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Catalytic asymmetric epoxidation of aliphatic enones using tartrate-derived magnesium alkoxides†

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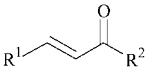
Simple aliphatic enones can be converted into the corresponding epoxides in 71–93% ee using *tert*-butylhydroperoxide in the presence of a catalyst derived from dibutylmagnesium and di-*tert*-butyl tartrate.

The asymmetric epoxidation of electron-deficient alkenes, especially enones, is currently the focus of much activity, and advances in this area have been recently reviewed.[1] As this review makes clear, while there are many effective methods for the asymmetric epoxidation of enones bearing aryl-substituents **1** (R^1 and/or R^2 = Ar),[2–6] it appears at present that the only method which is generally applicable to the epoxidation of easily enolisable purely aliphatic enones involves the use of the La–BINOL catalysts developed by Shibasaki.[7] Recent optimisation of this system by the addition of $Ph_3As{=}O$ has resulted in an effective catalytic system using 5 mol% of the La–BINOL complex,[8] with good yields and enantiomeric excesses up to 99%, although 95% ee is a more typical outcome.



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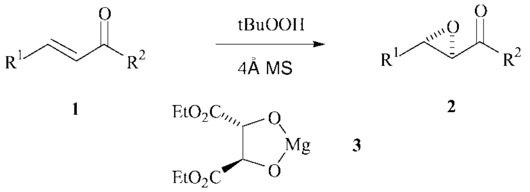
We reported earlier that simple chalcone derivatives **1** (R^1 and R^2 = Ar) could be converted into the corresponding epoxides with good to excellent ee using a much less expensive catalyst, prepared from diethyl tartrate and dibutylmagnesium.[9] However, this system was not especially effective for the epoxidation of aliphatic enones, resulting in very poor conversions, although with promising ees around 80%. In this communication, we report how we have been able to modify our original procedure so that it is effective for the asymmetric epoxidation of simple aliphatic enones with high ee.‡

As a model system, we investigated the epoxidation of non-3-en-2-one **1b**. Our first breakthrough came when we established that the addition of 4 Å molecular sieves allowed reasonable conversion into the corresponding epoxide **2b** (Scheme 1). As a further modification, we established that it was possible to prepare the presumed catalyst precursor **3**, simply by addition of L-(+)-diethyl tartrate to a solution of dibutylmagnesium in heptane, followed by removal of the solvent and drying. Characterisation of this amorphous material confirmed that it possessed the molecular composition expected for an oligomer of the species **3**, and the IR spectrum revealed the presence of two carbonyl bands (1741 and 1689 cm^{-1}), clearly indicative of at least one ester group coordinating to the magnesium in a way that is very reminiscent of the analogous titanium–tartrate complex characterised by Sharpless.[10] The material was insoluble in all solvents tested, and it was therefore not possible to obtain an NMR spectrum.

This amorphous material proved to be an effective catalyst for the epoxidation of aliphatic enones using *tert*-butyl



Scheme 1 Asymmetric epoxidation of aliphatic enones using preformed catalyst **3**.

Table 2 Asymmetric epoxidation of non-3-en-2-one **1b** using dialkyl tartrate esters

R	Conversion (%)[a]	Ee (%)[a]
Me	6	63
C_2H_5	21–31	80–85
Bn	23	85
c-$C_{12}H_{23}$	88	90–93
c-C_5H_9	80	92–93
c-C_6H_{11}	70	92
t-Bu	**96**	**93–95**

[a] Conversions and ee values were measured using chiral phase GC

Table 1 Asymmetric epoxidation of aliphatic enones **1** using preformed catalyst **3**

Enone	R^1	R^2	Time/h	Epoxide	Conversion[a] (yield, %)	Ee (%)[a]
1a	C_4H_9	CH_3	120	**2a**	89% (54)	75
1b	C_5H_{11}	CH_3	120	**2b**	81% (54)	79
1b	C_5H_{11}	CH_3	24[b]	**2b**	82% (nd)	82
1c	C_6H_{13}	CH_3	120	**2c**	86% (52)	71
1d	CH_3	Et	144	**2d**	94% (40)	67
1e	3,5-Di-Br-C_6H_3	CH_3	72	**2e**	88% (47)	65

[a] Conversions and ee values were measured using chiral phase HPLC or GC. Conditions are provided in the ESI.† Isolated yields refer to homogeneous material purified by flash chromatography.[b] After an initial 10 mol% of the catalyst **3**, additional portions were added after 4 h (5 mol%) and after a further 4 h (10 mol%).

