Polymer-supported Ti(IV) and Mn(III) Asymmetric Alkene Epoxidation Catalysts

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Background: Epoxides represent a very important group of speciality and fine chemicals because they are derived directly from alkenes, a primary petrochemical source, and because of the breadth of opportunity they offer the organic synthetic chemist in terms of the highly selective reactions they undergo, often requiring only very mild conditions. Since most epoxides also bear at least one stereogenic centre the strategic importance of these molecules in synthesis is even higher. The most important asymmetric alkene epoxidation catalyst systems that have been discovered are those reported by Sharpless and his co-workers utilising tartrate ester complexed Ti(IV) centres[1] and by Jacobsen and his co-workers utilising chiral Mn(III) salen complexes.[2] The former system provides high conversions and high enantioselectivity (enantiomeric excess, ee%) in the case of allylic alcohol substrates, while the latter is likewise effective in the case of non-functional *cis*-internal alkenes, especially cyclic systems. Both catalytic systems are homogeneous and exploitation of both involve rather laborious work-up procedures. Generally no attempt is made to recover and re-use these catalysts.

The potential advantages in converting a process catalysed by a homogeneous metal complex into one involving a heterogeneous polymer-supported analogue have been well rehearsed.[3] Suffice to say that on a laboratory scale supported metal complex catalysts considerably facilitate product work-up and isolation, while on a large scale such heterogeneous species allow processes to be run continuously using packed or fluidised bed columns with considerable financial advantages both in terms of capital expenditure on plant and with regard to recurrent costs.

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Results and Discussion

Ti(IV) Poly(tartrate ester) Complexes as Catalysts in Allylic Alcohol and Related Epoxidations

Before our own work was initiated on the Sharpless system we were aware of only one report on the synthesis and evaluation of a polymer-supported analogue.[4] In 1983 Farrall and co-workers immobilised a single tartrate residue on a 1% crosslinked polystyrene resin and performed Sharpless epoxidation of geraniol under literature conditions. Typically yields of the desired product were 60-70% and enantiomeric excess 50-60%. The polymer ligand was also reported to be recyclable. In retrospect this was a very good result and it is surprising the work was not followed up earlier. Interestingly Cazaux and Caze reported their results on the immobilisation of an asymmetric aminol Mo(VI) complex in 1993[5]; and again they employed this to catalyse epoxidation of geraniol. Their results were poorer and the polymer catalyst was reported to be unstable. That the chiral polymer Mo(VI) complex was less effective is not surprising since low molecular weight soluble complexes of Mo(V) of similar structure are also less selective than the Ti-tartrate complex.

Our own approach has been to utilise poly(tartrate ester)s as the macromolecular ligand to complex Ti(IV) thus combining the roles of the polymer support and the optically active ligand. The objective was to produce a weight and atom-efficient system, while also minimising possible mass transfer problems within the support. Initially linear poly(tartrate ester)s **1** were synthesised (Figure 1) using conventional acid catalysed polycondensation procedures.[6] Formation of macromolecule-Ti(IV) complexes from these polytartrates and $Ti(O^iPr)_4$, and use with *t*-butylhydroperoxide (TBHP) as an oxygen source under typical Sharpless conditions gave good yields of epoxide from *trans*-hex-2-en-1-ol with ee% up to 80%. Perhaps equally importantly there is a strong "polymer effect". Polytartrate (**1a**) gave essentially a racemic product. This ligand and its Ti complex are essentially insoluble in the reaction medium. Solubility improves with (**1b**), while the Ti complex of (**1c**) is completely soluble and the reaction essentially

homogeneous. This species gave the highest ee% and led us to prepare (**1d**) which itself, along with its Ti complex, are soluble in CH_2Cl_2. In the event no further improvement in ee% was observed with this macromolecular ligand.

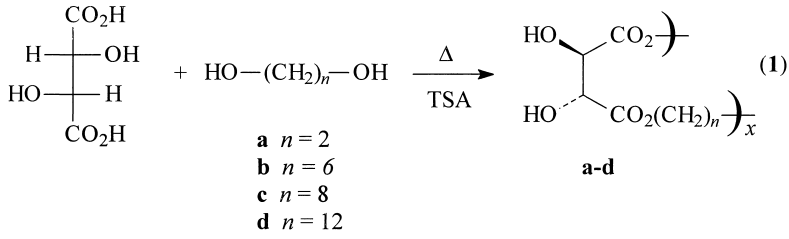


Figure 1 Synthesis of linear poly(tartrate ester)s for use in Sharpless epoxidations

