Available online at www.sciencedirect.com

SCIENCE DIRECT®

Journal of Molecular Catalysis A: Chemical 251 (2006) 123–128

JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL

www.elsevier.com/locate/molcata

Effective asymmetric oxidation of enones and alkyl aryl sulfides

Melissa Hinch[a], Olivier Jacques[a], Carmelo Drago[a], Lorenzo Caggiano[a], Richard F.W. Jackson[a,*], Charles Dexter[b], Mike S. Anson[c], Simon J.F. Macdonald[c]

[a] Department of Chemistry, University of Sheffield, Dainton Building, Sheffield S3 7HF, United Kingdom
[b] Rhodia Pharma Solutions, Dudley, Cramlington NE23 7QG, United Kingdom
[c] GlaxoSmithKline, Medicines Research Centre, Stevenage SG1 2NY, United Kingdom

Abstract

Asymmetric epoxidation of aliphatic enones can be achieved with good conversions and high levels of enantiomeric excess using a catalyst, formulated as **6**, derived from dibutylmagnesium and a range of dialkyl tartrates, with *tert*-butylhydroperoxide as the oxidant. This process works best with the addition of small amounts of water and 4 Å molecular sieves, and can be scaled up to good effect. Optimisation of Bolm and Bienewald's vanadium-based method for asymmetric oxidation of alkyl aryl sulfides by aqueous hydrogen peroxide using Schiff bases derived from *tert*-leucinol as ligands, confirmed that the ligand **12** derived from 3,5-diiodosalicylaldehyde is the optimum choice.

Keywords: Asymmetric; Nucleophilic epoxidation; Magnesium; Sulfur oxidation; Vanadium

1. Catalytic asymmetric epoxidation of enones

Since the pioneering studies of Julia and Colonna [1,2], who discovered the first effective method for the catalytic asymmetric epoxidation of chalcone derivatives using a combination of polyamino acid, base and aqueous hydrogen peroxide, a great deal of effort has been devoted to improving the practicality of this method [3–11], and to discovering new methods to achieve this transformation. In this latter regard, chiral phase transfer catalysts in combination with a base and a suitable oxidant have proved to be effective [12–19], as has the use of various metal-based systems. Initial results included the stoichiometric use of alkylzinc alkylperoxides [20,21], the use of chiral polybinaphthyl zinc complexes as catalysts with *tert*-butylhydroperoxide as oxidant [22], and the catalytic use of zinc/BINOL derivatives [23]. Each of these approaches generally only works well for enones in which at least one of the substituents is an aromatic residue (or another residue which prevents enolisation), and this is a limitation. Arguably the most general method for the catalytic asymmetric epoxidation of enones is that discovered by Shibasaki and co-workers, using a combination of lanthanide alkoxides and (substituted) BINOL derivatives, with *tert*-butylhydroperoxide as the oxygen source [24,25]. This reagent system not only epoxidises simple *trans*-aliphatic enones, but is also able to epoxidise *cis*-aliphatic enones [26] preserving the original stereochemistry of the alkene in the *cis*-epoxide product. Recent work has shown how the process can be adapted for the epoxidation of a range of unsaturated carboxylic acid derivatives [27,28], culminating in a process for epoxidation of unsaturated esters [29]. A comprehensive review of the whole area of asymmetric epoxidation has very recently been published [30], which updates an earlier, more specific, review on nucleophilic epoxidation [31].

2. Results and discussion

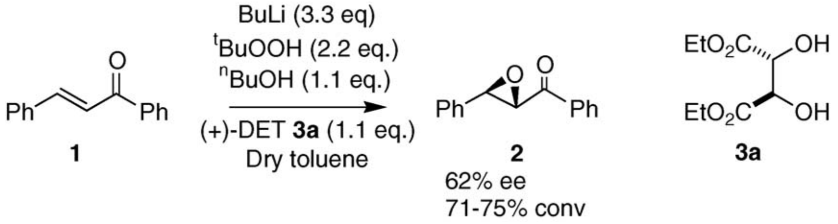
Our contributions in this field have been based on the use of main group metals. We first established that treatment of chalcone **1** with a reagent prepared from lithium *tert*-butylperoxide, prepared from *n*-butyllithium and *tert*-butylhydroperoxide (dried by azeotropic distillation using the method of Sharpless) [32], and a stoichiometric amount of diethyl tartrate **3a** gave the corresponding epoxide **2** in reasonable yield, and 62% ee (Scheme 1). It was essential that a stoichiometric amount of lithium butoxide was also present [33].

In contrast, when use of the corresponding magnesium system was explored, it was discovered that in this case only a catalytic amount of base (dibutylmagnesium) and chiral ligand

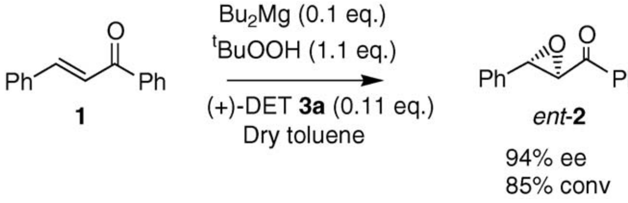
---

[*] Corresponding author. Tel.: +44 114 222 9464; fax: +44 114 222 9319.
E-mail address: r.f.w.jackson@shef.ac.uk (R.F.W. Jackson).

