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Efficient soluble polymer-supported tartrate/Ti catalyst for asymmetric oxidation of prochiral sulfides

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Abstract—A group of soluble polymer-supported chiral tartrate ligands was prepared by liquid-phase synthesis with ligand diversity strategy. Moderate to excellent chemical yields and enantiomeric excesses were obtained by using soluble polymer-supported tartrate ester in asymmetric oxidation of prochiral sulfides using $Ti(O\text{-}i\text{-}Pr)_4$/cumyl hydroperoxide, and the workup was greatly simplified. The influence of substituent in chiral tartrate ligands on the enantioselectivities of the reaction was disclosed.

Optically active sulfoxides are important chiral reagents, building blocks and pharmaceutical targets.[1] As an efficient method for asymmetric synthesis of sulfoxides, recently chiral metal complexes in combination with an oxidant have attracted much attention and a variety of catalytic systems therefore have been developed.[2] The use of chiral complexes involving titanium and tartrate, first introduced by Modena and Kagan independently, is one of the most efficient and prominent catalysts for enantioselective sulfoxidations.[2,3]

Some heterogeneous versions of asymmetric sulfoxidations have also been described. In 2003, Sudalai et al. developed a heterogeneous catalytic system with WO_3 as a catalyst precursor, $(DHQD)_2$-PYR as a ligand and aqueous hydrogen peroxide as terminal oxidant.[4] The catalysis afforded the corresponding oxidation product with up to 65% ee. WO_3 was recovered by simple filtration and recycled at least five times. In 2005, Ding et al. described a new strategy with self-supported concept for the heterogenization of chiral titanium complexes by the in situ assembly of bridged multitopic BINOL ligands with $[Ti(O\text{-}i\text{-}Pr)_4]$ without using a support.[5] The assembled heterogeneous titanium catalysts showed excellent enantioselectivity in the oxidation of sulfides (up to >99% ee). The catalysts were highly stable and could be readily recycled and reused for over one month (at least eight cycles) without significant loss of activity and enantioselectivity.

However, there is no report of the immobilization of the Ti-tartrate ester-based asymmetric sulfoxidation catalyst using soluble-polymers for catalyst separation and reuse. Synthetic approaches utilizing soluble polymers couple the advantages of homogeneous solution chemistry such as high reactivity, lack of diffusion phenomena and ease of analysis with the advantages of solid phase methods, such as the use of excess of reagents, easy isolation and the purification of products. Therefore, this approach has been extensively applied in organic synthesis and catalysis in the past 10 years.[6] Recently the synthesis of soluble polymer-supported tartrate esters and their successful use with $[Ti(O\text{-}i\text{-}Pr)_4]$ and *tert*-butyl hydroperoxide (TBHP) as the oxidant in Sharpless epoxidation with high chemical yield and good to excellent ee had been reported.[7] Having interest in the application of soluble polymer-supported tartrate esters in the sulfide oxidations, here we describe the construction of a library of soluble polymer-bound tartrate ligands and their use in the asymmetric oxidation of prochiral sulfide.

In order to increase the loading as much as possible, polyethylene glycol monomethyl ether (MeOPEGOH, MW2000) was chosen as soluble support. It possesses lowest molecular weight in the MeOPEGOHs that are good solid at room temperature. A small library of tartrate esters **L1**–**L8** were synthesized from the one-pot reaction of L-(+)-tartaric acid, MeOPEGOH (MW2000) and alcohols (ROH) with molar ratio of MeOPEGOH/ROH = 1:4.25 and acid/(MeOPEGOH + ROH) = 1:2.10 by the known procedure (Scheme 1).[7,8]