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† Electronic supplementary information (ESI) available: conditions for enantiomeric purity determination for epoxyketones derived by di-*tert*-butyl tartrate mediated epoxidation. See http://www.rsc.org/suppdata/cc/b1/b109421a/

Table 3 Asymmetric epoxidation of aliphatic enones **1** using di-*tert*-butyl tartrate as ligand

Enone	R^1	R^2	Time/h	Epoxide	Conversion[a] (yield, %)	Ee (%)[a]
1a	C_4H_9	CH_3	24	**2a**	92% (53)	91
1b	C_5H_{11}	CH_3	24	**2b**	96% (59)	93
1c	C_6H_{13}	CH_3	24	**2c**	92% (63)	92
1d	CH_3	Et	24	*ent*-**2d**	95% (67)	71[b]
1e	3,5-Di-Br-C_6H_3	CH_3	24	**2e**	Nd (62)	81

[a] Conversions and ee values were measured using chiral phase HPLC or GC. Conditions are provided in the supplementary material. Isolated yields refer to homogeneous material purified by flash chromatography.[b] L-(−)-di-*tert*-butyl tartrate was used.

hydroperoxide in the presence of 4 Å molecular sieves. The only drawback was that the conversion to epoxide, whilst initially fast, rapidly slowed down, presumably as a result of catalyst inactivation. However, good conversions could be achieved by portionwise addition of further solid catalyst **3** (total of 25 mol%), which was a straightforward solution to the problem. Addition of 25 mol% catalyst initially resulted in very poor conversion. Although in our early experiments we added the catalyst **3** over a period of 3–5 d, it subsequently became clear that the additional catalyst could be added much more quickly, and good conversions could be achieved by addition of a total of 25 mol% catalyst over a period of 24 h. Our results are summarised in Table 1.

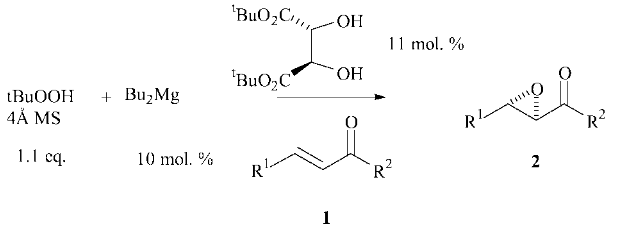
While these results were encouraging, the enantiomeric excesses that we obtained were lower than those obtained by Shibasaki. Although in our initial screening of ligands for the epoxidation of chalcone derivatives we had identified diethyl tartrate as the optimum choice, the most profitable approach to the optimisation of our catalyst now appeared to be a re-appraisal of other related ligands under the new optimised conditions for epoxidation of aliphatic enones. We therefore screened a series of tartrate esters, in which the catalyst was simply prepared *in situ*.

Thus, *tert*-butyl hydroperoxide was dried over 4 Å molecular sieves, Bu_2Mg was then added, followed by addition of the ligand and finally non-3-en-2-one. These conditions were very closely related to our original conditions for the epoxidation of chalcone derivatives, with the use of 4 Å molecular sieves as the only significant alteration to this earlier procedure. Our results are reported in Table 2, and two striking features are evident. Firstly the use of tartrate esters derived from secondary or tertiary alcohols gave much higher conversions with only 10 mol% catalyst, and secondly the observed ee's were now over 90%.

From these results, the optimum ligand appears to be commercially available di-*tert*-butyl tartrate, but the more easily prepared and cheaper dicycloalkyl tartrates all give good results. Use of L-(+)-di-*tert*-butyl tartrate for the epoxidation of a range of other aliphatic enones resulted in equally good results for the long chain aliphatic enones, Scheme 2, although the challenging substrate **1d** still falls short of a usable level of enantiomeric excess. Our results are reported in Table 3.

The higher enantiomeric excesses obtained using the bulkier ester derivatives may be rationalised on simple steric grounds, but the apparently higher catalytic activity of the corresponding magnesium tartrate derivatives of these bulkier tartrate esters is not so immediately explained. The most probable explanation is that the magnesium catalysts formed from the bulkier tartrate esters are simply less prone to hydrolysis, and hence to inactivation.

The magnesium tartrate system appears to offer the prospect of an alternative to the excellent La–BINOL system in which although the amount of catalyst required is higher (typically 10 mol% for the Mg system, compared with 1–5 mol.% for the La–BINOL system), the cost of the catalyst precursors is several orders of magnitude less.



Scheme 2 Asymmetric epoxidation of aliphatic enones using *in situ* generated catalyst.

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Notes and references

‡ **General procedure for the asymmetric epoxidation of aliphatic enones using di-*tert*-butyl tartrate:** *tert*-butyl hydroperoxide (3.7 M in toluene, 1.1 mmol, 1.1 eq.) was dried over activated powdered 4 Å molecular sieves (200 mg, activated for 4 h at 200 °C) for 2 h. Bu_2Mg (1 M in heptane, 0.1 mmol, 0.1 eq.) was added. After stirring for 30 min, L-(+)-di-*tert*-butyl tartrate (0.11 mmol, 0.11 equiv.) was added. After an additional period of 30 min stirring, the aliphatic enone (1 mmol) was added, and the mixture was stirred for 24 h. The conversion and enantiomeric excess were checked either by chiral phase GC or HPLC. We have observed that best results are obtained with solutions of *tert*-butyl hydroperoxide that have been stored over 4 Å molecular sieves for an extended period.

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