An optimised and recoverable tartrate surrogate for sharpless asymmetric epoxidations

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ABSTRACT

The tetrahydroxy diester **7d** (R = ^{i}Pr) is almost as effective as diisopropyl tartrate in SAE reactions of (*E*)-allylic alcohols and can be recovered and re-used following a relatively simple work-up procedure.

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The Sharpless asymmetric epoxidation (SAE) reaction (Scheme 1) is now very much a part of modern synthetic strategy, despite its seemingly restrictive limitation to (*E*)-allylic alcohols **1**, in terms of being able to deliver useable enantiomeric enrichments in the product epoxy-alcohols **2**. Due to the imagination of many synthetic chemists, naturally led by the Sharpless group, this restriction has been significantly obviated, such that this transformation now resides amongst the 'classics' of synthetic organic chemistry.[1]

In its original form, the reaction was not without its drawbacks, one of which was the need to remove the stoichiometric amount of tartrate ester, used to form the complex which delivers the oxygen to the allylic alcohol **1** in an asymmetric manner. This was largely negated by the introduction of the 'catalytic' procedure, the essence of which is the incorporation of molecular sieves to remove any adventitious water.[2] In contrast to many other catalytic procedures,[3] little effort has been made to develop a procedure which allows for the recovery of tartrate from an SAE, presumably because of its ready availability and low cost, as well as its relatively benign nature.[4,5] However, in these more environmentally aware times, such recoveries have become highly desirable, even essential. In any event, large-scale SAEs would benefit considerably from such a procedure, as disposal of impure tartrate by-products would be inconvenient and expensive; the absence of a tartrate ester hydro-

lysis step would also be an advantage, especially when the synthesis produced an especially sensitive epoxide.

Detailed studies by the Sharpless group have reached the conclusion that the key initial moiety in SAEs is the dimeric tartrate complex **3** (Scheme 2).[6] Incorporation of the reacting species, the allylic alcohol and the hydroperoxide, then lead to the reactive complex **4** in which the oxygen transfer occurs.
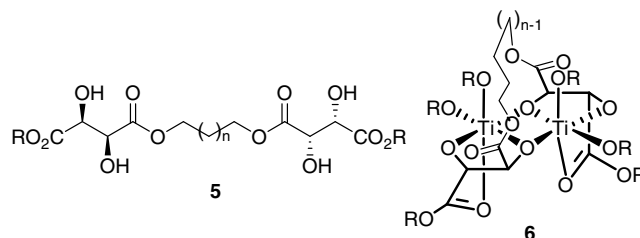
A particularly relevant series of experiments reported by Sharpless in support of these ideas was the successful use of a series of *dimeric* tartrate surrogates **5**, which presumably were incorporated into complexes **6**, but only when the connecting bridge was long enough (Scheme 3).[7]
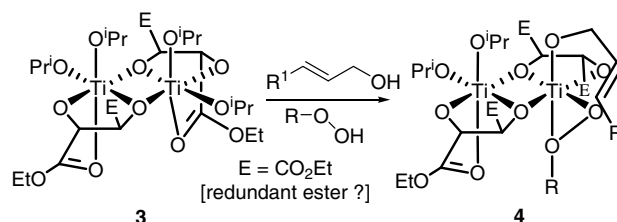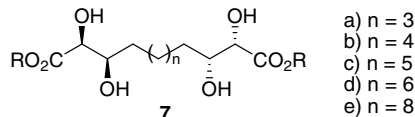

Scheme 2.
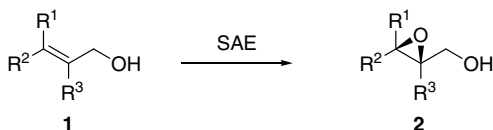
Scheme 1.

Scheme 3.

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Throughout, such connecting ester groups in complexes **6**, as well as those designated 'E' in the 'standard' complexes **3** and **4** (Scheme 2), appear to be 'bystanders', in the sense that they do not seem to participate directly in the epoxidation process, although Sharpless has stipulated that all four ester groups are necessary for the kinetic resolution of racemic allylic alcohols. In view of this, we reasoned that the simpler diesters **7** could act as tartrate surrogates for 'standard' SAEs. These should have greater stability than the 'dimeric' esters **5**, especially with respect to transesterification[7] and also, being tetra-ols, perhaps possess sufficiently unique solubilities, features that in combination might render them amenable to recovery and recycling.


