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An improved heterogeneous asymmetric epoxidation of homoallylic alcohols using polymer-supported Ti(IV) catalysts

Jaana K. Karjalainen, Osmo E. O. Hormi * and David C. Sherrington
Department of Chemistry, University of Oulu, PO Box 333, FIN-90570 Oulu, Finland

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Abstract

Heterogeneous asymmetric epoxidation of homoallylic alcohols has been achieved using polymer-supported Ti(IV) catalysts with *tert*-butyl hydroperoxide as oxidant. The enantioselectivities and chemical yields obtained are significantly higher (ee values up to 80%) than with monomeric tartrate ligands. © 1998 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Chiral epoxy alcohols are versatile building blocks of high synthetic utility which are widely used in organic synthesis.[1] Despite their potential value only very few reports on the enantioselective synthesis of 3,4-epoxy alcohols have been published,[2,3] and none of these describe a highly efficient enantioselective procedure. We have previously reported on the synthesis of linear and branched/crosslinked poly(tartrate)s and have shown these optically active ligands to be highly effective in asymmetric epoxidations of *trans*- and *cis*-allylic alcohols with titanium tetraisopropoxide and *tert*-butyl hydroperoxide.[4–6] Thus we have been encouraged to examine the efficiency of these polymer-supported catalysts towards the epoxidation of homoallylic alcohols. In the present paper we would like to report a much improved method for the synthesis of chiral 3,4-epoxy alcohols.

2. Results and discussion

The branched/crosslinked polyester **3** was prepared by condensation polymerisation of L-(+)-tartaric acid and 1,8-octanediol as shown in Scheme 1.[5] The branching/crosslinking degree was determined as described previously by ^{1}H NMR.[5] These polymer ligands containing varying degrees of branching were

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* Corresponding author. E-mail: osmo.hormi@oulu.fi

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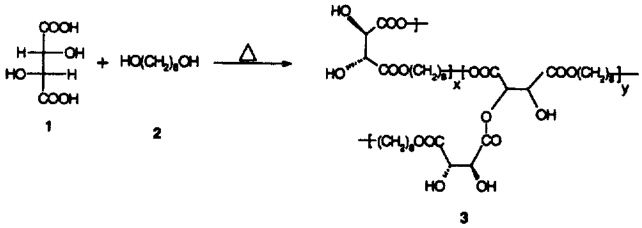
tested with four different homoallylic alcohols (Tables 1–4). We have previously pointed out that a high level of branching/crosslinking of the polymer ligand inhibited the enantioselective epoxidation of allylic alcohols.[5,6] However, in the case of homoallylic alcohols the effect was surprisingly much less significant.

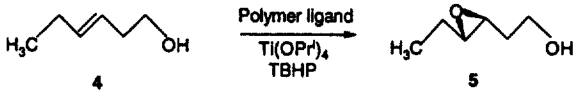


Scheme 1. Preparation of branched/crosslinked poly(tartrate)s. *Reagents and conditions*: toluene-*p*-sulfonic acid (3 mass%), 20 mol% excess of diol **2**, ca. 130°C, 4 days

The results summarised in Tables 1 and 2 allow us to make some interesting observations. There is no significant effect on enantioselectivity of the branching of the polymer ligand. Even using the polymer ligand having a degree of branching of 16% (Table 2, entry 4) still gave satisfactory enantioselectivity. The enantioselectivities varied from 38–54% as determined by chiral HPLC. The literature procedure[2] using monomeric L-(+)-dimethyl tartrate with titanium isopropoxide (Table 1, entry 1 and Table 2, entry 1) was followed, but the enantioselectivities as well as the chemical yields were both lower than using our polymer-supported analogue. However, Sharpless et al.[2] have reported slightly better enantioselectivities using L-(+)-diethyl tartrate with titanium isopropoxide, but both the enantioselectivities and the chemical yields were still lower than using our polymer-supported catalysts. The lack of substrate reactivity still remains a problem. In some cases the rate of reaction was high (Table 1, entry 4, Table 2, entry 3) but generally reaction times of up to 1 week were required to obtain 50% conversion. The reaction products were also prone to rearrangement to form isomeric tetrahydrofuranols. In some cases about 10–20% of uncharacterised by-products with long retention times were detected by GC or some non-GC-detectable side products were apparent from a shortfall in the mass balance. The recovery of polymer catalyst by simple filtration aids the isolation of products. The complex work-up required in the Sharpless procedure is remarkably simplified and foaming emulsions are avoided. One of the attractive features of using these polymer-supported catalysts is that a large excess of catalyst can be used to accelerate the reactions and yet the work-up and isolation of product remains very simple. Indeed all the reactions were found to proceed much better with substrate:Ti:tartrate ratios in the range 100:100:200 to 100:200:400, i.e. using roughly stoichiometric levels of Ti and tartrate. However, the systems remain catalytic in that TBHP needs to be activated by the Ti/tartrate complex.

