Asymmetric Catalysis

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# Highly Enantioselective Epoxidation of Styrenes Catalyzed by Proline-Derived $C_1$-Symmetric Titanium(Salan) Complexes**

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Catalytic enantioselective epoxidation of olefins is a pivotal process for providing enantioenriched epoxides, which are very important molecules in a broad range of chemical transformations.[1,2] In particular, styrene oxide derivatives are useful and versatile chiral building blocks in asymmetric organic transformations. Although a wide variety of chiral catalysts (including transition-metal-based complexes and organocatalysts) have been developed for the asymmetric epoxidation of olefins, there are few catalysts that can achieve high enantioselectivity in the epoxidation of styrene derivatives.[3–5] Manganese(salen)-catalyzed and Shi's ketone-catalyzed systems are the well-established methods for asymmetric epoxidation of unfunctionalized olefins. However, the enantioselectivity (generally 80–90% *ee*) observed in the epoxidation of styrenes is inadequate when compared to the higher level of enantioselectivity in other olefins,[4–6] and here the use of economically acceptable and environmentally sustainable hydrogen peroxide as an oxidant would be more favorable.[7] In fact, our research group has introduced asymmetric epoxidation of unfunctionalized olefins using aqueous hydrogen peroxide as the oxidant in the presence of titanium(salalen) **1** and salan **2** catalysts (Figure 1; salen = *N*,*N*′-bis(salicylidene)ethylenediamine anion, salan = reduced salen, salalen[8] = half-reduced salen).[9,10] Although a variety of olefins such as terminal, *cis*-disubstituted, and trisubstituted olefins have been effectively converted into the epoxides in high enantiomeric excesses, the enantioselectivity observed in the epoxidation of styrene derivatives was insufficient. Even with the highly elaborate titanium(salalen) complex **1**, in which the ligand has two chiral centers and two chiral axes, the *ee* value of styrene oxide was only 93%.[9a] Herein, we report the development of simpler and highly enantioselective titanium catalysts for the epoxidation of styrenes. The catalysts are derived from the naturally occurring α-amino acid proline, and achieve high enantioselectivity of up to 98% *ee*.

In the previous study, we had prepared a variety of salan ligands and examined their catalytic performance in asymmetric epoxidation of olefins.[10b] As a result, we found that the substitution of the phenolic benzene ring with another group had a substantial impact on the catalyst durability, but the asymmetric induction was affected to only a certain extent by the substitution. Thus, we presumed that the 1,2-diamine moiety played a major role in the asymmetric induction. Indeed, the replacement of 1,2-cyclohexanediamine with 1,2-diphenylethylenediamine significantly reduced the enantioselectivity. This result strongly indicates that the tuning of the diamine moiety leads to improvement of the asymmetric induction. However, other $C_2$-symmetric 1,2-diamine derivatives showed inferior results. Meanwhile, the other option is to employ $C_1$-symmetric 1,2-diamines: the effective differentiation of the two amine functionalities of salan ligands is a problem that needs to be solved when taking into condideration our proposal that amine-hydrogen atom(s) on the ligand play a crucial role in making an active peroxotitanium species more electrophilic through hydrogen bonding (Figure 2). Moreover, we proposed that salan ligands adopt a *cis*-β configuration in the peroxotitanium complex. Also, as two stereoisomers (Δ and Λ) are possible at the chiral metal center, the selective formation of a single isomer is another key to success.

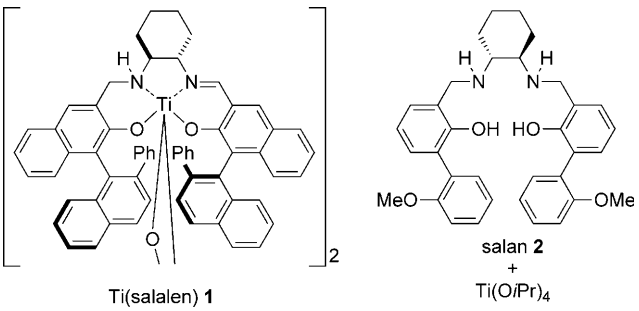


***Figure 1.*** Ti(salalen) **1** and Ti(salan) **2** catalysts.

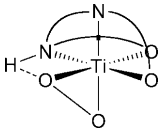

***Figure 2.*** The proposed active species that is activated by hydrogen bonding. O–N–N–O represents the ligand backbone.