With the above result in hand the synthesis of (**1c**) was repeated to provide more polymeric ligand for use with more substrates. In the course of producing further batches it was discovered that using slightly more forcing preparation conditions it was possible to produce branched poly(tartrate ester)s (**1e**) and even crosslinked species (Figure 2), the degree of branching being evaluated from ^{1}H nmr spectra (400 MHz).[7] Somewhat to our

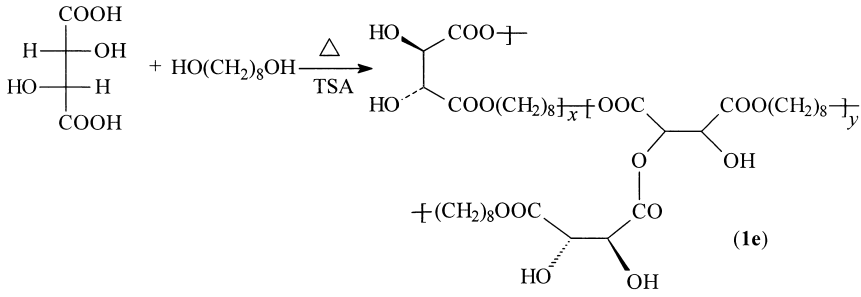
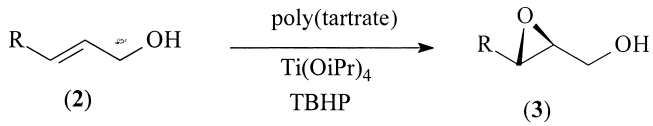


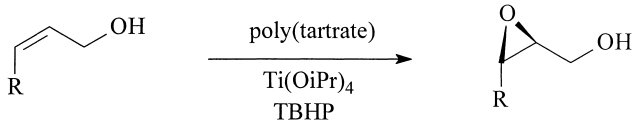
Figure 2 Synthesis of branched poly(octamethylene-L-(+)-tartrate).

surprise polymers with a degree of branching ≤15% were totally soluble in DMSO but formed insoluble Ti complexes under conditions of the Sharpless reaction. Furthermore, these heterogeneous polymer catalysts gave higher levels of induction in epoxidation of *trans*-allylic alcohols[7] (**2a, b, c** Figure 3, Table 1) than the soluble linear analogues used earlier. In addition, since the catalysts are heterogeneous, work-up of the reaction is considerably facilitated irrespective of the nature of the substrate and the product. In some potential applications the Sharpless methodology has proved too problematical to implement (*e.g.* water-soluble substrates) and under these circumstances our branched heterogeneous system offers technological potential.



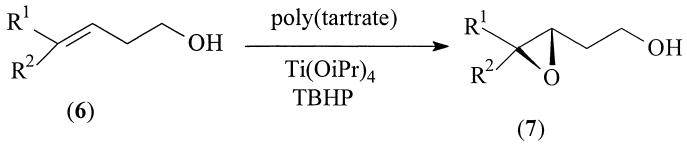
(**2**) (**3**)

R = C_3H_7, (**2a**) (**3a**) C_8H_{17}, (**2b**) (**3b**) Ph, (**2c**) (**3c**)



(**4**) (**5**)

R = C_2H_5, (**4a**) (**5a**) C_3H_7, (**4b**) (**5b**) $PhCH_2OCH_2$, (**4c**) (**5c**)



(**6**) (**7**)

$R^1 = C_2H_5$ $R^2 = H$ (**6a**) (**7a**)
$R^1 = H$ $R^2 = C_2H_5$ (**6b**) (**7b**)
$R^1 = CH_3$ $R^2 = CH_3$ (**6c**) (**7c**)
$R^1 = H$ $R^2 = H$ (**6d**) (**7d**)

Figure 3 Sharpless epoxidation of *cis*- and *trans*-allylic and homoallylic alcohols catalysed by poly(tartrate ester) (**1e**).

