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# Asymmetric epoxidation of olefins catalyzed by Ti(salan) complexes using aqueous hydrogen peroxide as the oxidant*

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*Abstract*: Ti(salan) complexes were found to be efficient catalysts for asymmetric epoxidation with aqueous hydrogen peroxide as the oxidant. In the presence of pH 7.4 phosphate buffer, the reaction of various conjugate olefins proceeded smoothly to afford the corresponding epoxides in high yield with high enantioselectivity, even on a multigram scale. Ti(salan) complexes could be prepared from $Ti(OiPr)_4$ and the corresponding salan ligand and directly used without isolation and purification.

*Keywords*: asymmetric synthesis; oxidation; epoxide; titanium; hydrogen peroxide.

## INTRODUCTION

Optically active epoxides are of great importance as versatile and useful chiral building blocks in organic synthesis [1]. Asymmetric epoxidation of olefins is the most direct and effective approach to synthesizing enantio-enriched epoxides, and many research efforts have been devoted to the development of the efficient catalysts for this process [2]. Among them, transition-metal complexes, such as titanium/tartrate and manganese/salen as well as chiral ketones, are some of the most successful catalysts and are frequently used in organic synthesis. Although various enantio-enriched epoxides are accessible by using these epoxidation methods, they require stoichiometric oxidants of low atom efficiency. For example, an alkyl hydroperoxide, such as TBHP or CHP, is the typical oxidant for the titanium/tartrate system, and the manganese system employs iodosylbenzene or sodium hypochlorite. In the ketone-catalyzed epoxidation, oxone is generally used as the oxidant. However, epoxidation methods with these stoichiometric oxidants potentially generate a large amount of waste materials derived from the oxidants used. From the viewpoint of protecting the environment and conserving natural resources, the use of a highly atom-efficient oxidant is recommended. Considering this requirement, apart from molecular oxygen, hydrogen peroxide is the oxidant of choice. It has a high active oxygen content (47 %), and the byproduct is only water. Additionally, its aqueous solution (30 %) is inexpensive and easy to handle. Consequently, the development of asymmetric epoxidation using aqueous hydrogen peroxide as the oxidant has attracted much attention in recent studies [3].

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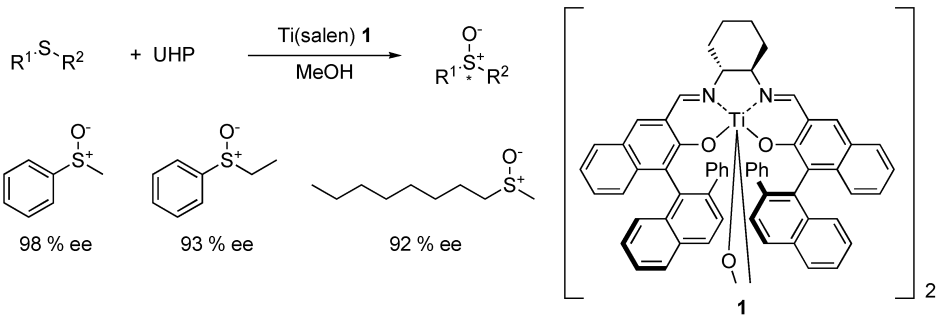
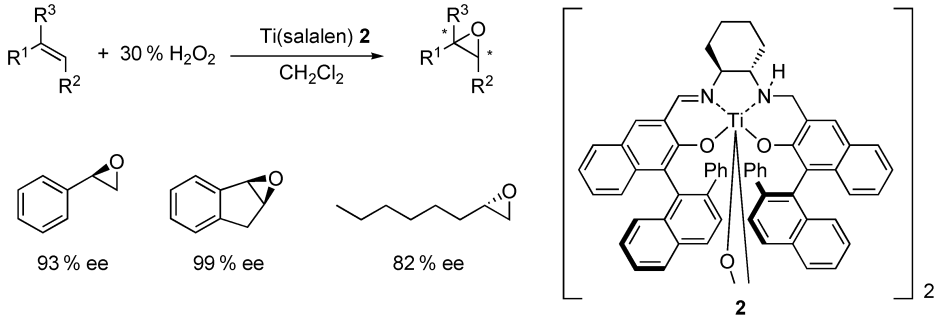
## OUR BACKGROUND