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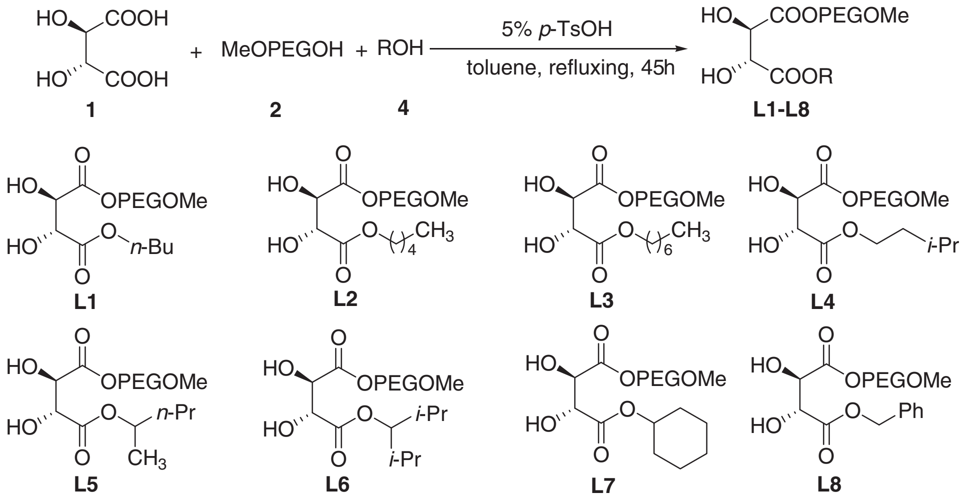
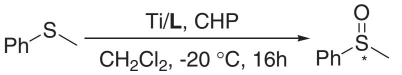


Scheme 1. Synthesis of PEG-supported tartrates.

After the reaction, the solvent toluene was removed by distillation under reduced pressure; then the resulting solid was dissolved using a small amount of CH_2Cl_2. Diethyl ether was added to the resulting solution to precipitate tartrate ester under ice-salt cooling, and tartrate esters were obtained by filtration.

With the ligand library mentioned above in hand, brief screening of the library with eight kinds of MeOPEG-supported tartrate esters was carried out with the combination of Ti(O-*i*-Pr)/**L**/substrate = 50:200:100 by Kagan's procedure[9] in the asymmetric oxidation of methyl phenyl sulfide (Table 1). It was observed that methyl phenyl sulfide underwent the oxidation with 80% cumyl hydroperoxide (CHP) at −20 °C in the presence of 50 mol % of **L**-Ti(IV) complex prepared by in situ mixing **L** and Ti(O-*i*-Pr)$_4$. To our delight, up to 98% ee was achieved with the tartrate ligand **L1** prepared from the straight chain alcohols (Table 1, entry 1). Similar ligands **L2**–**L4** also indicated excellent enantioselectivity (entries 2, 3 and 8). Although comparing to the size of PEG monoether group, the effect of another alkoxyl group, especially the straight chain alkoxyl groups, on the performance of the ligands should not be so significant, in fact, it is (entries 2 and 3). When the catalyst loading was decreased, the enantioselectivity dramatically went bad (entries 5–7). The steric effects of R group have big influence on the enantioselectivity of the oxidation. Ligands **L6** and **L7** with bulky R substituents in the Ti-catalyzed oxidation reaction gave 8% ee and 85% ee, respectively (entries 10 and 11). Ligands **L8** with aromatic benzyl group could give 88% ee (entry 12). The electronic property of R group appears to have some influence on the enantioselectivity in the oxidation. Especially, **L5** with another chiral carbon in R group gave racemic oxidation product in 58% yield (entry 9). This can be explained by the mechanism proposed by Kagan.[8] In the bimetallic species catalyzed oxidation reaction, the tartrate acts as a tridentate ligand and the chiral carbon of ester part may influence the nucleophilic attacking direction of sulfide.

Table 1. Asymmetric oxidation of phenyl methyl sulfide with **L**/Ti complex



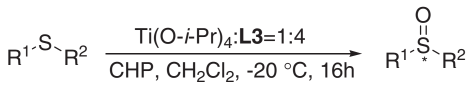
Entry	Ligand	Ti (mol %)	Ti:L	Yield[a] (%)	ee[b] (%)
1	**L1**	50	1:4	63	98
2	**L2**	50	1:4	88	90
3	**L3**	50	1:4	62	95
4	**L3**	50	1:2	52	39
5	**L3**	30	1:4	79	86
6	**L3**	15	1:4	88	72
7	**L3**	10	1:4	90	59
8	**L4**	50	1:4	90	97
9	**L5**	50	1:4	58	0
10	**L6**	50	1:4	54	8
11	**L7**	50	1:4	78	85
12	**L8**	50	1:4	85	88

[a] Isolated yield.

