ChemComm
FEATURE ARTICLE

Asymmetric epoxidation of electron-deficient olefins

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Received (in Cambridge, UK) 6th March 2000, Accepted 26th April 2000
Published on the Web 9th June 2000

In recent years, methods for the asymmetric epoxidation of electron-deficient olefins, particularly α,β-enones, have attracted widespread attention. A critical review is presented of these methods, which include epoxidations with chiral metal hydroperoxides, asymmetric phase-transfer methods, the use of polyamino acid catalysts and the use of chiral dioxiranes.

1. Introduction

Epoxidation holds a venerable place in the history of catalytic asymmetric synthesis. The development by Sharpless in the early 1980s of a system which can efficiently and predictably produce either enantiomer of an epoxide from an allylic alcohol using substoichiometric quantities of titanium and tartrate, paved the way for much of today's catalytic asymmetric synthesis.[1] Following this discovery, much progress has been made towards the asymmetric epoxidation of other classes of olefins; in particular the manganese–salen reagents of Jacobsen and Katsuki perform admirably in the asymmetric epoxidation of unfunctionalised, and particularly conjugated (*Z*)-disubstituted olefins.[2] More recently, the work of several groups has indicated that dioxiranes generated *in situ* from Oxone® and chiral ketones show great promise as asymmetric epoxidation reagents for a range of alkenes.[3]

On the other hand, no system for the asymmetric epoxidation of electron-deficient olefins has gained widespread popularity amongst synthetic organic chemists. Indeed, only recently have systems been described which allow the epoxidation of a wide range of enones with high enantioselectivity. This review introduces and compares the most significant and general of these epoxidation methods.

Most of the methods for the enantioselective epoxidation of electron-deficient alkenes are essentially asymmetric variants of the Weitz–Scheffer epoxidation[4] using alkaline H_2O_2; they are thus selective for electron-deficient alkenes in the presence of other olefins. A number of more general epoxidation methods have been applied to electron-poor olefins, and these are presented towards the end of this review.

As this survey is designed to cover those methods which may be generally applicable and synthetically useful for a range of olefins, we have chosen to exclude methods which rely on a different structural feature (such as an allylic alcohol) for the asymmetric epoxidation of an electron-deficient alkene.[5] In addition, isolated reports of epoxidations not developed with synthetic utility in mind, such as the isolation of a cell-free extract with quinone mono-oxygenase activity,[6] have been omitted.

2. Chiral ligand–metal peroxide systems

Several methods for the asymmetric epoxidation of electron-deficient alkenes rely on the use of a chiral ligand coordinated to the metal atom of a metal peroxide, which then executes a Weitz–Scheffer reaction. A number of metals, including zinc, lithium, magnesium and various lanthanides, have been used for this purpose and these methods are discussed in further detail below. In addition, Strukul and coworkers have described an asymmetric epoxidation process mediated by a platinum–diphosphine–peroxide complex, but the yields and enantioselectivities obtained in this reaction are moderate at best.[7]

a. Zinc-mediated asymmetric epoxidation

In 1996, Enders *et al*. disclosed that (*E*)-α,β-unsaturated ketones can be epoxidised in asymmetric fashion using stoichiometric quantities of diethylzinc and a chiral alcohol, under an oxygen atmosphere, to give *trans*-epoxides (Scheme 1).[8] Following screening of 35 optically active alcohols, (1*R*,2*R*)-*N*-methylpseudoephedrine (**1**) was selected as the alcohol which gave the best enantioselectivities. Furthermore, it was found that **1** could be recovered in almost quantitative yield from the reaction mixture.

More recently, Pu and coworkers have reported the use of a chiral polybinaphthyl **2** in similar reactions;[9] slightly in excess of 1 equivalent (based on the monomer binaphthyl unit) of **2** was necessary for the reaction to proceed.

As can be seen from Table 1, Enders' system gives excellent yields for several classes of enone for which the Pu conditions lead to much lower yields.[10] Furthermore, while the two methods are comparable in giving a moderate ee for the

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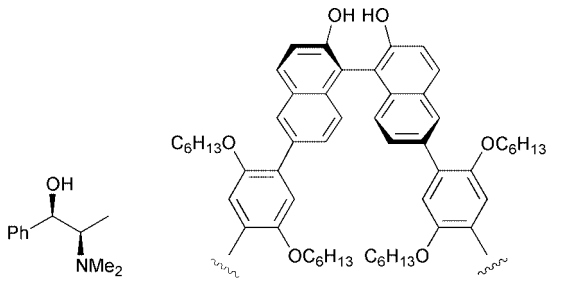
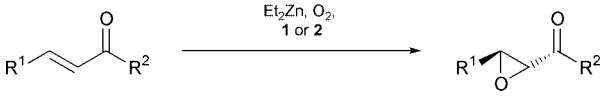
DOI: 10.1039/b001780i





Scheme 1

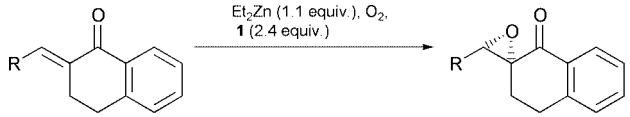
Table 1 Comparison of the Enders[8] and Pu[9] ligands

R^1	R^2	Method[a]	Yield (%)	Ee (%)
Ph	Ph	A	94	61
		B	41	71[b]
Pr^i	Ph	A	97	92
		B	18	25[b]
Me	Ph	A	96	85
$Ph(CH_2)_2$	Bu^t	A	99	90

[a] A = **1** (2.4 equiv.), Et_2Zn (1.1 equiv.), O_2; B = **2** (1.1 equiv.), Et_2Zn (1.05 equiv.), O_2. [b] The predominant isomer was the enantiomer of that illustrated.

epoxidation of chalcone, Enders' system also shows high asymmetric induction for alkyl-substituted enones.