In 2001, we developed a highly enantioselective oxidation of sulfides using Ti(salen) complex **1** as the catalyst (Scheme 1) [4]. In the presence of a urea/hydrogen peroxide adduct (UHP) as the oxidant, various sulfides were effectively converted to the corresponding sulfoxides. Reactions of dialkyl sulfides as well as alkyl aryl sulfides furnished the sulfoxides with high enantioselectivity. In addition, thioacetals were good substrates for this oxidation method, and mono-sulfoxides were obtained in high yield with high enantioselectivity [5]. While Ti(salen) complex **1** is an efficient catalyst for asymmetric sulfide oxidation, it could not catalyze the epoxidation of olefins. In the course of further studies on Ti-catalyzed oxidations, we reported the synthesis of chiral Ti(salalen) complexes and disclosed that Ti(salalen) complex **2** is an excellent catalyst for the asymmetric epoxidation of olefins with aqueous hydrogen peroxide as the oxidant (Scheme 2) [6,7]. With complex **2**, various epoxides could be obtained with high enantioselectivity. Reactions of terminal, *cis*-disubstituted and trisubstituted conjugate olefins smoothly proceeded with high to excellent enantioselectivity. It is noteworthy that the reaction was stereospecific and that reactions of *cis*-olefins gave only the corresponding *cis*-epoxides. Moreover, an unproductive decomposition of hydrogen peroxide was not observed. The efficiency of this catalytic system can be recognized by its high turnover number of 4600 recorded in the reaction of 1,2-dihydronaphthalene. The most striking feature of this system is the result of aliphatic olefins that are one of the most challenging substrates for asymmetric epoxidation. Reactions of terminal aliphatic olefins gave the corresponding epoxides with high enantioselectivity. For example, reaction of 1-octene furnished the epoxide with 82 % ee. In addition, reaction of *cis*-disubstituted aliphatic olefins also showed good to high enantioselectivity.




**Scheme 1** Ti(salen)-catalyzed asymmetric sulfide oxidation.




**Scheme 2** Ti(salalen)-catalyzed asymmetric epoxidation.

## Ti(SALAN)-CATALYZED ASYMMETRIC EPOXIDATION

In the sulfide oxidation using Ti(salen) complex **1** and UHP, NMR studies revealed the participation of a titanium peroxo complex as the active species [4]. As described above, the peroxo complex could effectively oxidize sulfides but could not oxidize olefins. On the other hand, the combination of the Ti(salalen) complex and aqueous hydrogen peroxide could efficiently oxidize olefins as well as sulfides. We speculated that this contrast in the reactivity is associated with the difference between the active species: the peroxo complex derived from complex **2** and hydrogen peroxide should be further activated by hydrogen bonding between the amino proton of the salalen ligand (Fig. 1) [6]. Based on this speculation, we were intrigued by the catalysis of Ti(salan) complexes (Fig. 2) [8]. They also have amino protons, and they can be easily prepared and tuned. In contrast, the synthetic procedure for the Ti(salalen) complex **2** was quite limited by the ligand structure and could be hardly applied to preparation of the related Ti(salalen) complexes.

