Catalytic Enantioselective Epoxidation of Unfunctionalized Olefins: Utility of a Ti(O*i*-Pr)$_4$–Salan–H_2O_2 System

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Abstract: Salan ligands bearing an *ortho*-substituted phenyl group at C3 and C3′ were found to serve as an effective auxiliary of a Ti(O*i*-Pr)$_4$–salan–H_2O_2 system for enantioselective epoxidation. Simple olefins were converted into the corresponding epoxides in good to excellent enantioselectivity.

Key words: asymmetric catalysis, epoxidations, titanium, hydrogen peroxide, salan ligand

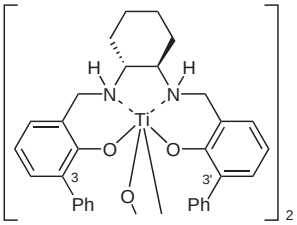

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Figure 1 Di-μ-oxo titanium–salan complex (**1**)

Optically active epoxides exist in many natural products and are of importance as versatile building blocks in organic synthesis. Asymmetric epoxidation of olefins is the most direct and useful method for the preparation of chiral epoxides and enormous numbers of epoxidation reactions have been reported.[1] However, the development of highly enantioselective epoxidation of unfunctionalized olefins using aqueous hydrogen peroxide as an oxidant is still a challenging theme for synthetic chemists and significant efforts have been devoted toward this area.[2]

Recently, we have found that a di-μ-oxo titanium–salalen complex is an effective catalyst for asymmetric epoxidation of unfunctionalized olefins with aqueous hydrogen peroxide.[3] Although the complex induces good to excellent enantioselectivity in epoxidation of various olefins, its structure is rather complicated and it measures nearly two thousands in molecular weight. Moreover, the synthetic method including intramolecular Meerwein–Ponndorf–Verley reduction as the key step was poorly applicable to the preparation of related titanium–salalen complexes. In order to overcome these problems, we turned our attention to a di-μ-oxo titanium–salan complex, which could be prepared more easily than the corresponding titanium–salalen complex. In the preliminary study, complex **1** (Figure 1) bearing a phenyl group at C3 and C3′ was found to show high enantioselectivity in epoxidation of various olefins.[4] However, high catalyst loading was needed to achieve satisfying yields. Consequently, we focused on the improvement of titanium–salan-catalyzed epoxidation.

First, we examined catalytic activities of various titanium–salan complexes in epoxidation of styrene. Each complex was prepared in situ from Ti(O*i*-Pr)$_4$ and a corresponding salan ligand in dichloromethane and the resultant solution was used without isolation and purification.[5] The results are summarized in Table 1. Presence of an *ortho*-substituted phenyl group at C3 and C3′ achieved increased effectiveness of salan ligands in both yield and enantioselectivity. The enantioselectivity was not very affected by the electronic nature of the substituent. Particularly, salans **2b**, **2g**, **2k** and **2l** showed better results than the prototype **2a**, in terms of enantioselectivity and yield. The reactions with the ligand such as **2e** or **2n** possessing a sterically more hindered 3,3′-aryl group, however, gave very low yield (entries 5 and 14). The epoxidation of 1,2-dihydronaphthalene with them also proceeded sluggishly and decreased ee were obtained.[6]

We chose salan **2b**, with which the highest enantioselectivity was observed, and salan **2g**, with which good enantioselectivity and the best yield were realized, as the test ligands and investigated epoxidation of various olefins using 5 mol% of Ti(O*i*-Pr)$_4$ and 6 mol% of a salan ligand (Table 2).[7] The epoxidation of cyclic olefins gave excellent enantioselectivity (entries 3–6). Generally, the reactions with salan **2g** gave better yields than those with **2b**. However, when the epoxidation produced an acid-sensitive epoxide such as indene oxide, 2,2-dimethyl-2*H*-chromene oxide or 4-methyl-1,2-dihydronaphthalene oxide, the reaction with **2g** gave an inferior yield to that with **2b**, due to a decomposition of the product (entries 3, 6, and 8). Epoxidation of acyclic olefins also proceeded with high enantioselectivity greater than 87% ee (entries 1, 2, and 7). The reaction was stereospecific and no formation of *trans*-epoxide was observed in the epoxidation of *cis*-enyne (entry 7).

Although the detailed mechanism is unclear at the present, we have proposed that a peroxo species, which is activated by hydrogen bonding between the amino proton and the oxygen atom of the peroxo unit, is the active species in the epoxidation using di-μ-oxo titanium–salan complex

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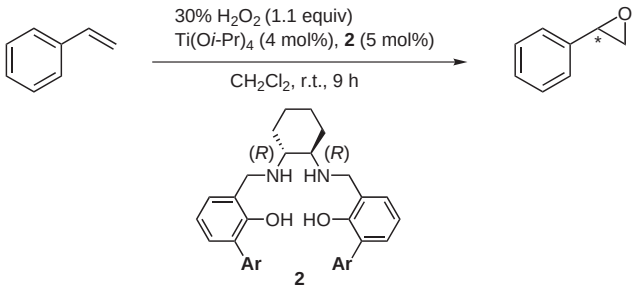
Table 1 Asymmetric Epoxidation of Styrene