Tables 3 and 4 give the results of the asymmetric epoxidation of two other homoallylic alcohols. In these two cases great difficulties were observed using low molecular weight tartrate (DMT and DET). With our polymer-supported ligands we managed to reduce somewhat the formation of side-products in the epoxidation of 4-methyl-3-penten-1-ol. In the homogeneous reactions, titanium-assisted epoxide opening occurs to give diols (Table 3). With this substrate both the enantioselectivity and the chemical yield are better with the polymer tartrate than with the monomeric tartrate ligand. The reactions were also relatively fast (up to 3 days) compared to the epoxidation of *cis*/*trans*-3-hexen-1-ols. The epoxidation of 3-buten-1-ol is problematic in terms of lack of substrate reactivity. The chemical yields were much lower than with the other substrates and the isolation of the product was difficult using flash chromatography. However, in this case the large excess of polymer ligand facilitated the conversion to 20% at −20°C in 2 weeks. Interestingly, the enantioselectivities obtained were higher than with any other substrates (up to 80%). This same feature was also observed with monomeric ligand.[2]

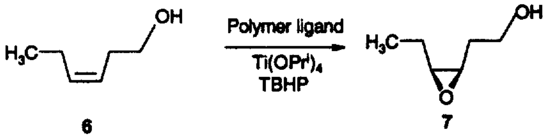
Table 1
Asymmetric epoxidation of *trans*-3-hexen-1-ol **4** with TBHP in the presence of L-(+)-polyester **3** and $Ti(OPr^i)_4$ in CH_2Cl_2 at −20°C



Entry	Ligand [(%), branching / crosslinking]	Molar ratio substrate:Ti:tartrate	Reaction time / days	Epoxide yield (%)[a]	Ee%[b]
1[c]	DMT[d]	100:100:120	10	58	29
2	3 (0%)	100:200:400	21	26	54
3	3 (8%)	100:200:400	5	45	54
4	3 (13%)	100:200:400	1	75	38

[a] From GC analysis with internal standard dodecane correcting for response factors. [b] Determined by chiral HPLC analysis (Chiralcel OD or OB or Chiralpak AS, RI detection, 9:1 hexane/isopropanol, flow rate 0.5 ml/min). [c] Literature procedure was followed, see Ref. 2. [d] DMT = L-(+)-dimethyl tartrate.

Table 2
Asymmetric epoxidation of *cis*-3-hexen-1-ol **6** with TBHP in the presence of L-(+)-polyester **3** and $Ti(OPr^i)_4$ in CH_2Cl_2 at −20°C

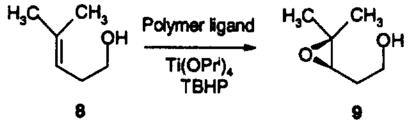


Entry	Ligand [(%), branching / crosslinking]	Molar ratio substrate:Ti:tartrate	Reaction time / days	Epoxide yield (%)[a]	Ee%[b]
1[c]	DMT[d]	100:100:120	6	15	28
2	3 (10%)	100:200:400	21	20	51
3	3 (13%)	100:200:400	1	52	41
4	3 (16%)	100:100:200	13	33	41

[a] From GC analysis with internal standard dodecane correcting for response factors. [b] Determined by chiral HPLC analysis (Chiralcel OD or OB or Chiralpak AS, RI detection, 9:1 hexane/isopropanol, flow rate 0.5 ml/min). [c] Literature procedure was followed, see Ref. 2. [d] DMT = L-(+)-dimethyl tartrate.

The asymmetric epoxidation of homoallylic alcohols using polymer-supported catalyst has several characteristic features when compared with the epoxidation of allylic alcohols.[7] The reactivity and enantioselectivity are markedly lower than with allylic alcohols. The lengthening of the carbon chain by one methylene unit presumably results in a more a flexible Ti complex and hence poorer enantiocontrol. However, the more rigid environment of the polymeric ligand seems to some extent to compensate, giving significant improvement over simple tartrate esters.[8] The absolute configuration of the homoallylic epoxy alcohols produced are opposite to that of the allylic epoxy alcohols. This same feature has been observed with the monomeric tartrate system.[2]

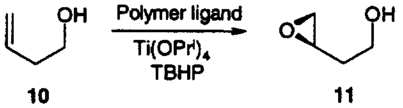
Table 3
Asymmetric epoxidation of 4-methyl-3-penten-1-ol **8** with TBHP in the presence of L-(+)-polyester **3** and Ti(OPr^i)$_4$ in CH$_2$Cl$_2$ at −20°C



Entry	Ligand [(%), branching / crosslinking]	Molar ratio substrate:Ti:tartrate	Reaction time / days	Epoxide yield (%)[a]	Ee%[b]
1[c]	DMT[d]	100:100:120	3	16	6
2	**3** (3%)	100:100:200	1	31	36
3	**3** (13%)	100:200:400	2	47	34

[a] From GC analysis with internal standard dodecane correcting for response factors. [b] Determined by chiral HPLC analysis (Chiralcel OB or Chiralpak AS, RI detection, 9:1 hexane/isopropanol, flow rate 0.5 ml/min). [c] Literature procedure was followed, see Ref. 2. [d] DMT = L-(+)-dimethyl tartrate.