Based on the Sharpless results (Scheme 3), it seemed likely that we would require a connecting chain of at least six atoms [i.e., **7**; $n > 3$]; conversely, too long a chain might render the necessary complexes insufficiently stable. Requiring a very rapid asymmetric synthesis of the diesters **7**, we thought that the best option was to generate the two diol units using the other great Sharpless invention, the AD-reaction.[8] We therefore required a series of bis-unsaturated esters **8** (Scheme 4).

Initially, we used a variety of highly (E)-selective Wittig-type homologations of the corresponding dialdehydes,[9] but in all cases, irritatingly small quantities of (E,Z)- and/or (Z,Z)-isomers proved refractory to either removal or isomerisation. This problem was only obviated when we turned to the Grubbs' metathesis method,[10] the results of which were remarkable. Using only 1 mol % of the second generation catalyst, reactions between a cycloalkene **9** (or the corresponding 1,ω-diene) and just over 2 equiv of an acrylate **10** in gently refluxing dichloromethane overnight delivered in all cases ≥85% isolated yields of the diesters **8**, solely as the (E,E)-isomers. Further optimisation, using scrupulously clean reagents and solvent, revealed that catalyst levels as low as 0.13 mol % were equally effective, a useful finding in view of both catalyst cost and its complete removal (Scheme 5).[11]

Guided by literature precedent,[8] the final double bis-hydroxylation was carried out using (DHQD)$_2$PHAL and it delivered excellent yields of the diesters **7**, following crystallisation from chloroform–hexane mixtures. Each had an ee value of >99%, according to both chiral HPLC and GC analyses.[12]
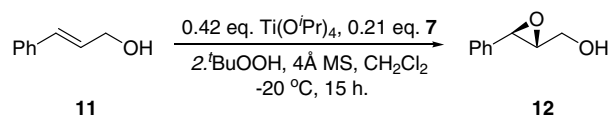
In an initial screening of the central idea, we chose to use cinnamyl alcohol **11** as the substrate both because 'standard' SAE conditions (Scheme 6) are known to deliver the corresponding epoxy-
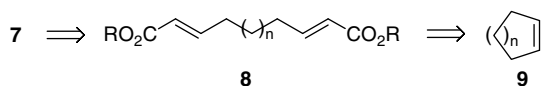
Scheme 4.
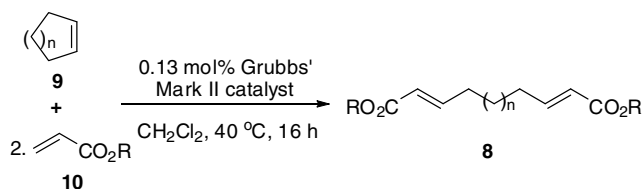
Scheme 5.

Scheme 6.

Table 1
SAE of cinnamyl alcohol **11** using ligand **7** (dietheyl ester)

| n	mol % **7**	% ee **12**
34	15	12
4	17	92
5	21	95
6	21	96
8	21	96
D-DIPT	21	99

alcohol **12** with around 99% ee[1] and because this product is quite sensitive and hence, literally, something of an 'acid test'. In these initial studies, the tartrate surrogates used were the ethyl esters of structures **7** (see below).

We were delighted to find that our first set of experiments met with success. The results are summarized in Table 1.[13] With the exception of the smallest diethyl diester ligand [**7**; $n = 3$], all gave excellent levels of enantiomeric enrichment in the product epoxy-alcohol **12**. In all cases, the conversion of cinnamyl alcohol **11** was >95% after 15 h reaction time. We therefore concluded that, for this epoxidaton at least, the diester ligand should have a minimum value for 'n' of 6, when it was almost as effective as the original diisopropyl tartrate [D-DIPT; Table 1]. Of course, the failure of diester [**7**; $n = 3$] to produce high ees lends further weight to the veracity of the intermediate dimeric complexes **4** (Scheme 2).