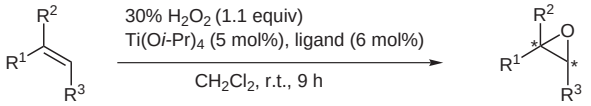
Entry	Ar	Yield (%)[a]	ee (%)[b]	Config[c]
1	Ph (**2a**)	27	78	*S*
2	*o*-$MeOC_6H_4$ (**2b**)	62	89	*S*
3	*m*-$MeOC_6H_4$ (**2c**)	39	81	*S*
4	*p*-$MeOC_6H_4$ (**2d**)	28	83	*S*
5	2,6-di(MeO)C_6H_3 (**2e**)	5	67	*S*
6	*o*-MeC_6H_4 (**2f**)	52	85	*S*
7	*o*-$CF_3C_6H_4$ (**2g**)	71	87	*S*
8[d]	*o*-EtC_6H_4 (**2h**)	48	87	*R*
9	*o*-$EtOC_6H_4$ (**2i**)	49	83	*S*
10	*o*-$BnOC_6H_4$ (**2j**)	55	85	*S*
11[d]	*o*-Biphenyl (**2k**)	56	88	*R*
12[d]	1-Naphthyl (**2l**)	65	87	*R*
13[d]	2-Naphthyl (**2m**)	36	85	*R*
14	9-Anthracenyl (**2n**)	11	85	*S*

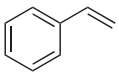
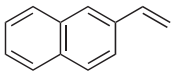
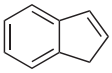
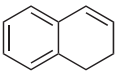
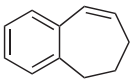
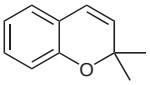
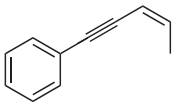
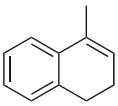
[a] Determined by ^{1}H NMR (400 MHz) spectroscopic analysis.
[b] Determined by HPLC analysis (CHIRALCEL OD-H).
[c] Determined by comparison of the elution order with that of the authentic sample in HPLC analysis.
[d] (*S*,*S*)-Salan was used.

(**1**, Figure 2).[4] The X-ray study of the complex **1** has revealed that it has a *cis*-β structure,[4] in which two phenyl groups at C3 and C3′ lie close to each other and the ligand conformation is stabilized by a CH–π interaction between the phenyl group and the benzene ring of the salan skeleton. The peroxo species is also expected to adopt a *cis*-b configuration. With the ligand possessing an *ortho*-disubstituted phenyl group, the two groups should cause a steric repulsion and the stabilization through the CH–π interaction should be precluded; thus, introduction of an *ortho*-disubstituted phenyl group should have a significant effect on a configuration of a peroxo species and adversely affect the desired epoxidation. In contrast, an *ortho*-monosubstituted phenyl group should not exert the adverse effect but probably strengthen the asymmetric atmosphere constructed by a salan ligand.

In conclusion, the Ti(O*i*-Pr)$_4$–3,3′-(*ortho*-substituted phenyl)salan (**2b** or **2g**)–H_2O_2 system was found to be more effective for asymmetric epoxidation of unfunctionalized olefins than the Ti(O*i*-Pr)$_4$–3,3′-phenylsalan (**2a**)–H_2O_2 system. The salan ligands are readily available and small in molecular size,[4] and the asymmetry-inducing ability of **2b** or **2g** in the epoxidation of conjugated olefins is almost equal to that of the sophisticated salalen ligand.[3] Thus, the present study demonstrates the high potentiality of 3,3′-(*ortho*-substituted phenyl)salan as the chiral auxiliary. Clarification of the precise role of the *ortho*-substituents and applications of the system to other oxidation reactions are in progress.

Table 2 Asymmetric Epoxidation of Various Olefins



Entry	Ligand	Olefin	Yield (%)[a]	ee (%)	Config[b]
1	**2b**		68	89[c]	*S*
	2g		80	87[c]	*S*
2	**2b**		82	90[d]	*S*
	2g		83	90[d]	*S*
3[e]	**2b**		86	98[f]	1*S*,2*R*
	2g		77	98[f]	1*S*,2*R*
4	**2b**		89	98[f]	1*S*,2*R*
	2g		93	98[f]	1*S*,2*R*
5	**2b**		66	97[g]	5*S*,6*R*
	2g		78	98[g]	5*S*,6*R*
6	**2b**		75	>99[f]	3*S*,4*S*
	2g		44	>99[f]	3*S*,4*S*
7	**2b**		84	94[c]	2*R*,3*S*
	2g		92	96[c]	2*R*,3*S*
8[e]	**2b**		81	96[f]	1*R*,2*S*
	2g		71	93[f]	1*R*,2*S*

[a] Determined by ^{1}H NMR (400 MHz) spectroscopic analysis.
[b] Determined by comparison of the elution order with that of the authentic sample in HPLC analysis.
[c] Determined by HPLC analysis (CHIRALCEL OD-H).
[d] Determined by HPLC analysis (CHIRALCEL OJ-H).
[e] Reaction time was 6 h.
[f] Determined by HPLC analysis (CHIRALCEL OB-H).
[g] Determined by HPLC analysis (CHIRALPAK AS-H).

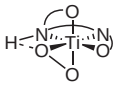


Figure 2 Proposed active species

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References and Notes

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(5) We have already reported that the in situ prepared titanium–salan complex was equally efficient to the isolated di-μ-oxo titanium–salan complex (**1**, ref. 4).

(6) Compound **2e**: 47%, 92% ee; compound **2n**: 23%, 87% ee.

(7) **General Experimental Procedure.**
To a CH_2Cl_2 solution of salan ligand (6 mol%, 0.50 mL) was added a CH_2Cl_2 solution of Ti(O*i*-Pr)$_4$ (5 mol%, 0.50 mL) under nitrogen atmosphere and the resultant solution was stirred at r.t. After 1 h, olefin (0.10 mmol)and subsequently 30% H_2O_2 (0.11 mmol) were added and the mixture was stirred at r.t. for 9 h. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography to give an epoxide. An ee was determined by HPLC analysis using a chiral stationary phase described in the footnote to Table 2.