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Efficient soluble polymer-supported Sharpless alkene epoxidation catalysts

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High chemical yields and good enantiomeric excesses are obtained by using soluble polymer-supported tartrate ester in the epoxidation of *trans*-hex-2-en-1-ol using Ti(OPr^i)$_4$/ *tert*-butyl hydroperoxide.

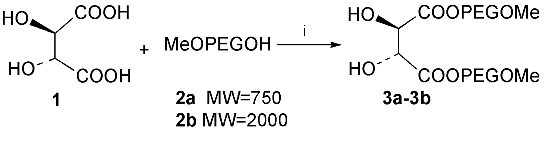
Since the initial solid-phase synthesis of oligopeptides was introduced by Merrifield,[1] the use of insoluble polymers as supports for reagents and catalysts for various reactions has increased and achieved wide recognition.[2–7] Although insoluble polymer-supported reactive species have many advantages, there are limitations associated with these species.[8] Soluble polymer-bound ligands, reagents, or catalysts as an alternative to insoluble polymer-bound reagents or catalysts have undergone considerable progress in recent years.[9–11] 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 use of excess of reagents, easy isolation and purification of products.

However, there are few reports of the immobilization of the Sharpless Ti–tartrate ester-based asymmetric alkene epoxidation catalyst using souble-polymers. The linear poly(tartrate ester) system developed by Sherrington and coworkers was successful,[12] the observed enantioselectivity for epoxidation was up to 79% ee (enantiomer excess). However compared with the 98% ee obtained by the solution-phase reaction with L-(+)-dimethyl tartrate, the enantioselectivity was moderate and the catalytic system requires improving. We now report the synthesis of a group of tartrate esters and their use with titanium tetraisopropoxide [Ti(OPr^i)$_4$] and *tert*-butyl hydroperoxide (tBHP) as the oxidant in epoxidising *trans*-hex-2-en-1-ol in high chemical yield and good ee.

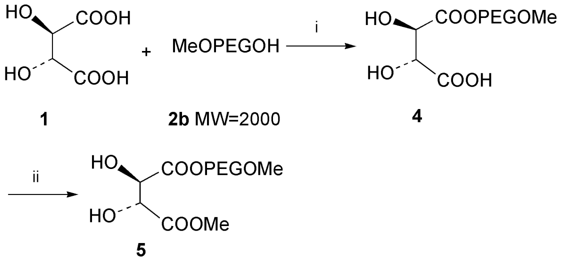
Tartrate esters **3a** and **3b** were synthesized from L-(+)-tartaric acid and polyethylene glycol monomethyl ether as described by Yamamoto and coworkers[13] (Scheme 1). After reaction, the solvent toluene was removed by distillation under reduced pressure at the end of the reaction and the resulting solid was then dissolved using a small amount of CH_2Cl_2. Diethyl ether was added to the resulting solution to precipitate the tartrate ester under ice-salt cooling, and tartrate esters were obtained by filtration. Tartrate **5** was synthesized from L-(+)-tartaric acid by two steps (Scheme 2). Tartrates **3a**, **3b** and **5** were identified by ^{1}H NMR and IR.[14]

Tartrates **3a**, **3b** and **5** were used as ligands in the epoxidation of **6** with Ti(OPr^i)$_4$/tBHP as shown in Scheme 3. Powdered activated 4 Å molecular sieves, tartrate ligand and Ti(OPr^i)$_4$ were first mixed in CH_2Cl_2 at −20 °C, then tBHP in isooctane was added and the mixture stirred for 1 h at −20 °C before **6** in CH_2Cl_2 was added. The resulting mixture was stirred for an additional 5 h at −20 to −15 °C, then the GC yield was determined. The mixture was treated according to workup A[15] with some modification. The CH_2Cl_2 was removed by distillation under reduced pressure at 25 °C, then diethyl ether added to the resulting mixture to precipitate the tartrate under vigorous stirring conditions, and filtered to obtain the slightly yellow tartrate ligand, with a recovery level of >98%. The filtrate was treated with ferrous sulfate and tartaric acid as described in workup A.[15] Product **7** was isolated *via* Kugelrohr distillation, and after **7** was derivatized as its acetate, the ee was determined with a chiral capillary gas chromatography column the chiral stationary phase of which was 2,6-di-*O*-benzyl-3-*O*-heptanoylcyclodextrin. Each peak was identified by GC/MS. Results are summarized in Table 1. The enantioselectivities varied significantly with different ligand : Ti ratios. With **3a**, **3b** and **5**, up to 93, 93 and 90% ee were obtained, respectively. Generally, isolated yields were low because of the small scale of the reactions, and neither GC yields nor isolated yields were optimized. There should, however, be considerable scope for optimization. Surprisingly, (−)-(2*S*,3*S*)-*trans*-**7** was obtained using **3a**, yet (+)-(2*R*,3*R*)-*trans*-**7** was obtained using **3b** or **5**. This was established by measuring the optical rotation and also by GC analyses. After the sample of **7** prepared using **3a** and another sample prepared using **3b** or **5** was mixed, the ee of the resulting mixture was lower than the ee of each single sample. The different absolute configuration of **7** resulting from different ligands may involve a contribution from molecular weight variation and conformational factors, but the influence of the linear polymer chain is not clear.