Table 4
Asymmetric epoxidation of 3-buten-1-ol **10** with tBHP in the presence of L-(+)-polyester **3** and Ti(OPr^i)$_4$ in CH$_2$Cl$_2$ at −20°C



Entry	Ligand [(%), branching / crosslinking]	Molar ratio substrate:Ti:tartrate	Reaction time / days	Epoxide yield (%)[a]	Ee%[b]
1[c]	DMT[d]	100:100:120	4	5	48
2	**3** (0%)	100:200:400	14	20	60
3	**3** (10%)	100:200:400	14	20	80
4	**3** (13%)	100:200:400	14	27	54

[a] From GC analysis with internal standard dodecane correcting for response factors. [b] Determined by chiral HPLC analysis (Chiralcel OB or Chiralpak AS, RI detection, 9:1 hexane/isopropanol, flow rate 0.5 ml/min). [c] Literature procedure was followed, see Ref. 2. [d] DMT = L-(+)-dimethyl tartrate.

3. Conclusion

We have demonstrated a significantly improved synthesis of chiral 3,4-epoxy alcohols. The enantioselectivities obtained vary from 30 to 80% with reasonable chemical yields (up to 75%). A large excess of polymer-supported catalyst can be used to improve reaction rates while avoiding complex work-up. In some cases, the polymer-supported catalyst even reduces by-product formation, for example titanium-assisted epoxide opening to give diols.

4. Experimental

4.1. General

The ^{1}H NMR and ^{13}C NMR spectra were obtained on Bruker AM200 MHz or Bruker DPX400 MHz spectrometers. Chemical shifts (δ) are given in ppm relative to TMS. Gas chromatographic (GC) analyses were carried out on a Perkin–Elmer 8500 equipped with a FID employing a 25 m column packed with fused silica (phase layer 0.25 μm). The enantiomeric composition of the epoxide was measured by HPLC using chiral Daicel Chiralcel OB or Chiralpak AS columns (25 cm×0.46 cm) together with a Daicel Chiralcel OB or Chiralpak AS 5 cm×0.46 cm pre-column (RI-detection, eluent: 9:1 *n*-hexane:isopropanol, flow rate: 0.5 ml/min). High resolution GC–MS analyses were performed by the Mass Spectrometry Labotarory of the University of Oulu, Finland. Optical rotations were determined on Perkin–Elmer 243 B polarimeters using a 1 cm^3 capacity, 1 dm path length, quartz cell. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh) with diethyl ether/petroleum ether (40–60°C) in various proportions as eluent. Absolute configurations were determined by comparison of the observed rotation by polarimetry with the literature value.

4.2. Materials

Pre-activated and powdered 4 Å molecular sieves were available from Aldrich Chemical Co. and they were used as received. Cooling was accomplished through the use of the an acetone–liquid nitrogen bath. The dichloromethane used did not contain methanol and therefore was not distilled but was stored over $CaCl_2$. Aqueous 70% *tert*-butyl hydroperoxide (TBHP) was obtained from the Aldrich Chemical Co. Reagents handled by syringe were measured by weight or by volume.

4.3. General procedure for asymmetric epoxidation of homoallylic alcohols

The literature procedure for the epoxidation of allylic alcohols was followed with minor modifications.[2] An oven-dried three-necked round-bottomed flask equipped with a magnetic stirbar, nitrogen inlet, septum and bubbler was charged with 4 Å powdered, activated molecular sieves, polymer ligand **3** and dry CH_2Cl_2. The flask was cooled to −20°C and $Ti(OPr^i)_4$ (via syringe) was added dropwise with stirring. The reaction mixture was stirred at −20°C and after about 1 hour, 3 equiv. of TBHP in iso-octane was added with a syringe at a moderate rate. The resulting mixture was stirred at −20°C for at least 1 hour. The substrate (dissolved in dry CH_2Cl_2) was added dropwise with a syringe, being careful to maintain the reaction temperature between −15°C and −20°C. The mixture was stirred for an additional 3–12 hours at between −15°C and −20°C. The reaction mixture was stored in a freezer for up to 3 weeks. The reaction was monitored by gas chromatography (GC) using dodecane as an internal standard. The polymer was filtered from the reaction mixture and washed thoroughly with CH_2Cl_2. Work-up was then performed. The crude product was purified by flash chromatography [eluent: petroleum ether (40–60°C):diethyl ether, 1:1→1:2→100% diethyl ether] and analysed by ^{1}H NMR, GC and HRMS. All compounds showed satisfactory spectroscopic and analytical data.