Enders' reagent has also been used for the asymmetric epoxidation of a series of β-alkylidene-α-tetralones (Scheme 2, Table 2).[8b] It appears that the enantioselectivity of the process generally increases as the substituent, R, increases in size. The reaction, however, fails for other α-substituted enones; it was surmised that this may be due to the requirement for an *s-cis* conformation of the enone moiety.

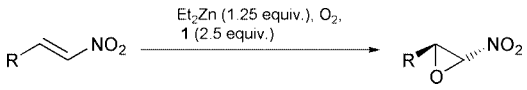


Scheme 2

Table 2 Epoxidation of alkylidenetetralones using Enders' ligand[8b]

R	Yield (%)	Ee (%)
H	40	3
Me	85	80
Et	65	90
Pr^i	98	> 99
Ph	62	64

In addition to enones, the diethylzinc/oxygen/**1** system has been used for epoxidation of some (*E*)-nitroalkenes (Scheme 3, Table 3).[11] The absolute stereochemistry of the nitroepoxides was assumed by analogy with the enone substrates.



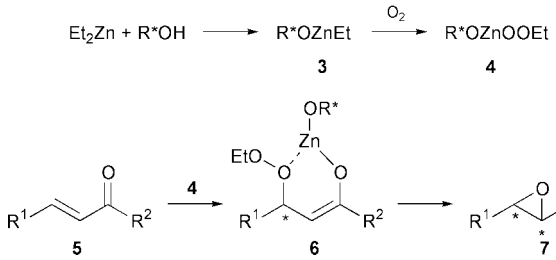
Scheme 3

Both Enders and Pu have proposed similar reaction pathways, based on the Weitz–Scheffer mechanism, for their

Table 3 Epoxidation of nitroalkenes using Enders' ligand[11]

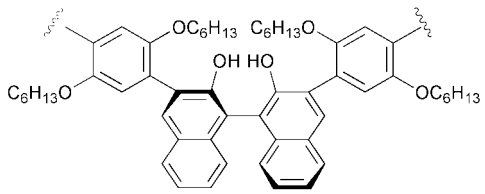
R	Yield (%)	Ee (%)
$Ph(CH_2)_2$	64	37
Pr^i	53	42
Bu^t	57	82

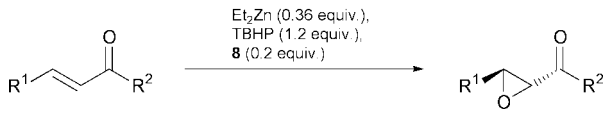
asymmetric epoxidations (Scheme 4). It is suggested that diethylzinc reacts with the chiral ligand (**1** or **2**) to give a zinc alkoxide **3**, with the loss of ethane. Reaction of **3** with molecular oxygen then gives rise to a chiral metal peroxide **4**. Stereoselective conjugate addition of this peroxide to an enone **5** affords intermediate zinc enolate **6**, which then collapses to the chiral epoxide **7** and a zinc dialkoxide.



Scheme 4

Improving upon the stoichiometric process described above, Pu and coworkers have developed a variant which is catalytic in zinc and ligand, using the modified polybinaphthyl **8**.[9] In this epoxidation process, oxygen is replaced as the stoichiometric oxidant by *tert*-butyl hydroperoxide (TBHP) (Scheme 5, Table 4). Under these adapted conditions, both chalcone derivatives and alkyl-substituted enones are epoxidised with high yields and acceptable levels of enantiocontrol.





Scheme 5

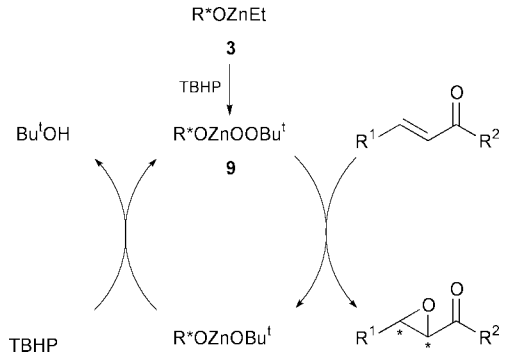
Table 4 Catalytic asymmetric epoxidation using Pu's ligand[9]

R^1	R^2	Yield (%)	Ee (%)
Ph	Ph	95	74
p-ClC_6H_4	Ph	81	79
Pr^i	Ph	94	81
Bu^t	Ph	67	64

For this catalytic process, a slight modification of the mechanism in Scheme 4 has been proposed (Scheme 6). In this case, the initially formed chiral zinc alkoxide **3** reacts with TBHP to give zinc peroxide species **9**, with the loss of a second ethane molecule. Following formation of the epoxide, ligand exchange of *tert*-butyl alcohol for a TBHP molecule regenerates the chiral zinc peroxide **9**.