Table 1 Asymmetric epoxidation of *cis*- and *trans*-allylic and homoallylic alcohols using poly(octamethylene tartrate) (**1e**) $Ti(OiPr)_4$/TBHP

Alkene	Epoxide	Poly(tartrate) % branching	Molar ratio alkene:Ti: tartrate	Temper -ature (°C)	Time	Isolated Yield (%)	Ee(%)
(**2a**)	(**3a**)	3	10:25:5	-20	6h	53	87
(**2b**)	(**3b**)	6	10:2:6	-15	12h	40	98
(**2c**)	(**3c**)	6	10:25:5	-20	6.5h	38	89
(**4a**)	(**5a**)	10	10:10:20	-20	7d	51	86
(**4b**)	(**5b**)	10	10:10:40	-20	6d	48	80
(**4c**)	(**5c**)	10	10:20:40	-20	6d	18	68
(**6a**)	(**7a**)	8	10:20:40	-20	5d	45	54
(**6b**)	(**7b**)	10	10:20:40	-20	21d	20	51
(**6c**)	(**7c**)	3	10:10:20	-20	1d	31	36
(**6d**)	(**7d**)	10	10:20:40	-20	14d	20	80

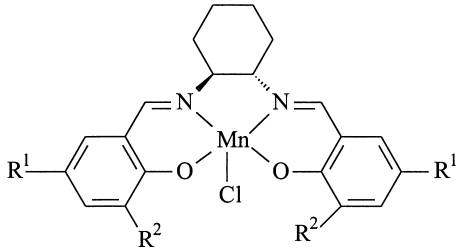
Somewhat intriguingly those poly(tartrate ester)s which are fully crosslinked and hence insoluble even in DMSO, and for which solution phase ^1H nmr data cannot be obtained, gave disappointingly low levels of enantioselectivity in epoxidations. Why this should be so it not clear. It may be that the fully crosslinked polymers inhibit formation of a high proportion of the specific Ti complex required to provide high levels of asymmetric induction. It may also be that mass transfer limitations disturb the balance of reaction steps.

The potential importance of these poly(tartrate ester) ligands becomes more apparent on widening the alkene substrates investigated. Generally dialkyltartrate esters provide lower levels of enantiocontrol in epoxidation of *cis* allylic alcohols than they do with the *trans*-isomers. The poly(tartrate ester) (**1e**) shows consistently higher ee% with these substrates (**4a, b, c**) than the simple alkyl esters Table 1.[8] Perhaps even more surprisingly, whereas the Sharpless methodology is of almost no practical value in the case of homoallylic alcohols, poly(tartrate ester) (**1e**) offers levels of ee% which could be of real value for some of the substrates (**6a-d**) Table 1.[9] Why the polymer ligand should offer this more

remote enantiocontrol is not clear, but there may well be an important message here for those interested in developing novel optically active ligands and complexes.

Mn(III) Macromolecular Chiral Salen Complexes as Catalysts in Alkene Epoxidation

Not surprisingly, the scientific and technological interest in Jacobsen's Mn(III) chiral salen epoxidation catalyst (**8**), coupled with its high cost, difficulty in use and work-up, and its inability to be recycled have led to a number of attempts to produce more practical heterogeneous polymer-supported analogues.[10-16]



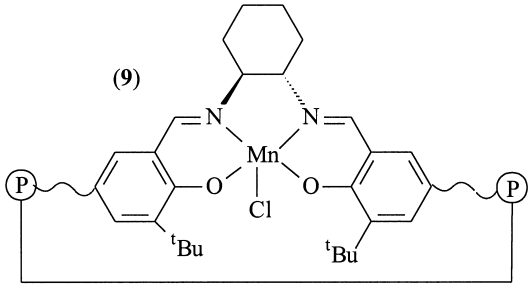
(**8**)

$R^1 = R^2 = {}^tBu$

As it turns out it is extremely difficult to prepare salen ligands which are non-symmetric in terms of the substituents on the two benzene rings. This is because monocondensation of a diamine with a salicylaldehyde to yield an amino derivatised Schiff base is almost impossible and inevitably almost irrespectively of how the reaction is performed the second amino group undergoes fast condensation as well, to yield the *bis*-Schiff base *i.e.* the salen structure. The earlier attempts to produce a polymer-supported analogue of Jacobsen's catalyst focussed on synthesising styryl derivatives of the chiral salen ligand, and inevitably this led to di-styryl monomers. Polymerisation of these therefore yielded crosslinked polymers in which it would be expected that the salen ligand would be located on crosslinks (**9**). A great deal of careful evaluation was performed by both the Italian[14,15] and the Indian groups[10-13] using a number of alkenes, various reaction

conditions and a number of oxidants. Overall the results proved rather disappointing. Although some of the supported systems displayed good activity, the level of enantiocontrol was low with the best ee% recorded being ~60%. Interestingly both groups did suggest that recovery and recycling of their polymers was possible, though there was no data given.

