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Heterogeneous asymmetric epoxidation of *cis*-allylic alcohols: use of polymer-supported Ti(IV)-catalyst

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Abstract

Heterogeneous asymmetric epoxidation of *cis*-allylic alcohols with titanium isopropoxide and *tert*-butyl hydroperoxide has been achieved using a branched/crosslinked poly(tartrate ester) ligand. The enantioselectivities and chemical yields obtained are at least comparable to low molecular weight tartrate ligands. © 1998 Published by Elsevier Science Ltd. All rights reserved.

The asymmetric epoxidation of alkenes is central to many of the recent developments in the stereoselective synthesis of chiral molecules.[1] Our earlier studies have established the advantages of using a polymer-supported Ti(IV)-catalyst in the epoxidation of *trans*-allylic alcohols.[2–4] In line with our continuing interest in this area, we have now undertaken the investigation of the epoxidation of *cis*-allylic alcohols.

Allylic alcohols having a *cis*-3-substituent are typically the most sluggish of allylic alcohols to be epoxidised.[5] Using the conventional low molecular weight Sharpless tartrate–titanium isopropoxide system these *cis*-allylic alcohols give variable enantiofacial selectivity.[6] Nevertheless, asymmetric epoxidation of these substrates is effective and in most cases the enantiomeric purity is at least 80%.

The numerous attractive features of a polymer-supported asymmetric organic synthesis are well recognised. For example the isolation of the chiral product, free of the chiral catalyst or auxiliary, is simplified. In addition many successful chiral catalytic systems are moisture or air-sensitive organometallic species and polymer-supported analogues can be used and be recovered more easily without exposure to water and/or air.[7]

We have previously reported on the synthesis of branched/crosslinked poly(tartrate ester)s and have studied the use of these optically active poly(tartrate ester) ligands in asymmetric epoxidations of *trans*-allylic alcohols with titanium tetraisopropoxide and *tert*-butyl hydroperoxide.[3,4] In the present paper

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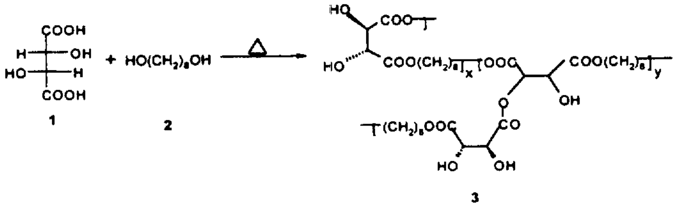
we would like to report the results obtained using these branched poly(tartrate ester)s as ligands in the epoxidation of *cis*-allylic alcohols.

The branched/crosslinked polyester **3** was prepared by condensation polymerisation of L-(+)-tartaric acid and 1,8-octanediol as shown in Scheme 1.[3] The degree of branching/crosslinking was determined as described before by ^{1}H NMR.[4] We have previously pointed out that a high level of branching/crosslinking of the polymer ligand inhibits the enantioselective epoxidation of *trans*-allylic alcohols.[4] Accordingly we have now used poly(tartrate ester)s having a degree of branching of 10%, 14% and $\gg$15% in epoxidations of *cis*-allylic alcohols.



Scheme 1.

Table 1 shows the results obtained. As expected, the reaction times needed to achieve significant conversion were longer than in the epoxidation of *trans*-allylic alcohols. After one week the conversion varied between 20–51% depending on the substrate. The results of the asymmetric epoxidation of *cis*-2-penten-1-ol are shown in entries 1 and 2. Using a polymer ligand having a 10% degree of branching the conversion was 51% after 7 days in a freezer and the enantioselectivity of the reaction was high (86%). The enantioselectivity dropped significantly (48% ee) using the crosslinked polymer ligand. Using the monomeric diethyltartrate–titanium isoproxide system the reported yield was 60% with 80% ee.[8] The results of asymmetric epoxidation of *cis*-2-hexen-1-ol (entry 4) are also comparable to the results using the monomeric analogue. The conversion was 48% after 6 days with 80% ee. The polymer ligand having a 14% degree of branching (entry 5) resulted in better enantioselectivity than the low molecular weight tartrate ligand (DMT, entry 6). Using stoichiometric levels of diisopropyl tartrate–titanium isopropoxide the reported conversion was 60% with 80% ee.[9]

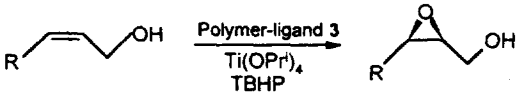
The rate of epoxidation of *cis*-4-benzyloxy-2-buten-1-ol was the slowest (entries 7–9). The conversion after 7 days was only 20% and the enantioselectivity of the reaction was 66–68%. In the reported enantioselectivity using L-(+)-diethyl tartrate as the ligand varied from 85% (for catalytic levels) to as high as 92% (for stoichiometric levels).[6,10] In the present work the monomeric dimethyl tartrate–titanium isopropoxide system was used to compare with a polymeric analogue.[11] The results are shown in Table 1. Generally the polymer ligand **3** gives better enantioselectivity than the monomeric dimethyl tartrate ligand. The high level of branching/crosslinking ($\gg$15%) of the polymer ligand inhibits the enantioselective epoxidation of *cis*-allylic alcohols.