b. Lanthanide-BINOL systems

Shibasaki *et al*. have developed a series of complexes of general form $LnM_3(BINOL)_3$, $AlM(BINOL)_2$ and $GaM(BINOL)_2$ (Ln

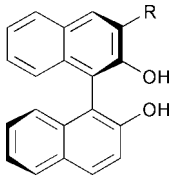


Scheme 6

= lanthanide, M = alkali metal) which have been shown to catalyse a range of transformations, such as Diels–Alder cyclisation, aldol condensation and Michael addition, in an asymmetric fashion.[12] It is believed that these bimetallic catalysts are effective owing to the presence of a Brønsted basic and a Lewis acidic site which serve to orientate the substrate and reagent in a chiral environment such that reaction may occur; Shibasaki compares this to the behaviour of some enzymes.

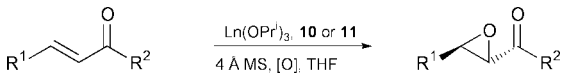
It was found that $LaNa_3[(R)\text{-BINOL}]_3$ catalyses the epoxidation of chalcone by *tert*-butyl hydroperoxide (TBHP) to afford (2*S*,3*R*)-epoxychalcone in 92% yield and 83% ee. Unfortunately, this epoxidation method did not prove to be generally applicable to other enones.[13*a*]

In the case of some Michael additions, Shibasaki and coworkers had previously found that alkali metal-free complexes were effective catalysts. Following this precedent, it was found that reaction of an equimolar mixture of (*R*)-BINOL **10** and $La(OPr^i)_3$ in the presence of 4 Å molecular sieves generates a complex capable of catalysing the asymmetric epoxidation of a range of (*E*)-enones. In this case, cumene hydroperoxide (CMHP) proved to be the most effective oxidant (*e.g.* chalcone was epoxidised in 93% yield and 83% ee). Alternative ligands were investigated and a substantial improvement in enantioselectivity was observed with 3-hydroxymethyl-BINOL **11**



10 R = H
11 R = CH_2OH

($Ln(OPr^i)_3$: **11** = 1:1.25). It was found that the optimum lanthanide was dependent on the nature of the enone; aryl ketones were more effectively epoxidised using a La–**11**–CMHP system whilst alkyl ketones responded better to Yb–**11**–TBHP (Scheme 7, Table 5, methods A and B).[13*a*] Recently, Shibasaki and coworkers used this method for a diastereoselective epoxidation as part of a synthesis of some prostaglandins.[13*b*]



Scheme 7

Shibasaki has made some interesting observations concerning the mode of action of these catalysts. He suggests (citing ^{13}C NMR evidence) that they adopt an oligomeric structure, allowing one Ln–BINOL moiety to act as a Brønsted base to deprotonate the hydroperoxide whilst a second Ln–BINOL unit

Table 5 Comparison of lanthanide–BINOL based epoxidation systems[13*a*,14,15]

R^1	R^2	Method[a]	Yield (%)	Ee (%)
Ph	Ph	A	93	91
		C	99	81
		D	99	96
Pr^i	Ph	A	95	94
		D	89	93
Ph	Me	B	83	94
		C	92	94
		D	92	93
n-C_5H_{11}	Me	B	71	91
Ph	Pr^i	B	55	88
		C	82	93
		D	67	96

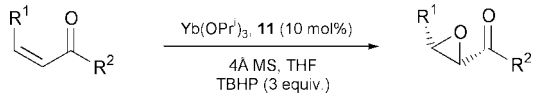
[a] A = ($La(OPr^i)_3$–**11**) (5 mol%), CMHP (1.5 equiv.), 4 Å sieves;[13*a*] B = ($Yb(OPr^i)_3$–**11**) (5–8 mol%), TBHP (1.5 equiv.), 4 Å sieves;[13*a*] C = ($Yb(OPr^i)_3$–**10**) (5 mol%), TBHP (1.5 equiv.), 4 Å sieves, water (22.5 mol%);[14] D = ($La(OPr^i)_3$–**10**) (5 mol%), TBHP (1.5 equiv.), 4 Å sieves, triphenylphosphine oxide (15 mol%).[15]

acts a Lewis acid, activating and controlling the orientation of the enone. A chiral amplification effect, whereby the ee of the product epoxide can exceed that of the ligand, was provided as evidence for this dual role.[13*a*]

More recently, Shibasaki and coworkers[14] have reported a method for improving the activity of the Yb–BINOL **10**–TBHP system allowing enantioselectivities to be attained which are comparable with the more expensive Yb–**11** catalyst. Addition of water (4.5 equivalents relative to $Yb(OPr^i)_3$) to a catalyst generated from $Yb(OPr^i)_3$: BINOL **10** (2 : 3) was found to give optimal results (Scheme 7, Table 5, method C). Surprisingly, it was found still to be necessary to add molecular sieves to this system in order to obtain effective catalysis. The catalysts generated from ligand **11** are not improved by the addition of water in an analogous manner and it should be noted that, as the above modification is of the ytterbium-based catalyst, ees are lower in the case of aryl ketones. Shibasaki has advanced an explanation for the effect of water, suggesting that it coordinates to ytterbium and controls the orientation of the hydroperoxides to form an appropriate asymmetric environment for the epoxidation.