Taking into consideration these prerequisites, we planned to incorporate a pyrrolidine ring in the diamine moiety and focused our attention on proline (Scheme 1). Proline seemed to be best suited for our purpose, because 1) it can be readily transformed into a 1,2-diamine form, 2) differentiation of the two amine functionalities is feasible by introducing the right-side amine moiety as a secondary amine, 3) ring strain induced by the pyrrolidine ring makes its titanium complex

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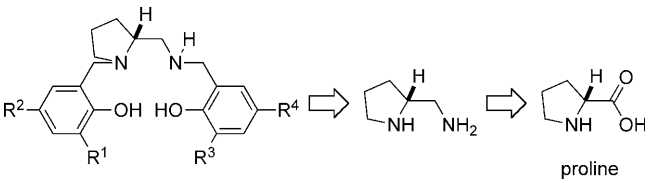
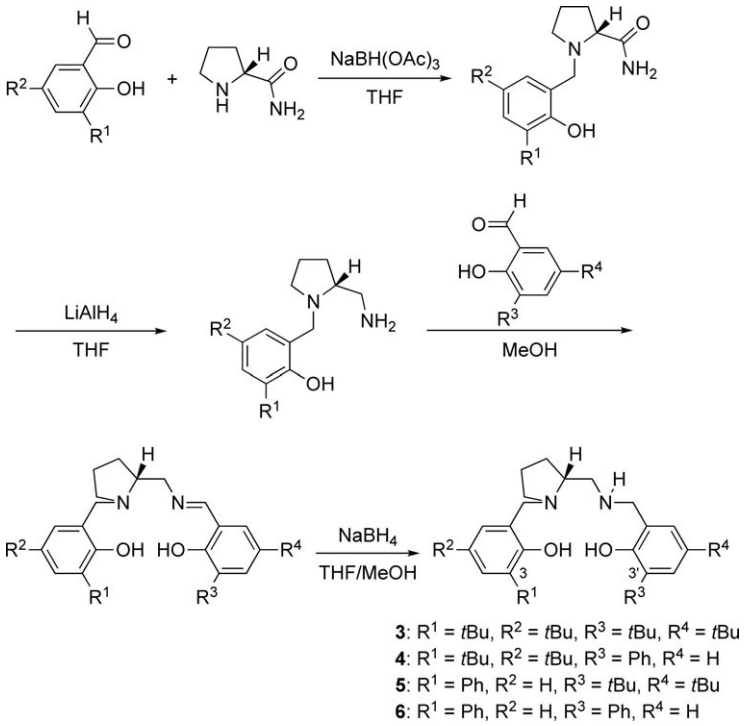



***Scheme 1.*** Retrosynthetic analysis of the proline-derived salalen ligand.

a single *cis*-β structure,[11,12] 4) an N–H functionality can be incorporated, and 5) both enantiomers are commercially available in enantiopure form.

The synthetic route is illustrated in Scheme 2.[13] Reductive amination between salicylaldehydes and commercially available prolinamide, which can be readily prepared from proline, gave amide intermediates. Reduction of the amide functionality by lithium aluminum hydride and the subsequent dehydrating condensation with another salicylaldehydes afforded the salalen compounds. Further reduction of the imine bond gave the desired proline-derived $C_1$-symmetric salan ligands **3**–**6**.