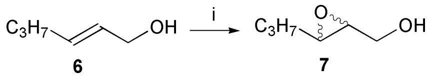
^{1}H NMR spectroscopic analysis showed the recovered tartrate to have the same characteristic peaks as before the reaction, indicating that in principle the soluble polymer-ligand might be reused. The ligand **3b** was recycled four times, but only moderate ee values were obtained. The ee from the first to fourth recycle were 49, 44, 32 and 30%, respectively. Although the recycle results were not satisfactory, the recovery of ligand



Scheme 1 *Reagents and conditions*: MeOPEGOH=MeO–$(CH_2CH_2O)_n$–CH_2CH_2OH; i, *p*-toluenesulfonic acid (5 mass%), *ca.* 115 °C, 45 h.



Scheme 2 *Reagents and conditions*: MeOPEGOH=MeO–$(CH_2CH_2O)_n$–CH_2CH_2OH; i, *p*-toluenesulfonic acid (5 mass%), *ca.* 115 °C, 45 h; ii, CH_2N_2, rt.



Scheme 3 *Reagents and conditions*: i, tartrate ester (6–48 mol%), Ti(OPr^i)$_4$ (5–20 mol%), Bu^{t}OOH (2 equiv.), 4 Å sieves, CH_2Cl_2, −20 °C to −15 °C, 5 h.

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Table 1 Epoxidation of *trans*-hex-2-en-1-ol with tBHP catalysed by L-(+)-tartrate ester and Ti(OPr^i)$_4$

Ligand	Molar ratio **6**:Ti:tartrate	*T*/°C	Reaction time[a]/h	Epoxide yield[b] (%)	Isolated yield[c] (%)	Ee (%)	Abs. config.
DMT[d]	100:5:6	−30	3	91	44	⩾98	(−)-2*S*, 3*S*-*trans*
DET[e]	100:5:6	−20	2.5	—	85	94	(−)-2*S*, 3*S*-*trans*
LPL[f]	100:17:20	−20	7	92	58[g]	79	(−)-2*S*, 3*S*-*trans*
CPL[h]	100: 25:50	−20	6	87	53	87	(−)-2*S*, 3*S*-*trans*
3a	100:5:6	−20	5	68	47	5	(−)-2*S*, 3*S*-*trans*
3a	100:20:24	−20	5	81	61	70	(−)-2*S*, 3*S*-*trans*
3a	100:20:48	−20	5	90	66	93	(−)-2*S*, 3*S*-*trans*
3b	100:5:6	−20	5	72	55	64	(+)-2*R*, 3*R*-*trans*
3b	100:5:10	−20	5	85	60	93	(+)-2*R*, 3*R*-*trans*
3b	100:10:12	−20	5	75	49	24	(+)-2*R*, 3*R*-*trans*
3b	100:20:24	−20	5	80	62	3	(+)-2*R*, 3*R*-*trans*
5	100:5:6	−20	5	79	60	90	(+)-2*R*, 3*R*-*trans*

[a] From addition of **6**. [b] By GC analyses. [c] After workup and Kugelrohr distillation. [d] DMT = L-(+)-dimethyl tartrate, see ref.12. [e] DET = L-(+)-diethyl tartrate, see ref. 15. [f] LPL = linear polytartrate ester ligand, see ref. 12. [g] After additional 12 h in freezer. [h] CPL = crosslinked polytartrate ester ligand, see ref. 16.

by simple precipitation and filtration aids in the isolation of products. The complex work-up required in the Sharpless procedure is considerably simplified and emulsions are avoided.

At present, we are further optimizing these reactions and epoxidising other substrates and pursuing the mechanism of catalysis and evaluating the recyclable characteristics of soluble polymer-supported tartrate ligands. We are also preparing analogs of the above ligands in an attempt to produce highly practical reusable soluble polymer-supported Sharpless epoxidation catalysts.

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14 *Characterization data* for **3a**, **3b** and **5**: **3a**, δ_H(DMSO-d$_6$) 5.52 (d, 2H), 4.40 (d, 2H), 4.19 (m, 4H), 3.32–3.64 (m, polyethylene glycol peaks), 3.24 (s, 6H). IR (film, cm^{-1}) 3450, 1750, 1250, 1110. **3b**, δ_H(DMSO-d$_6$) 4.41 (d, 2H), 4.19 (m, 4H), 3.32–3.64 (m, polyethylene glycol peaks), 3.24 (s, 6H). IR (KBr, cm^{-1}) 3400, 1745, 1245, 1110. **5**, δ_H(DMSO-d$_6$) 4.41 (s, 1H), 4.32 (d, 1H), 4.19 (m, 4H), 3.26–3.64 (m, polyethylene glycol peaks), 3.24 (s, 6H). IR (KBr, cm^{-1}) 3400, 1740, 1280, 1110.

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