Inanaga and coworkers have investigated the effect of a range of additives on Shibasaki's La–BINOL **10** catalyst. Comparison of lutidine-*N*-oxide, 1,3-dimethyl-2-imidazolidinone, tri-*n*-butylphosphine oxide, triphenylphosphine oxide, tri-*o*-tolylphosphine oxide, tri-*p*-tolylphosphine oxide and HMPA revealed that triphenylphosphine oxide is the most effective additive.[15] For the epoxidation of chalcone the addition of triphenylphosphine oxide (15 mol%) produced an improvement in ee from 73 to 96%. Similarly high ees were found for three alkyl ketones; unlike Shibasaki's lanthanum complexes, this catalytic system is applicable to alkyl and aryl enones (Scheme 7, Table 5, method D). It was suggested that the activation is due to the disruption of the oligomeric structure of the catalyst by coordination of the phosphorus-based ligand.

Shibasaki has shown that the unmodified Yb–**11** catalyst is also effective for the epoxidation of (*Z*)-enones to the corresponding *cis*-epoxides (Scheme 8, Table 6).[16] The trans-



Scheme 8

formation proceeds with good yields and high stereoselectivity for aliphatic enones. In the case of aromatic enones, the reaction is less effective owing to formation of substantial (up to 32%) amounts of the unwanted *trans*-epoxide. Interestingly the use of a given enantiomer of the BINOL derived ligand **11** generates

Table 6 Epoxidation of (*Z*)-olefins to afford *cis*-epoxides[16]

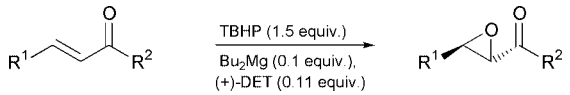
R^1	R^2	Yield (%)	Ee (%)
n-C_5H_{11}	Me	74	94
Pr^n	$(CH_2)_2Ph$	78	93
n-C_5H_{11}	Pr^n	80	96
Me	Ph	60	82
Pr^n	Ph	51	88

the opposite sense of stereochemistry at the β-carbon compared to the epoxidation of (*E*)-enones; thus the (*R*)-**11** catalyst converts (*Z*)-enones to the (2*S*,3*S*)-epoxides. The Yb–**11** catalyst also proved effective in the epoxidation of a trisubstituted enone, $Me_2C=CHCOPh$ being converted to the corresponding epoxide in 78% yield and 87% ee.[16]

c. Diethyl tartrate-metal peroxides

Jackson and coworkers have reported the epoxidation of enones using metal peroxides modified by chiral ligands.[17] Initial work investigated the effect of stoichiometric quantities of a range of chiral ligands on the addition of lithium *tert*-butyl peroxide (generated *in situ* from *tert*-butyl hydroperoxide (TBHP) and *n*-butyllithium) to chalcone. Diethyl tartrate (DET) was found to be the most effective ligand and an equivalent of lithium *tert*-butoxide was required for the reaction to proceed. The use of 1.1 equivalents of (+)-DET in a non-coordinating solvent, typically toluene, afforded the (2*R*,3*S*)-epoxide in 71–75% yield and 62% ee.

Attempts to use substoichiometric quantities of the ligand in this reaction were ineffective; however, replacement of *n*-butyllithium by dibutylmagnesium gave a system in which the use of only 11 mol% of DET and 10 mol% of the base was necessary for high levels of asymmetric induction on a range of chalcone-type enones (Scheme 9, Table 7). Interestingly the catalytic magnesium system generates epoxides antipodal with those obtained using the stoichiometric lithium system.



Scheme 9

Table 7 Asymmetric epoxidation using Jackson's system[17]

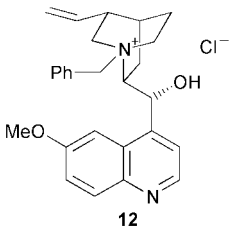
R^1	R^2	Yield (%)	Ee (%)
Ph	Ph	61	94
p-ClC_6H_4	Ph	54	81
p-MeC_6H_4	Ph	36	84
Ph	2-Naphthyl	46	92

3. Phase-transfer catalysis

Phase-transfer catalysis, developed initially in the mid-1960s, typically uses an organic salt (such as a quaternary ammonium salt) to transport inorganic ions into an organic phase. By using chiral ammonium salts, it is possible to induce asymmetry in reactions such as enolate alkylations, Michael additions and Darzens reactions.[18]

The most common phase-transfer reagents used for the asymmetric epoxidation of enones are alkylated *Cinchona* alkaloids. A handful of papers using other chiral phase-transfer salts has appeared,[19] but ees for these epoxidations are low (≤37%).

