from diethyl ether and dichloromethane to give crystalline complex **7** in 60% yield.

General procedure for epoxidation: Titanium complex **7** (1.8 mg, 1 μmol) and olefin (0.1 mmol) were dissolved in an appropriate solvent (1.0 mL) in a nitrogen atmosphere. After addition of 30% aqueous hydrogen peroxide (0.101 mmol), the resultant mixture was stirred at room temperature for the time indicated in Table 1. The solvent was removed in vacuo and the residue was purified by chromatography on silica gel (pentane/Et_2O 40:1) to give the corresponding epoxide. The *ee* values were determined by HPLC on a chiral stationary phase or by ^{1}H NMR analysis using [Eu(hfc)$_3$] (hfc = 3-(heptafluoropropylhydroxymethylene)-D-camphorate) under the conditions described in the footnotes to Table 1.

Received: April 15, 2005
Published online: July 6, 2005

Keywords: asymmetric catalysis · enantioselectivity · epoxidation · hydrogen peroxide · titanium

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