Various optimisation experiments using the apparent optimal eight-methylene ligand [**7**; $n = 6$] showed that it worked just as well at a level of 10 mol % and gave slightly increased ees at −10 °C. Lower levels of ligand and increased temperatures all gave lower ees. It was also self-evident that using titanium iso-propoxide with the diethyl diester [**7**; R = Et] was simply illogical, especially in view of the hoped-for long-term survival of such tartrate surrogates. A brief study of alternative ester groups showed that use of the di-iso-propyl ester [**7d**; R = ^{i}Pr] made no difference to the ee value of epoxy-alcohol **12**, while the corresponding dimethyl ester was much less effective, probably because of its much reduced solubility, an encouraging sign for possible ligand recovery. We therefore chose to focus entirely on the di-iso-propyl ester of the eight-methylene ligand [**7d**; R = ^{i}Pr] and examine SAE reactions of other representative allylic alcohols: (E)-2-hexen-1-ol **13**, prenyl alcohol **14** and geraniol **15**. The results are collected in Table 2.

When run at −20 °C, SAE of the hexenol **13**, as outlined in Scheme 6 and using ligand **7d** as its di-iso-propyl ester, gave essentially the same result, in terms of both chemical and optical yields, as is obtained using the 'usual' SAE conditions with di-iso-propyl tartrate.[1] The more sterically demanding terpenoid alcohols **14** and **15** also gave very similar chemical yields, which lowered mainly because of product volatility, but ees were some 10% lower than those obtained using tartrate. The latter two substrates were

Table 2
SAE of allylic alcohols 13–15 using ligand 7d [R = ^{i}Pr]
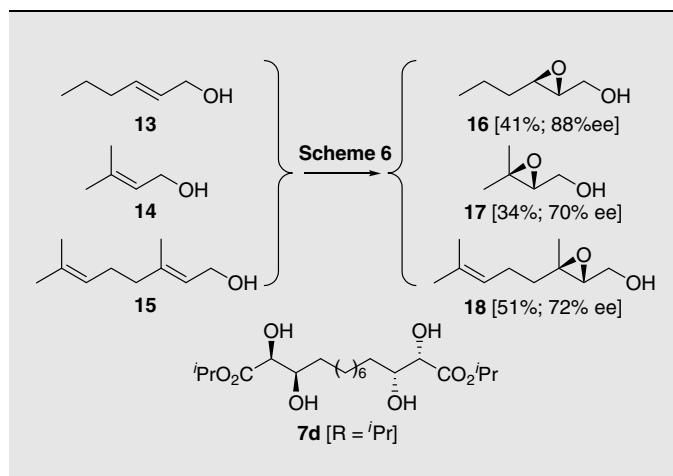
not tested using the Sharpless dimeric tartrate surrogates 5 (Scheme 3).[7] Possibly, the greater steric bulk of these two alcohols may interact adversely with the connecting bridge in the dimeric complex necessary to secure very high ee values (see Schemes 2 and 3).

Having established the viability of ligands 7 in SAE reactions, we then turned to the central premise, that of their recovery and re-use. It soon became clear that this was not going to be easily achieved. Hydrolysis of the titanium complexes without inducing a similar reaction of the ligand ester groups and their epimerisation were continual problems, as was formation of intractable complexes of the ligand 7 and the liberated titanium salts; the poor solubility of ligands 7 contributed to this. However, using aqueous citric acid[14] to break up such complexes did allow relatively straightforward product separation. An optimum protocol was as follows: a completed SAE, maintained at −20 °C, was quenched using aqueous citric acid, and all organic material was extracted into ethyl acetate. The combined extracts were washed with 2 M aqueous potassium carbonate and water, then dried and concentrated. The residue was taken up in a minimum of warm chloroform, and this solution was added slowly to vigorously stirred pentane (12 volumes). The precipitated ligand was filtered off, and the filtrate and washings were evaporated to leave the crude epoxy-alcohol. The ligand was then taken up into ethyl acetate and the resulting solution was washed sequentially with aqueous 2 M sodium hydroxide, 2 M hydrochloric acid, aqueous potassium carbonate, water and brine. Evaporation of the dried solution then left ligand 7 of sufficient purity that its subsequent use maintained the expected ee levels of the resulting epoxy-alcohols; it could also be crystallised from CHCl₃–hexane mixtures. The results obtained from a typical set of runs on a 1–2 mmol scale are collected in Table 3; each epoxidation was carried out as summarised in Scheme 6. Yields and ees were comparable throughout the four runs with similar runs using fresh ligand. Especially encouraging was the very high ee obtained in the fourth run using cinnamyl alcohol

11 as the substrate, indicating that little or no degradation of the ligand had occurred. Higher yields of ligand recovery were possible if the various aqueous washings were back-extracted and crystallisation mother liquors processed further. Most likely, on larger scales, ligand returns would be higher.