The possibility of using a chiral phase-transfer salt in a biphasic Weitz–Scheffer epoxidation was first investigated by Wynberg and coworkers in the mid-1970s. A series of papers was published in which phase-transfer catalysts **12** and **13** were



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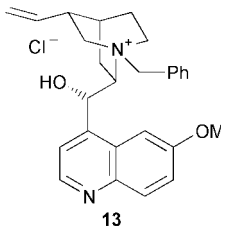

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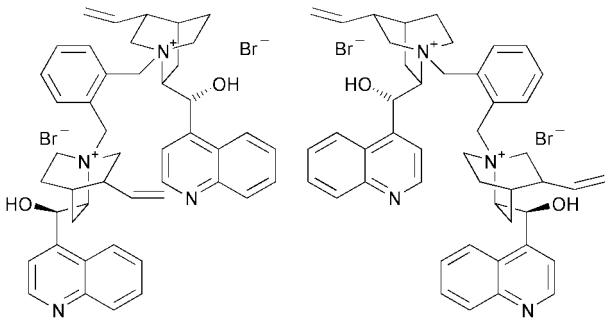
produced by *N*-benzylation of quinine and quinidine respectively.[20]

These compounds proved capable of catalysing the asymmetric epoxidation of a wide range of enones using aq. H_2O_2, *tert*-butyl hydroperoxide (TBHP) or sodium hypochlorite as oxidant; the ees obtained were in the range 0–54%. In an isolated example, an ee of 78% was obtained by Harigaya *et al.*, using **12** as the catalyst in the epoxidation of a 2-aryl naphthoquinone.[21]

Kawaguchi and coworkers have reported phase-transfer epoxidation using a related set of catalysts: a C_2-symmetrical pair, **14** and **15**, derived by reaction of the alkaloids cinchonidine and cinchonine respectively with α,α'-dibromo-*o*-xylene; and *N*-(9-fluorenyl)quininium bromide (**16**). These salts catalyse the epoxidation of cyclohexenone with ees up to 63%.[22]



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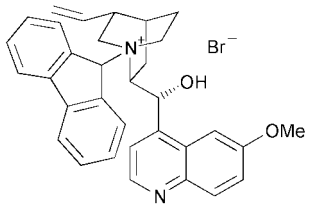

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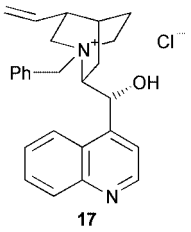
More recently, **12** and similar phase-transfer catalysts based on *Cinchona* alkaloids have been utilised by Taylor and coworkers for the asymmetric synthesis of the manumycin class of natural products. Best results were obtained using *N*-benzylcinchonidinium chloride (**17**), which mediated the epoxidation of enone **18** in 32% yield and 89% ee (Scheme 10).[23]

Two recent reports have shown significant improvements in phase-transfer catalysed asymmetric epoxidation. In 1998, Lygo and Wainwright described the use of catalysts **20** and **21**, derived from cinchonidine and cinchonine respectively; these differ from catalysts of the Wynberg type (**12** and **13**) as they incorporate a 9-anthracenylmethyl group in place of the benzyl group on the quinuclidine nitrogen, and bear a benzyl group on the secondary alcohol. In the presence of sodium hypochlorite as stoichiometric oxidant, these catalysts mediate the epoxidation of a wide range of substituted chalcones and alkyl-substituted enones with complete diastereoselectivity and with ees in the range 69–90% (Scheme 11, Table 8, method A); **12** and **13** provide products with opposite senses, but similar magnitudes, of stereoinduction.[24]



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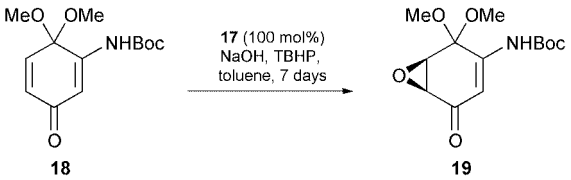

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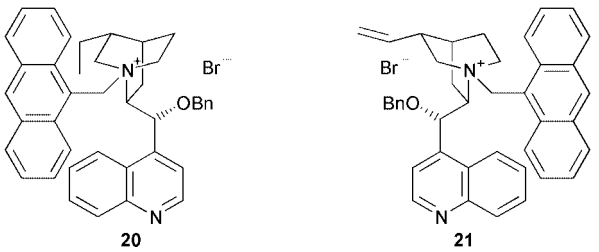
Scheme 10



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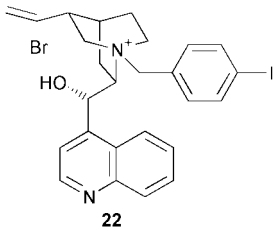

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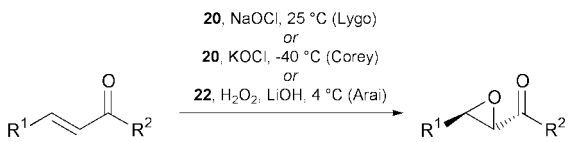


Scheme 11

Table 8 Comparison of the Lygo,[24] Corey[25] and Arai[26] epoxidations

R^1	R^2	Method[a]	Yield (%)	Ee (%)
Ph	Ph	A	90	86
		B	96	93
		C	97	84
Ph	*p*-BrC_6H_4	A	99	88
		B	92	93
p-$MeOC_6H_4$	Ph	A	87	82
		B	70	95
Cy	Ph	B	85	94
m-MeC_6H_4	Ph	C	100	92
n-C_6H_{13}	*p*-BrC_6H_4	A	89	84
n-C_5H_{11}	*p*-FC_6H_4	B	90	91
Ph	Bu^t	A	40	85
Bu^t	Ph	C	90	55

[a] A = **20** (0.1 equiv.), NaOCl (2 equiv.), 25 °C; B = **20** (0.1 equiv.), KOCl (5 equiv.), −40 °C; C = **22** (0.05 equiv.), aq. H_2O_2 (10 equiv.), LiOH (3 equiv.), 4 °C.