(**9**)



In tackling immobilisation of this catalyst ourselves we were conscious of the mechanistic proposals in the literature[17] all of which implied that local mobility of the complex should not be impaired. Locating the complex on a polymer crosslink would be expected to do just this! Accordingly therefore we set out with a number of design criteria as follows: i) the local molecular structure of the macromolecular Mn complex should mimic precisely the optimum structure of Jacobsen's catalyst (*i.e.* (**8**)); ii) the complex should be attached by a single flexible linkage to the polymer support to minimise any local steric restriction; iii) the catalyst should be attached to the polymer with sufficiently low loading to maximise site isolation of catalytic centres, hence minimising the possibility of inactive oxo-bridged dimer formation; and iv) the morphology of the support should be such that no mass transfer limitation arises, with all active sites freely accessible. Since of the oxidant, *m*-chloroperbenzoic acid with the co-oxidant *N*-morpholine *N*-oxide appeared to be the most productive reported in the literature we opted to use this oxidation system.

Our strategy to ensure mono-attachment of the salen ligand to the matrix was to build the ligand on the polymer with a loading level such that a large proportion of site-isolation would be achieved. In this way the mono-condensation of the enantiomerically pure

trans-1,2-diaminocyclohexane with the first matrix-bound salicylaldehyde residue would be assured, allowing the second condensation to be achieved with *e.g.* di-*t*-butylsalicylaldehyde. Our first synthesis (Figure 4) involved suspension polymerised resin beads derived from 4-(4-vinylbenzyloxy)salicylaldehyde and the accumulated analytical data suggested that the strategy had worked well.[18]

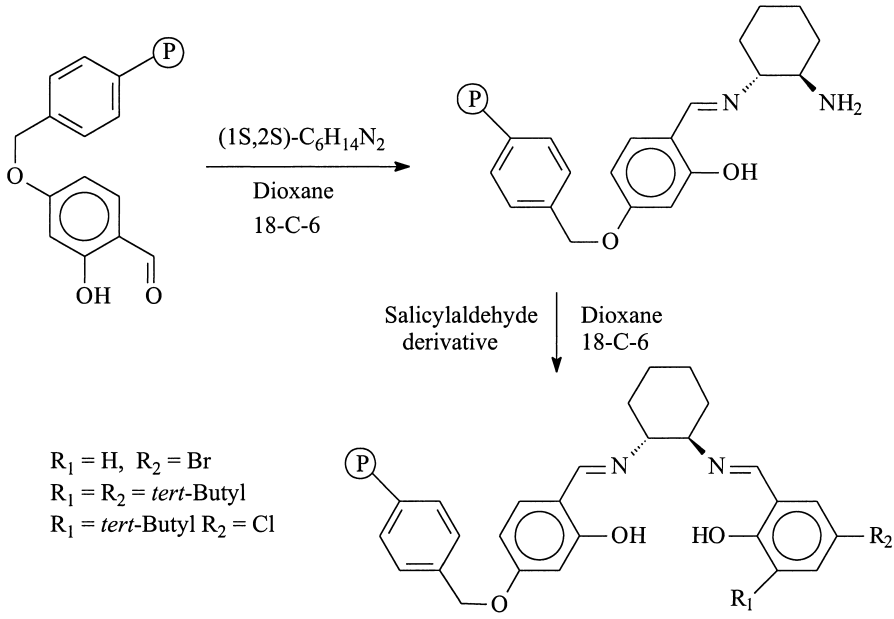


Figure 4 Synthesis of sited isolated chiral salen complexes supported on resin derived from a styryl salicylaldehyde.

Very disappointingly both gel-type and macroporous versions of this polymer ligand performed very poorly in asymmetric epoxidations of both indene and 3,4-dihydronaphthalene. The macroporous species were reasonably catalytically active but displayed only low enantiocontrol; the gel type species displayed both low activity and very poor selectivity. Crucially the first synthetic strategy produced a chiral polymer ligand with one missing *ortho*-*t*-butyl group and so accordingly a second group of resins were synthesised ensuring all the criteria listed above were met.[19] The route adopted is