The recovery of polymer-catalyst by simple filtration aids the isolation of products. The complex work-up required in the Sharpless procedure is considerably 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 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.

In summary, we have demonstrated that using polymer-supported Sharpless catalyst in the asymmetric epoxidation of *cis*-allylic alcohols the results obtained are comparable with, or better than, those achieved by using the optimised conventional low molecular weight ligand. The enantioselectivies obtained vary

Table 1

Comparison of DMT and polyester **3** prepared from L-(+)-tartaric acid in the asymmetric epoxidation of *cis*-2-allylic alcohols with TBHP (2 equiv.) and Ti(OPr^i)$_4$ in CH_2Cl_2 at −20°C[12]



Entry	R	Ligand [(%), branching / crosslinking][a]	Molar ratio substrate:Ti:tartrate	Reaction time (days)	Epoxide yield (%)[b]	Ee[c] (%)
1	**C_2H_5**	**3** (10 %)	100:100:200	7	51	86
2	**C_2H_5**	**3** (>> 15 %)	100:100:200	6	42	48
3	**C_2H_5**	**DMT**	100:10:14	7	57	78
4	**C_3H_7**	**3** (10 %)	100:200:400	6	48	80
5	**C_3H_7**	**3** (14 %)	100:200:400	21	29	75[d]
6	**C_3H_7**	**DMT**	100:50:100	13	54	38[e]
7	**$PhCH_2OCH_2$**	**3** (10 %)	100:100:200	7	20	66[f]
8	**$PhCH_2OCH_2$**	**3** (10 %)	100:200:400	6	18[g]	68
9	**$PhCH_2OCH_2$**	**3** (>> 15 %)	100:100:200	6	20[g]	38
10	**$PhCH_2OCH_2$**	**DMT**	100:10:14	7	38	60

[a]DMT = L-(+)-dimethyl tartrate. [b]From GC analysis with intenal standard dodecane correcting for response factors. [c]Determined by ^{1}H NMR analysis of the derived MTPA ester in benzene-d$_6$. [d]Determined also by chiral HPLC analysis (Chiralpak AS, RI-detection, 9:1 hexane/isopropanol, flow rate 0.5 ml/min): 75 ee%. [e]Ee% determined by chiral HPLC analysis (Chiralpak AS, RI-detection, 9:1 hexane/isopropanol, flow rate 0.5 ml/min). [f]Determined by chiral HPLC analysis (Chiralpak AS, RI-detection, 9:1 hexane/isopropanol, flow rate 0.5 ml/min). Determined also by ^{1}H NMR analysis of the derived MTPA ester in benzene-d$_6$: 62 ee%. [g]Isolated yield.

from 66–86% with reasonable chemical yields (up to 57%) using the polymer ligand having a degree of branching of 10%–14%. The crosslinked polymer ligand resulted in remarkably lower enantioselectivity (38–48% ee) with reasonable chemical yields. A large excess of polymer-supported catalyst can be used to improve reaction rates while avoiding added complications in the work-up.

It could also be interesting to investigate the circulation of the polymeric catalyst but, so far, we have made no thorough study to reuse the catalyst.

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11. The esters used conventionally in Sharpless epoxidations are dimethyl, diethyl and diisopropyl tartrates, and, with a few subtle exeptions, all are equally effective at inducing asymmetry. See for example Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*, Vol. 7, Eds. Trost, B. M., Fleming, I., Ley, S. V. Pergamon Press, Oxford 1991, pp. 389–436
12. *General procedure for asymmetric epoxidation*: The literature procedure for the epoxidation of allylic alcohols was followed with modifications. 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 $Ti(O\text{-}i\text{-}Pr)_4$ (via syringe) was added dropwise with stirring. The reaction mixture was stirred at −20°C and after about one hour, 2 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 one 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 −15°C to −20°C. The reaction mixture was stored in a freezer for approximately one week. The reaction was monitored by gas chromatography (GC) using dodecane as an internal standard. The polymer was filtered and the reaction mixture washed thoroughly with CH_2Cl_2. Workup was then performed. The crude product was purified by flash-chromatography (eluent: petrol ether (40°C–60°C):diethyl ether=1:1) and analysed by ^1H NMR, GC and HRMS. All compounds showed satisfactory spectroscopic and analytical data. The enantioselectivity of the epoxide was measured by ^1H NMR analysis of the derived MTPA ester in benzene-d_6 or by HPLC using a chiral Chiralpak AS 25 cm×0.46 cm column together with a Chiralpak AS 5 cm×0.46 cm pre-column (RI-detection, eluent: n-hexane:isopropanol=9:1, flow rate: 0.5 ml/min).