More recently, Corey and Zhang have shown that the use of catalyst **20** with potassium hypochlorite as the stoichiometric oxidant and a reaction temperature of −40 °C, gives epoxidation of a range of enones with ees of 90–99% (Scheme 11, Table 8, method B).[25] Epoxidation of β-alkylidene-α-tetralones, however, gives ees of only 61 and 76%; Corey interprets this as an indication that a non-planar enone geometry is favoured in the epoxidation reaction (*vide infra*).

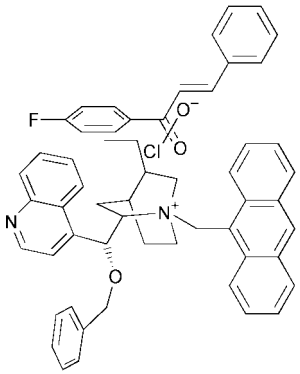


Fig. 1

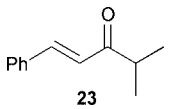
Further *Cinchona* catalysts have been developed by Arai *et al.*, who surveyed the alkylation of cinchonine with a range of substituted benzyl bromides.[26] Notably, *N*-(4-iodobenzyl)cinchoninium bromide (**22**) allows highly stereoselective oxidation of chalcone derivatives, although the ees are lower for alkyl-substituted enones (Scheme 11, Table 8, method C). Intriguingly, the epoxides obtained using this cinchonine-derived catalyst are generated with the opposite sense of stereoinduction to those from Lygo's cinchonine-derived catalyst **21**. The same authors also described a quinidine-based phase-transfer catalyst which was used to epoxidise substituted naphthoquinones and acyclic enones with ees ranging from 17 to 76%.[27]

Corey and Zhang[25] have posited a three-dimensional arrangement of ammonium cation **20**, benzal-4-fluoroacetophenone and hypochlorite ion to account for the observed stereoselectivity (Fig. 1). In this model, the fluorophenyl ring of the substrate is twisted out of conjugation with the carbonyl group and is wedged between the ethyl and quinoline substituents of the catalyst. The hypochlorite ion is contact ion-paired with the charged nitrogen and the carbonyl oxygen is placed as close to the N^+ as is permitted by van der Waals forces. This arrangement places the nucleophilic oxygen of the hypochlorite ion in proximity to the β-carbon of the enone, and positioned such that only one face of the enone is accessible.

4. Polyamino acid catalysed epoxidation[28]

In 1980 Juliá *et al*. reported the poly-L-alanine catalysed asymmetric epoxidation of chalcone (Scheme 12).[29] The Juliá reaction conditions were triphasic, consisting of the insoluble polyamino acid catalyst, an aqueous solution of NaOH and H_2O_2 and a solution of chalcone in an organic solvent. The polyamino acid catalyst could readily be prepared from the corresponding amino acid *via* conversion to the *N*-carboxy-anhydride (NCA) and then treatment with an initiator such as water, a simple primary amine or a polystyrene-bonded amine.[30] It was found that enantioselectivity of the epoxidation increased as the average chain length increased from 10 to 30 residues. Over a series of papers the group of Juliá and Colonna investigated this method for the epoxidation of chalcone and simple analogues.[29,31] Their contribution to this field has recently been reviewed elsewhere.[28c] An important feature of the Juliá–Colonna epoxidation is that the insoluble catalyst may be readily separated from the reaction products, washed and reused. It was reported, however, that on reuse the catalyst frequently gave reduced enantioselectivity, a phenomenon ascribed to degradation of the catalyst under the strongly basic reaction conditions.[31c] A limitation of the Juliá-Colonna methodology is the length of reaction; even relatively reactive substrates such as chalcone and simple derivatives require 24 hours for complete conversion.[31a] Less reactive substrates

either generate products in low yield and ee or fail to form any epoxide. In particular enolisable substrates such as **23** (60% yield, 62% ee)[32] and **24** (decomposition)[33] are poor substrates for the triphasic reaction conditions.



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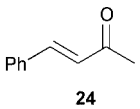

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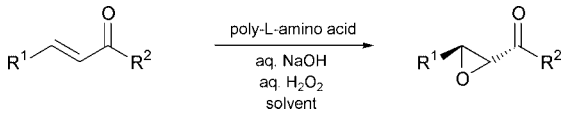
Nonetheless, a reasonable range of epoxides has been prepared using the triphasic reaction conditions by Juliá and Colonna and by others (Scheme 12, Table 9).