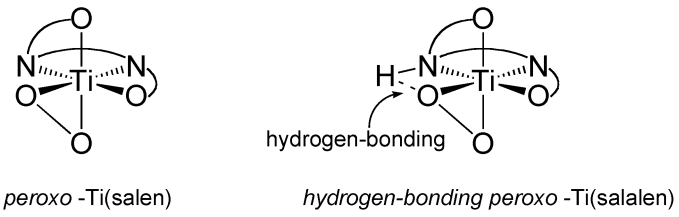



**Fig. 1** Proposed active species for Ti-catalyzed oxidations.

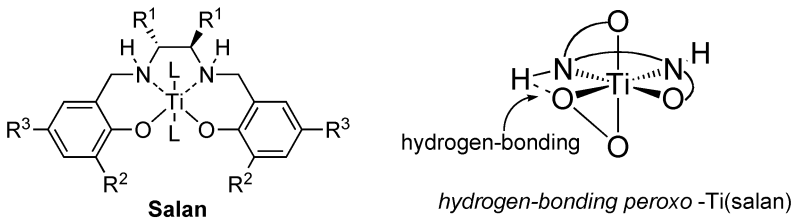
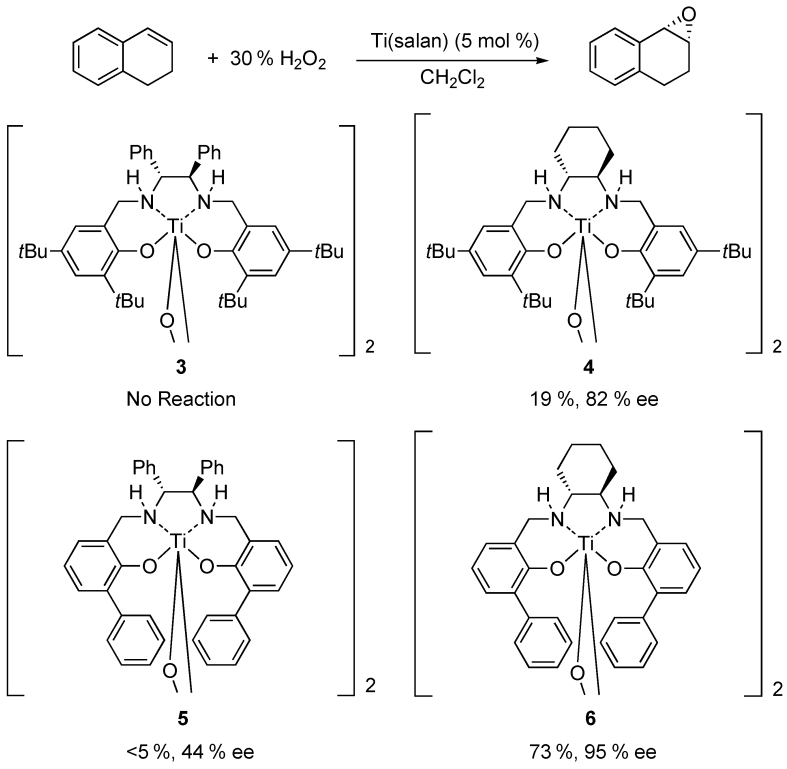