Perhaps as expected and in common with the 'standard' tartrate protocols, the ligands 7 gave much poorer results with both (Z)-allylic and homoallylic alcohols in terms of product ees. However, these did turn out to be very useful for the kinetic resolution of a selection of allylic alcohols. Interestingly, the related ligands 5 (Scheme 3) used by Sharpless were relatively ineffective in such resolutions,[7] although this is not an entirely fair statement, as titanium(IV) tetra-t-butoxide rather than iso-propoxide was used; this subsequently proved to be usually less capable of participating in this type of kinetic resolution[15] (Scheme 7).

In our experiments, we used the now-standard ligand [7d; R = ^{i}Pr] and 0.6 equiv of cumene hydroperoxide [CHP], under otherwise normal SAE conditions. Starting with an allylic alcohol 19 under these conditions, if the resolution were to be successful, the products should be predominantly the epoxy-alcohols 20, together with a smaller amount of isomers 21 and unreacted starting material 22, which should possess high levels of optical activity. In the event, such resolutions worked very well; the results are collected in Table 4.

Yields of the recovered allylic alcohols 24, 26, 28, 30, 32 and 34 were routinely in the region 35–45%, with losses usually due to volatility. The ees of the recovered alcohols[13] shown in Table 4 are followed in parenthesis by the related values obtained using the Sharpless procedure.[15] Overall, these results indicate that the present system is very suited to the kinetic resolution of sterically unencumbered allylic alcohols, with ees of the recovered alcohols only becoming lower in the case of the cyclohexyl-substituted substrate 23, wherein it appears that the presence of a bulky substitu-
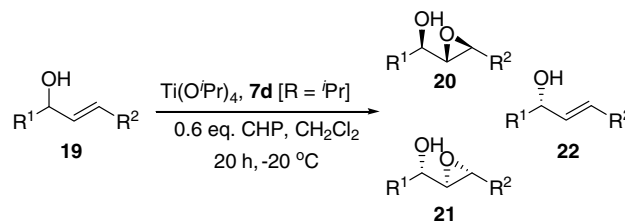
Scheme 7.

Table 4
Kinetic resolutions of allylic alcohols 19

Table 3
Ligand recovery using diester 7d [R = ^{i}Pr]

Allylic alcohol	Epoxide yield (%)	Epoxide ee (%)	Ligand yield (%)	Ligand mp
13	63	86	82	100–102 °C
13	47	84	77	100–101 °C
11	50	82	82	99–101 °C
11	76	97	81	98–100 °C

ent adjacent to the hydroxy group lowers the level of differentiation. However, similar increases in bulk at the opposite end of the allylic alcohol function [e.g., **33**] appear to have little effect. This is consistent with the proposed transition state geometries (Schemes 2 and 3), wherein one would expect substituents adjacent to the alcohol group to interact more significantly with the bulk of the connecting methylene chain than similar groups when attached to the end of the alkene function.

In conclusion, we contend that the ligand **7d** [R = ^{i}Pr] is a viable candidate as a recoverable tartrate surrogate in SAE reactions, especially as it can be prepared in optically pure form in just two straightforward and scalable steps. Clearly, such an effort would not be realistic for a 'one-off' reaction, but certainly such ligand recovery could contribute significantly with respect to costs and in environmental terms in bulk or routine operations, especially if its recovery were to be further optimised during large-scale reactions.

Acknowledgements

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13. GC analysis and ee determinations of epoxy-alcohol **12** derived from cinnamyl alcohol were carried out on an α-DEX 120 column with an oven temperature of 150 °C and the injection port and detector held at 250 °C. The column was fitted in a Hewlett Packard 5890 Series II Gas Chromatograph, equipped with FID and a 6890 series integrator. All samples (0.1–1.0 μL) were subjected to split injection under a column head pressure of 50 kPa of helium, with a gas flow rate of 1 ml/min. All other epoxy-alcohols were analysed as their trifluoroacetates (see Ref. 12), using an Astec Chiraldex GTA column at between 65 and 95 °C, depending on the analyte and conditions as described above. The ees of the resolved secondary alcohols (Table 4) were also determined but by directly using the Chiraldex GTA column at 35–110 °C. In all cases, ee values quoted are the average of three measurements.
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