*4.3.1. (+)-3(*R*),4(*R*)-Epoxyhexan-1-ol **5***

The epoxy alcohol **5** was prepared on a 3–10 mmol scale and isolated according to the general procedure. ^{1}H NMR (200 MHz, $CDCl_3$): δ=3.70 (t, J=6 Hz, 2H), 2.68–2.85 (m, 2H), 1.37–1.98 (m, 4H), 0.93 (t, J=7 Hz, 3H). MS (EI, *m/z*, relative intensity) 115 (<1, M^+-1), 99 (<1), 85 (100), 74 (15), 67 (20), 57 (99), 41 (67). HRMS (EI) calcd for $C_6H_{12}O_2$: 116.0837, found (M+1) 117.0878.

4.3.2. (+)-3(R),4(S)-Epoxyhexan-1-ol 7

The epoxy alcohol **7** was prepared on a 3–5 mmol scale and isolated according to the general procedure. ^1H NMR (200 MHz, C_6D_6): δ=3.58 (t, J=6 Hz, 2H), 2.85–2.93 (m, 1H), 2.57–2.66 (m, 1H), 2.26 (br s, 1H), 1.12–1.65 (m, 4H), 0.82 (t, J=7 Hz, 3 H). MS (EI, *m/z*, relative intensity) 115 (<1, M^+-1), 97 (<1), 85 (100), 74 (10), 67 (10), 57 (45), 41 (28). HRMS (EI) calcd for $C_6H_{12}O_2$: 116.0837, found 116.0857.

4.3.3. (+)-4-Methyl-3(R),4-epoxypentan-1-ol 9

The epoxy alcohol **9** was prepared on a 5 mmol scale and isolated according to the general procedure. ^1H NMR (200 MHz, $CDCl_3$): δ=3.75 (m, 2H), 2.83 (dd, J=5, 8 Hz, 1H), 2.73 (s, 1H), 1.54–1.91 (m, 2H), 1.27 (s, 3H), 1.23 (s, 3H). MS (EI, *m/z*, relative intensity) 101 (1, M^+-15), 85 (47), 71 (7), 69 (2), 59 (100), 57 (25), 43 (21). HRMS (EI) calcd for $C_6H_{12}O_2$: 116.0837, found (M+1) 117.0936.

4.3.4. (+)-3(R),4-Epoxybutan-1-ol 11

The epoxy alcohol **11** was prepared on a 14 mmol scale and isolated according to the general procedure. ^1H NMR (200 MHz, $CDCl_3$): δ=3.73 (t, J=6 Hz, 2H), 2.997–3.09 (m, 1H), 2.75 (t, J=5 Hz, 1H), 2.68 (s, 1H), 2.53 (dd, J=3, 5 Hz, 1H), 1.82–1.98 (m, 1H), 1.54–1.71 (m, 1H). MS (EI, *m/z*, relative intensity) 87 (9, M^+-1), 71 (2), 61 (3), 57 (100), 45 (17), 41 (12). HRMS (EI) calcd for $C_4H_8O_2$: 88.0524, found (M+1) 88.0511.

Acknowledgements

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8. In order to get further insight into the catalyst system, preliminary quantum chemical ab initio and DFT calculations on the model molecules of the chiral linear poly(tartrate ester)s with the different length spacers between the tartrate residues have been performed (structures shown in Ref. 4) (Hormi, O. E. O.; Pietilä, L. O.; Ahjopalo, L., unpublished results). An analysis of conformers possible for polymers with the length of the methylene units in the polymer backbone ($(CH_2)_n$, n=2, 6, 8, 12) revealed that intramolecular polymer–Ti complexes, where the tartaric units are adjacent in the chain, are feasible for 6, 8, 12. When n=2, such regular rigid structures are not possible due to the geometric constraints imposed by the short alkyl chain. Therefore, good enantioselectivity is expected only for the polymers with longer alkyl chains.

The same feature was also observed according to the results shown in Ref. 4. In the light of these results we think that the complex between the polymer and titanium is intramolecular. (a) *Turbomole 96.0/4.0.0 User Guide*, September 1996, San Diego: Molecular Simulations, 1996. (b) *Discover 96.0/4.0.0 User Guide*, September 1996, San Diego: Molecular Simulations, 1996. The pcff force field used in the calculations was modified to fit the torsional behaviour of some model molecules at the MP2/6-31G(d) level of theory. Details of the modifications will be described elsewhere (Korpelainen, V.; Ahjopalo, L.; Mannfors, B.; Pietilä, L. O. in preparation).