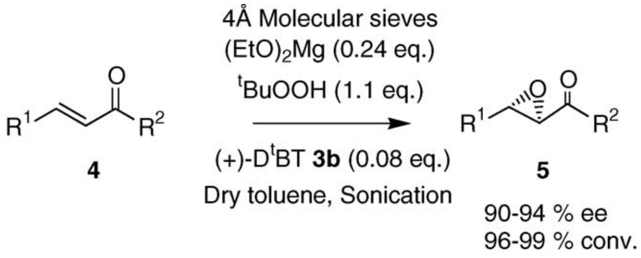
1381-1169/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2006.02.006



Scheme 1. Stoichiometric asymmetric epoxidation of chalcone using lithium *tert*-butylperoxide.



Scheme 2. Catalytic asymmetric epoxidation of chalcone.

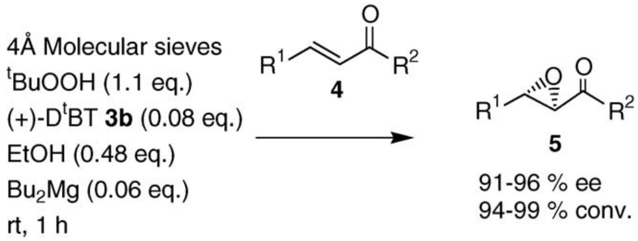


Scheme 4. Catalytic asymmetric epoxidation of aliphatic enones using $Mg(OEt)_2$ as the base and ultrasonication.

(diethyl tartrate) were required to effect epoxidation. The reaction was substantially more enantioselective, giving chalcone epoxide *ent*-**2** in 94% ee, and of the opposite absolute configuration to that obtained in the lithium system with the same enantiomer of ligand (Scheme 2) [33].

Application of the same reaction conditions to the epoxidation of simple aliphatic enones **4** gave results that were encouraging from the point of view of enantioselectivity (with the epoxy ketone products **5** being formed in up to 76% ee), but the conversions were modest (typically 33%), suggesting that catalyst inactivation was occurring. Reminiscent of the way that addition of activated 4 Å molecular sieves renders the Sharpless asymmetric epoxidation process catalytic [34,35], addition of powdered, activated 4 Å molecular sieves to our nucleophilic epoxidation system increased not only the conversion, but also the enantioselectivity. Exploration of a range of different tartrate derivatives showed that tartrate esters derived from secondary or tertiary alcohols performed the best, with di-*tert*-butyl tartrate **3b** giving high conversions (92–96%) and excellent enantioselectivity (up to 93%) of the product epoxy ketones **5** (Scheme 3) [36].

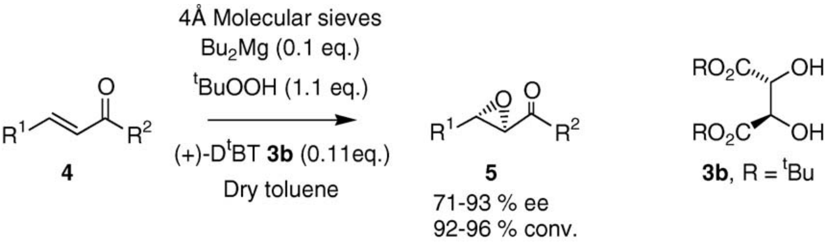
Given that the presumed catalyst was prepared by treatment of dibutylmagnesium with a dialkyl tartrate, it seemed reasonable to explore other magnesium bases. Provided ultrasonication was employed, magnesium ethoxide allowed similarly high levels of conversion and enantioselectivity to be attained (Scheme 4).



Scheme 5. Addition of ethanol allows the catalytic asymmetric epoxidation of aliphatic enones using $Mg(OEt)_2$ as the base without ultrasonication.

While the use of ultrasonication was effective, it was not especially convenient, and it was therefore gratifying to discover that addition of a small amount of ethanol could fulfill the same purpose. This modification also allowed a substantial reduction in the amount of base required (Scheme 5). After formation of the active catalyst (normally treatment for 1 h), epoxidation was usually complete within 18–24 h at room temperature.

The nature of the active catalytic species remains an open question, but it appears reasonable to speculate that it is the magnesium alkoxide **6b**, derived from the di-*tert*-butyl tartrate ligand. Such a species would be able to activate both the substrate enone **4** (by magnesium complexation to the carbonyl group), and the *tert*-butylhydroperoxide, by deprotonation. It seems likely that both of these steps take place within the chiral environment of the tartrate ligand, thus allowing facial discrimination in the attack of the nucleophilic *tert*-butylhydroperoxide



Scheme 3. Catalytic asymmetric epoxidation of aliphatic enones using Bu_2Mg as the base.