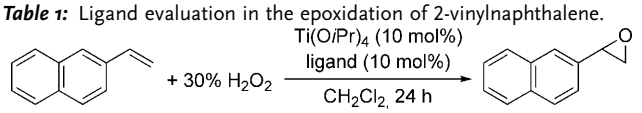
With new proline-derived salan ligands **3**–**6** in hand, we examined the asymmetric epoxidation of 2-vinylnaphthalene




***Scheme 2.*** Synthesis of proline-derived salalen ligands **3**–**6**.

as a model substrate. As expected, ligand **3** could promote the epoxidation, albeit with very low yield and enantioselectivity (Table 1, entry 1). Although substitution of the *tert*-butyl group at the C3′-position with a phenyl group resulted in the complete loss of enantioselectivity, the introduction of the C3-phenyl group significantly improved both the yield and enantioselectivity (compare entries 2 and 3 in Table 1).

***Table 1:*** Ligand evaluation in the epoxidation of 2-vinylnaphthalene.




| Entry | Ligand | *T* [°C] | Conc. [mol L$^{-1}$] | Conv. [%][a] | Yield [%][b,c] | *ee* [%][d,e] |
|---|---|---|---|---|---|---|
| 1 | **3** | 25 | 0.2 | 13 | 8 | 28 (*S*) |
| 2 | **4** | 25 | 0.2 | 10 | 3 | 1 (*R*) |
| 3 | **5** | 25 | 0.2 | 55 | 32 | 88 (*S*) |
| 4 | **6** | 25 | 0.2 | 38 | 9 | 78 (*S*) |
| 5 | **5** | 0 | 0.2 | 71 | 64 | 94 (*S*) |
| 6 | **6** | 0 | 0.2 | 46 | 38 | 92 (*S*) |
| 7[f] | **5** | −20 | 0.2 | 58 | 52 | 94 (*S*) |
| 8[f] | **6** | −20 | 0.2 | 52 | 44 | 96 (*S*) |
| 9[f] | **6** | −20 | 1.0 | 90 | 74 | 96 (*S*) |
| 10[f,g] | **6** | −20 | 1.0 | 96 | 95 (91) | 97 (*S*) |
| 11[f,g,h] | **6** | −20 | 1.0 | 44 | 43 | 97 (*S*) |

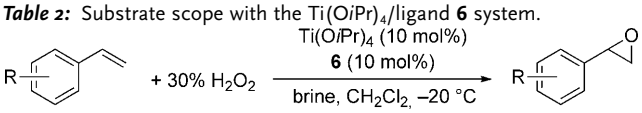
[a] Olefin conversion was determined by $^1$H NMR spectroscopy (400 MHz). [b] Epoxide yield was determined by $^1$H NMR spectroscopy (400 MHz). [c] Number in parentheses corresponds to the yield of isolated product. [d] Enantiomeric excess was determined by HPLC on a chiral stationary phase (Daicel CHIRALCEL OJ-H, eluent: *n*-hexane/*i*PrOH 99.9:0.1). [e] Absolute configuration was determined by comparison of the optical rotation with the literature value. [f] Reaction time was 48 h. [g] In the presence of brine. [h] 2 mol% of Ti(O*i*Pr)$_4$ and 2 mol% of **6**.

Ligand **6**, bearing phenyl groups at both the C3- and C3′-positions, also gave comparable enantioselectivity (Table 1, entry 4). Notably, the N-methylated ligand and the corresponding salalen ligand did not afford the epoxide. Thus, the importance of the N–H functionality was again confirmed. Lowering the reaction temperature led to significant improvement of both the yield and enantioselectivity, and ligand **6** showed higher enantioselectivity compared to ligand **5** at −20 °C (Table 1, entries 5–8). The concentration also affected the productivity of the reaction, and a higher yield was obtained at an olefin concentration of 1.0 mol L$^{-1}$ (Table 1, entry 9). Finally, the addition of brine gave the highest yield of 95% with 97% *ee* (Table 1, entry 10). Significantly, no by-product was observed by $^1$H NMR analysis under these reaction condition. The catalyst turnover number was as high as 22 in the presence of 2 mol% of the catalyst without eroding the enantioselectivity (Table 1, entry 11). As mentioned above, even with the highly elaborate titanium(salalen) **1**, which has four chiral components, the *ee* value observed in the epoxidation of styrene was only 93%. In comparison, this new proline-derived salan ligand has only one chiral center, but it achieves higher enantioselectivity.