Scheme 12

Table 9 Substrates epoxidised under Juliá–Colonna conditions

R^1	R^2	Catalyst[a]	Yield (%)	Ee (%)	Ref.
Ph	Ph	PLA	85	93	29
Ph	*o*-$MeOC_6H_4$	PLA	54	50	31*a*
Ph	2-Naphthyl	PLL	90	93	34
Ph	2-Furyl	PLL	85	87	34
Ph	2-Pyridyl	PLL	74	79	34
o-[$Ph(CH_2)_8$]C_6H_4	2-Naphthyl	PLL	82	95	35
p-$MeSC_6H_4$	2-Naphthyl	PLL	65	96	36
Ph	2-Thienyl	PLA	96	80	31*a*
2-Furyl	2-Naphthyl	PLL	75	> 96	34
2-Pyridyl	Ph	PLL	84	72	34
4-Pyridyl	2-Naphthyl	PLL	67	> 96	34
p-$MeOC_6H_4$	*o*-MOMO-C_6H_4	PLA	64	66	37
Ph	Bu^t	PLL	92	> 98	34
Ph	Cyclopropyl	PLL	85	77	38
Bu^t	Ph	PLL	85	90	34
β-Styryl	2-Naphthyl	PLL	78	> 96	34
β-Styryl	Bu^t	PLL	90	> 97	34
PhCO	Ph	PLL	76	76	38
Bu^tCO	Bu^t	PLL	> 95	> 95	38
Bu^tO_2C	Ph	PLL	66	≥95	38
$Bu^n{}_3Sn$	Ph	PLL	90	> 99	39

[a] PLL = poly-L-leucine, PLA = poly-L-alanine; see references for examples using poly-D-amino acids.

The limitations of poor catalyst recycling and low reactivity have been overcome in modifications reported by Roberts and coworkers. Two biphasic procedures have been developed which reduce reaction times for chalcone to under 30 minutes. The first of these is essentially anhydrous in nature.[33,40] Peroxide is delivered in the form of an anhydrous complex, typically urea–H_2O_2. Such complexes are cheap, stable and easy to handle and are safer than concentrated solutions of H_2O_2 in organic or aqueous solvents.[41] The inorganic base employed by Juliá and Colonna is replaced with a strong amidine base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the reaction is performed in an organic solvent such as THF. Under these conditions enolisable substrates, such as simple alkyl ketones, can be readily epoxidised.[33] These biphasic conditions constitute the most widely tested and reliable of the new class of polyamino acid catalysed epoxidation systems (Scheme 14, Table 12, method A). Examples reported by Roberts and coworkers typically use polyleucine, however it has recently been disclosed that poly-L-neopentylglycine can offer advantages of increased reaction rate and enantioselectivity.[42]

In order to maximise both rate and stereoselectivity for the biphasic reaction it is necessary to activate the catalyst under conditions analogous to the triphasic procedure. This activation procedure consists of stirring the polyamino acid in a mixture of 4 M aq. NaOH and toluene for 1–5 days (the exact activation time appears to depend on the batch of catalyst), before filtering, washing and drying the catalyst.[43]

It has been demonstrated that the poly-L-leucine catalyst can readily be recycled under these conditions; for example it has been shown that for the epoxidation of chalcone, catalyst used for five previous reactions still afforded epoxide in 96% ee, albeit with increased reaction time. For less reactive substrates the activity of the catalyst was found to drop more rapidly with recycling, however it was found that the original activity could be recovered by submitting the recycled material to the activation procedure.[44]

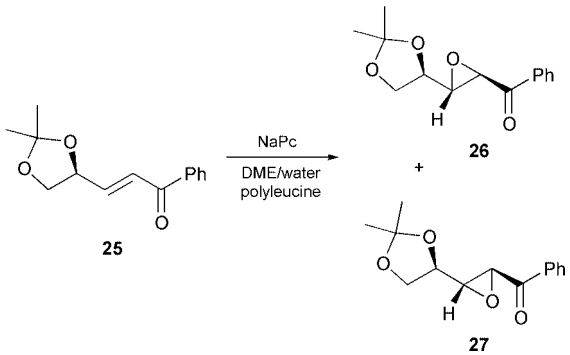
A disadvantage of the aforementioned biphasic conditions is that they are rather more expensive than the triphasic conditions owing to the use of a more costly oxidant and of 1.5 equivalents of DBU (attempts to use substoichiometric quantities have proved unsuccessful); thus these conditions are not ideal for large-scale work. An alternative procedure employs inexpensive sodium percarbonate (NaPc) as both oxidant and base.[43] Screening of a range of solvent systems for this oxidant revealed that organic–water mixtures are most effective, in particular DME–water gives rates and enantioselectivities comparable with the urea–H_2O_2/THF/DBU system (Scheme 14, Table 12, method B). The non-catalysed background reaction under these conditions was found to be considerably slower than under the urea–H_2O_2/THF/DBU conditions; thus increased substrate to catalyst ratios may be employed with minimal reduction in ee (Table 10).

Table 10 Epoxidation of chalcone using poly-L-leucine[43]

	10 mol% catalyst[a]		2 mol% catalyst[a]	
Conditions	Yield (%)	Ee (%)	Yield (%)	Ee (%)
Urea–H_2O_2/DBU/THF	85	> 95	92	89
NaPc/DME/H_2O	—	96	87	94

[a] Based on a single polymer chain as the catalytic unit.