[b] The ees were determined by chiral HPLC analysis using Chiralcel OD-H (hexane/*i*-PrOH = 90:10); The absolute configurations were determined as *S* by comparison of the HPLC results with the data in the literature.

To demonstrate the flexibility of this methodology, the oxidation of a series of sulfide was studied with Ti/**L** complexes under the optimized conditions. The screening of chiral ligands led us to understand the influence of R substituent in MeOPEG-supported ligands on the enantioselectivity. Although **L1**/Ti and **L4**/Ti complexes catalyzed the oxidation of methyl phenyl sulfide to give the best enantioselectivity (98% ee and 97% ee, respectively) in all catalysts, strangely, both **L1**/Ti and **L4**/Ti complexes showed relative lower enantioselectivity for other substrates. Finally, we chose ligand **L3** to construct the Ti-catalyst. As shown for aryl methyl sulfide (Table 2, entries 1–7), the oxidation afforded the corresponding chiral products in high yields (62–96%) with good to excellent enantioselectivities (81–99% ee). Outstanding selectivity of 99% ee was achieved in the oxidation of *p*-chlorophenyl methyl sulfide (entry 4). These

Table 2. **L3**–Ti (IV) catalyzed asymmetric oxidation of prochiral sulfides[a]



Entry	R^1	R^2	Yield[b] (%)	ee[c] (%)
1	C_6H_5	Me	62	95[d]
2	4-MeC_6H_4	Me	66	90[d]
3	4-$MeOC_6H_4$	Me	77	81[d]
4	4-ClC_6H_4	Me	91	99[e]
5	4-Br–C_6H_4	Me	82	95[f]
6	4-NO_2	Me	70	96[f]
7	2-Naphthyl	Me	96	88[d]
8	C_6H_5	Et	80	57[d]
9	C_6H_5	Bn	78	33[d]

[a] 50 mol % catalyst was used.

[b] Isolated yield.

[c] Ees were determined by using chiral HPLC analysis. The absolute configurations were determined as *S* by comparison of the HPLC results with the data in the literature.

[d] By Chiralcel OD-H column (hexane/*i*-PrOH = 90:10).

[e] By Chiralcel AS-H column (hexane/*i*-PrOH = 80:20).

[f] By Chiralcel OD-H column (hexane/*i*-PrOH = 99:1).

results indicated that the reaction system has some tolerance to the pattern and electronic properties of the substituent on the phenyl ring of substrates. It is worth noting that the enantiomeric excesses are in general compared to the corresponding low molecular template. Sulfides with benzyl or ethyl showed lower enantioselectivity than that with methyl (entries 8 and 9).

In our experiment, ^1H NMR spectroscopic analysis showed that the recovered tartrates have the same characteristic peaks as before the reaction, indicating that in principle the soluble polymer-supported ligand might be reused. Ligand **L3** was recycled four times, and the ees of first recycle to fourth recycle were 95%, 94%, 93% and 91%, respectively, and the isolated yields remained at 62–67%. The recovery of catalyst can be carried out by simple precipitation and filtration. The ligands were stable and generally the recovery was >97%. During the work-up, the product can be directly extracted with diethyl ether after the reaction was quenched, and this greatly simplifies the isolation of products.

In summary, the asymmetric oxidation of prochiral thioethers with cumyl hydroperoxide catalyzed by a soluble polymer-supported Ti-catalyst provides a simple and effective procedure for the preparation of chiral sulfoxides in good enantiomeric purity. The previous concept of constructing chiral ligand library by liquid-phase synthesis has been extended to the oxidation of prochiral thioethers.

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