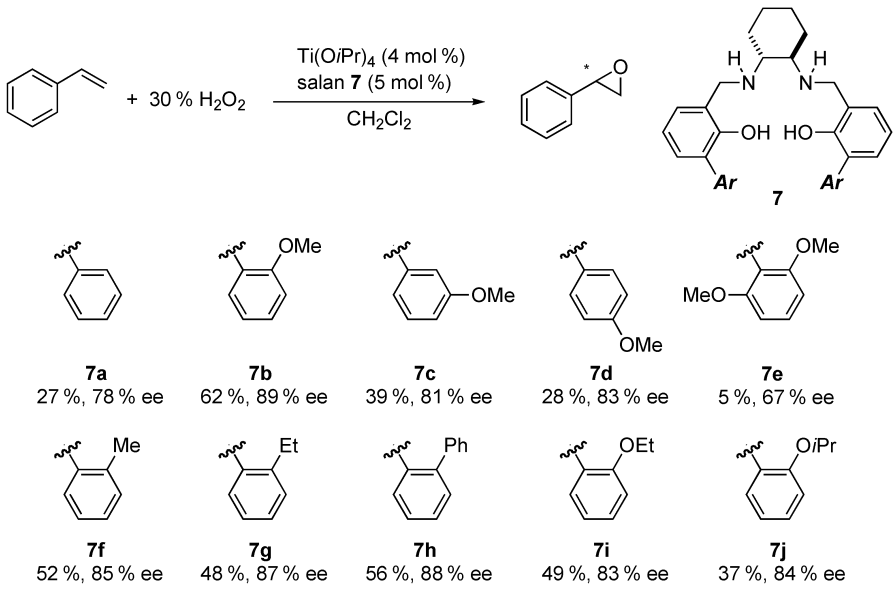

**Fig. 2** Working hypothesis.

We first synthesized four Ti(salan) complexes **3–6** and conducted asymmetric epoxidation of 1,2-dihydronaphthalene as the test substrate (Scheme 3) [8]. While reactions with complexes **3** and **5** derived from diphenylethylenediamine furnished no or little amount of the epoxide, those with complexes **4** and **6** bearing a cyclohexanediamine moiety gave the epoxide with high enantioselectivity. In particular, complex **6** was the most promising, and the epoxide was obtained in high yield with a high enantioselectivity of 95 %. In addition, complex **6** could be prepared in situ from Ti(O*i*Pr)$_4$ and the corresponding salan ligand in dichloromethane and used without isolation and purification.




**Scheme 3** Asymmetric epoxidation of 1,2-dihydronaphthalene with Ti(salan) complexes.

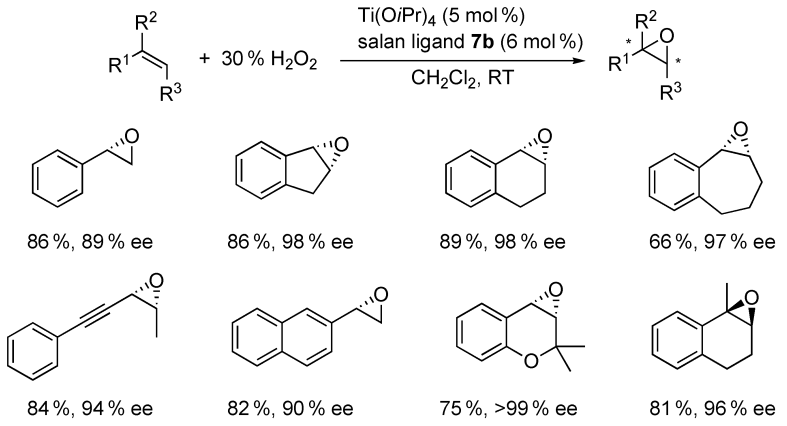
Consequently, we further investigated the ligand effect on the asymmetric epoxidation of styrene with the in situ protocol (Scheme 4) [9]. We introduced a methoxy group on the benzene ring at the C3 and C3' positions. In the case of the *ortho*-substitution, a significant positive effect was observed on




**Scheme 4** Comparison of various salan ligands.

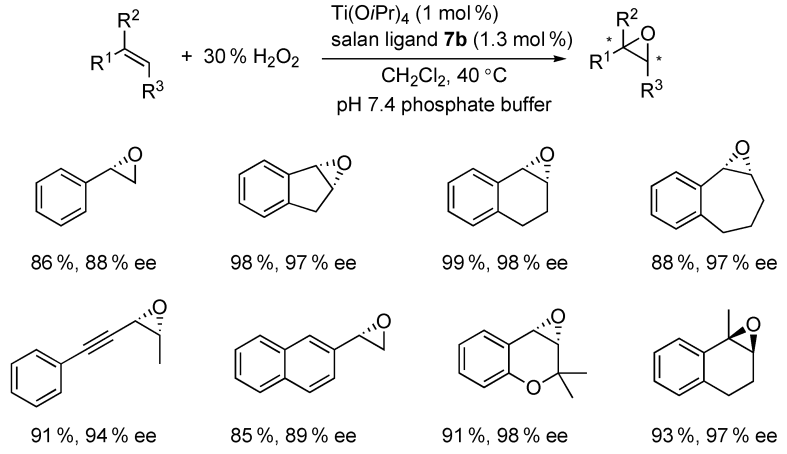
both yield and enantioselectivity. However, further substitution of another *ortho*-position adversely affected both parameters. Introduction of a substituent such as alkyl, phenyl, and alkoxy groups at the *ortho*-position also gave the epoxide in higher yield and enantioselectivity. Finally, compound **7b**, which has an *ortho*-methoxyphenyl group, was found to be the ligand of choice in terms of enantioselectivity and ease of preparation.