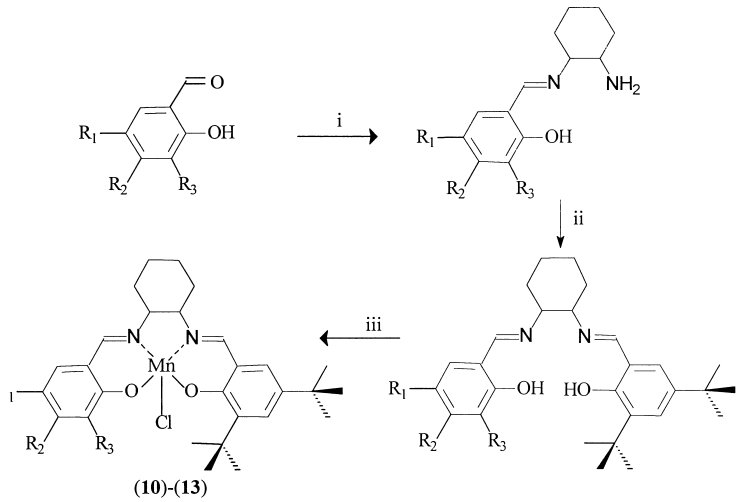
shown in Figure 5. The catalysts were evaluated in asymmetric epoxidations of a number of *cis*-internal alkenes and the results for 1-phenylcyclohex-2-ene are shown in Table 2.

Table 2 Asymmetric epoxidation of 1-phenylcyclohex-2-ene using MCPBA catalysed by polymer-supported chiral Mn(III) (salen) complex.

		Epoxide		
Catalyst	Configuration	Yield (%)	Ee(%)	Configuration
Jacobsen	*S,S*	72	92	(+)-(*R,R*)
(**10a**)	*R,R*	36	61	(-)-(*S,S*)
(**10b**)	*R,R*	47	66	(-)-(*S,S*)
(**11**)	*R,R*	49	91	(-)-(*S,S*)
(**12**)	*R,R*	5	5	(-)-(*S,S*)
(**13**)	*R,R*	5	~0	(-)-(*S,S*)

Only the species (**12**) and (**13**) performed poorly. In the case of (**12**) this is probably due to the rigidity of the maleimide copolymer from which it is derived. With (**13**) the link to the polymer is via the C-atom *ortho* to one of the phenol OH groups and clearly this is too sterically crowded. The results with (**10a, b**) and (**11**) are however very rewarding and represent the most active and enantioselective of polymer-supported systems reported to date; (**11**) in particular, performs as well as does the soluble Jacobsen model.

In practice, however, we have also observed a strong substrate dependence in the performance of our resins and indeed the soluble catalyst itself is very variable in its selectivity in our hands. We have succeeded in recycling the polymeric ligands, both without and with re-loading of Mn. In all cases we see a decline in catalytic activity and selectivity, and for the time being at least our view is that the catalyst itself is too fragile for all of it to survive work-up. The latter is however considerably simplified with the polymer-supported system and this is a major advantage. In due course more details will emerge from our laboratory.[20]



(10a) R_1 = P—OCH_2—, R_2 = H , R_3 = *tert* butyl Porous styrene-based resin

(10b) R_1 = P—OCH_2—, R_2 = H , R_3 = *tert* butyl Gel-type styrene-based resin

(11) R_1 = P—OCH_2—, R_2 = H , R_3 = *tert* butyl Porous methacrylate-based resin

(12) R_1 = P, P, N, OCH_2—, R_2 = H,R_3 = *tert* butyl Porous styrene-based resin

(13) R_1 = H , R_2 = H , R_3 = P—O—C(=O) Porous methacrylate-based resin

Reagents and conditions: i, (*R,R*)-1,2-diaminocyclohexane, CH_2Cl_2, room temp., 1 ii, 2,4-di-*tert*-butylsalicylaldehyde; iii, CH_2Cl_2, room temp., 12 h; vi, $Mn(OAc)_2$.4 EtOH, air, reflux, 30 h then LiCl.

Figure 5 Synthesis of site isolated salen complexes supported on styrene and methacrylate ester-based resins.

EXPERIMENTAL

Full experimental details are reported in refs. 7-9 and 18,19.

FUTURE DIRECTIONS

Two key factors are now in place which will maintain the area of macromolecule-metal complex catalysts very active and vibrant. The first is the drive towards more environmentally acceptable chemistry, where polymer-supported catalysts have a key role to play. The second is the proliferation of rapid combinatorial and parallel synthesis methods in the search for new drugs, new catalytic ligands and new materials. Performing these automatic syntheses in solution while utilising heterogeneous reagents, catalysts and scavengers is now increasingly seen as the optimum methodology. The demand for active and selective, particularly enantioselective macromolecule-metal complex catalysts has therefore never been higher and the race is now on to produce technologically useful systems.

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