The Ti(O*i*Pr)$_4$/ligand **6** system was successfully applied to the asymmetric epoxidation of a variety of styrene derivatives (Table 2). Styrene underwent the epoxidation with high enantioselectivity of 98% *ee* (Table 2, entry 1). An electron-donating methyl group was tolerant and the epoxides were obtained with high enantioselectivity (Table 2, entries 2–4). The reaction of styrenes with an electron-withdrawing chloro group was also highly enantioselective,

***Table 2:*** Substrate scope with the $Ti(OiPr)_4$/ligand **6** system.




| Entry | R | Conv. [%][a] | Yield [%][b,c] | *ee* [%][d,e] |
|---|---|---|---|---|
| 1 | H | 73 | 71 (60) | 98 (*S*) |
| 2 | *o*-Me | 70 | 70 (64) | 97 (+) |
| 3 | *m*-Me | 85 | 84 (70) | 98 (+) |
| 4 | *p*-Me | 80 | 80 (74) | 98 (*S*) |
| 5 | *o*-Cl | 21 | 16 (14) | 96 (*S*) |
| 6 | *m*-Cl | 69 | 66 (55) | 98 (*S*) |
| 7 | *p*-Cl | 67 | 66 (58) | 98 (*S*) |

[a] Olefin conversion was determined by $^1$H NMR spectroscopy (400 MHz). [b] Epoxide yield was determined by $^1$H NMR spectroscopy (400 MHz). [c] The numbers in parentheses correspond to the yield of isolated product. [d] Enantiomeric excess was determined by HPLC on a chiral stationary phase. [e] Absolute configuration was determined by comparison of the optical rotation with the literature value.

but the *ortho*-substitution retarded the reaction progress (Table 2, entries 5–7). In all cases, high enantioselectivity of 96–98% *ee* was achieved. The catalytic system was successfully applied to *cis*-olefins, and 1,2-dihydronaphthalene underwent the epoxidation in >99% yield with 97% *ee*. However, the reactions of 4-phenyl-1-butene and *trans*-β-methylstyrene, which are also challenging substrates in the field of catalytic asymmetric epoxidation, were very sluggish.

In summary, we have developed a novel $C_1$-symmetric salan ligands derived from proline as well as investigated the highly enantioselective epoxidation of styrene derivatives with a titanium catalyst and aqueous hydrogen peroxide as the oxidant. Synthetically valuable styrene oxides were obtained with high enantioselectivity ranging from 96 to 98% *ee*, irrespective of the electronic nature of the substituents and substitution pattern.[14] Further studies on asymmetric catalysis of metal complexes bearing the proline-derived ligands are now in progress in our laboratory.

## Experimental Section

General procedure for the asymmetric epoxidation of styrene derivatives with ligand **6**: Ligand **6** (46.5 mg, 10 mol%) was dissolved in a solution of $Ti(OiPr)_4$ (0.10 mol L$^{-1}$, 1.0 mL, 10 mol%) in dichloromethane. After stirring the mixture at room temperature for 30 min the styrene derivative (1.0 mmol) was added. The resultant solution was cooled to −20 °C before brine (0.5 mL) was added. After the addition of 30% hydrogen peroxide (170 μL, 1.5 mmol), the reaction mixture was stirred at −20 °C for 48 h. The mixture was extracted with dichloromethane, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on basic silica gel (eluent: *n*-pentane/diethyl ether 20:1 or *n*-pentane) to give the desired epoxide. The enantiomeric excess was determined by HPLC on a chiral stationary phase.

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