The substrate scope was examined with the in situ prepared Ti(salan) complex from $Ti(OiPr)_4$ and the salan ligand **7b** (Scheme 5) [9]. Reactions of terminal, *cis*-disubstituted and trisubstituted conjugate olefins gave the corresponding epoxides with high enantioselectivity. However, a high catalyst loading of 5 mol % $Ti(OiPr)_4$ and 6 mol % **7b** was necessary to obtain satisfactory yields. Moreover, in the reaction of indene and chromene, significant amounts of the epoxide ring-opening byproducts were observed. Indeed, we found that the pH of the aqueous phase gradually decreased as the reaction proceeded. Consequently, the reaction was carried out under pH control.



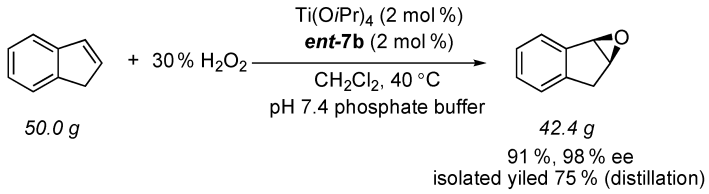

**Scheme 5** Asymmetric epoxidation under unbuffered conditions.

In the presence of pH 7.4 phosphate buffer, the formation of byproducts could be effectively suppressed, and a brief optimization of the reaction temperature and the substrate concentration yielded a highly practical asymmetric epoxidation that used only 1 mol % of the catalyst (Scheme 6) [10]. In all cases, epoxides were obtained in high yields and without the loss of enantioselectivity.



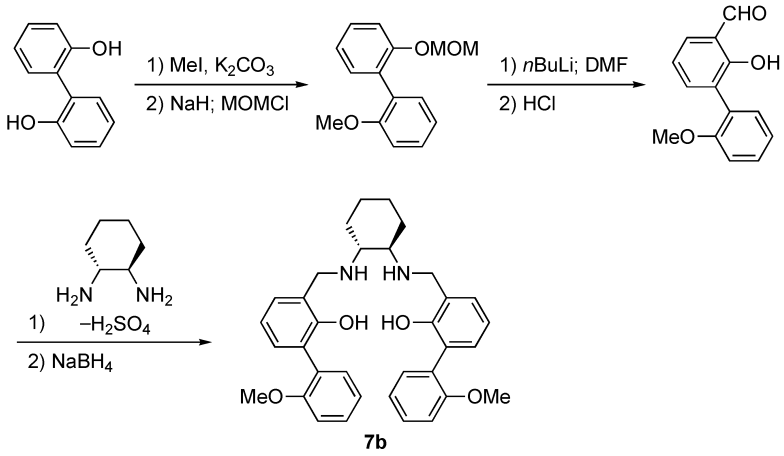

**Scheme 6** Asymmetric epoxidation under phosphate-buffered conditions.

This epoxidation protocol was efficiently applied to a multigram scale synthesis of indene oxide. 42.4 g of the epoxide could be obtained with 98 % ee after purification by distillation (Scheme 7) [11].




**Scheme 7** Asymmetric epoxidation of indene on a multigram scale.

Finally, the ease of preparation of ligand **7b** makes the present reaction truly practical. Ligand **7b** was prepared from commercially available 2,2'-biphenol in five steps (Scheme 8).




**Scheme 8** Synthesis of salan ligand **7b**.

## CONCLUSION

We have developed a general and highly practical asymmetric epoxidation using aqueous hydrogen peroxide as the oxidant. The catalyst can be prepared in situ, and the salan ligand is easily accessible.

## ACKNOWLEDGMENTS

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