The sodium percarbonate–DME–water conditions have proved particularly useful for the diastereoselective epoxidation of enones with an oxy-substituted γ-chiral centre. Use of sodium percarbonate–DME–water at −3 to 0 °C gives reasonable selectivity for the epoxidation of such substrates in both the matched and mismatched sense (Scheme 13, Table 11).[45]



25 **26** + **27**

Scheme 13

Table 11 Diastereoselective epoxidation of **25**[45]

Catalyst	*syn* **26**:*anti* **27**	Yield (%)	Matching
None	1:3.0	94	None
Poly-D-leucine	1:34	97	Matched
Poly-L-leucine	3.8:1	98	Mismatched

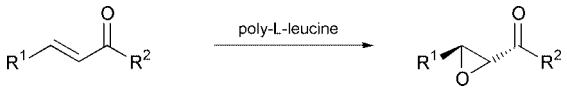
One further improvement reported by Roberts and coworkers is the introduction of a silica-supported polyamino acid catalyst.[46] It has been shown in the field of biotransformations that the immobilisation of enzymes on silica affords material

more active than the native enzyme when used in organic solvents. In addition, it has been found that this material is more readily recycled. Polyleucine was stirred as a suspension in THF with a range of solid supports and the properties of the resultant adsorbed materials were investigated. It was found that silica provided the best combination of improved activity and ease of filtration/recycling. Generally the silica-adsorbed material is active enough to allow as little as 2.5 mol% catalyst (based on 1 equivalent being a single polyamino acid chain) to be used without any reduction in enantioselectivity (Scheme 14, Table 12, method C).[46]

The polyleucine catalysed epoxidation shows some interesting selectivity. For example, the diene **28** is selectively epoxidised on the disubstituted double bond to afford the monoepoxide **29** in reasonable yield and good ee (Scheme 15).[48]

Generally α-substituted enones, such as α-methylchalcone are unreactive under polyleucine catalysed conditions. One exception to this is the case of cyclic enones derived from tetralone, indanone or benzosuberone (Scheme 16).[49] A similar explanation to that proposed by Enders *et al*., in which an *s-cis* conformation is required for epoxidation to occur, may account for this difference in reactivity.[8b]

Of all the epoxidation methods discussed in the current article the polyamino acid catalysed reaction is probably the one which is the least well understood from a mechanistic standpoint. A number of fundamental questions remain to be answered. The primary issues are the nature of the interaction between polyamino acid, substrate and/or oxidant and the relationship between the structure and the activity of the catalyst. Of these, the latter question is the more readily addressed. Studies by Juliá, Colonna and coworkers[31c] and by Roberts and coworkers[42] have found that polyleucine, polyalanine, polyisoleucine and poly(neopentylglycine) are effective catalysts. Of these the first two are known to favour an α-helical structure whilst polyisoleucine is reported to form a β-sheet. This seems to suggest that the secondary structure of the polyamino acid is not directly related to the catalysis. Less effective polyamino acids include polyvaline,[31c] polyphenylalanine[31c] and polyproline.[31d]



Scheme 14

Polyamino acids containing mixtures of L- and D-leucine have been prepared with a view to examining the importance of different regions of the polyamino acid chain. Investigation of material prepared by sequential polymerisation of D- and L-leucine *N*-carboxyanhydrides (NCAs) suggested that the amino terminal region plays a dominant role in determining which enantiomer of the product is generated.[50] In order to investigate this phenomenon further, Roberts and coworkers first demonstrated that a 20-mer of polyleucine prepared using a peptide synthesiser exhibits catalytic behaviour like that of the material prepared by NCA polymerisation. Such material is bound at the *C*-terminus *via* a hydroxymethyl phenoxyacetic acid linker and a polyethylene glycol graft to a polystyrene resin and is thus termed H-(L-Leu)$_{20}$-PEG-PS.[51] A series of oligopeptides of defined primary structure was then prepared and their behaviour as catalysts was examined.[52] It was shown that as few as five D-leucine residues at the *N*-terminus of a 20-mer of polyleucine is sufficient to overcome any catalytic effect of the 15 L-leucine residues which make up the rest of the polymer chain. Under the urea–H_2O_2/DBU/THF conditions the catalyst H-(D-Leu)$_5$-(L-Leu)$_{15}$-PEG-PS generated the epoxide corresponding to that afforded in the presence of poly-D-leucine in 52% ee. Moreover, the peptide H-(D-Leu)$_7$-(L-Leu)$_{13}$-PEG-PS catalysed formation of the same epoxide in 83% ee. In order to confirm that the bias towards the *N*-terminal region is not a reflection of the polymer support bound to the *C*-terminus the H-(D-Leu)$_5$-(L-Leu)$_{15}$-PEG-PS catalyst was cleaved from the support using TFA, recovered and tested again; although the ee was somewhat diminished by this procedure (21%), the major product was still the epoxide configured by a poly-D-leucine catalyst.

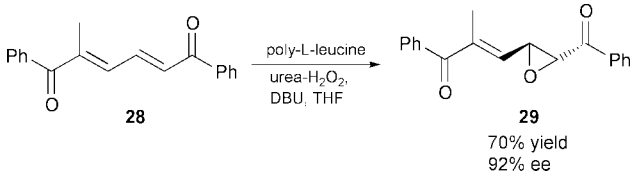
5. Bovine serum albumin catalysed epoxidation

In a series of papers, Colonna *et al*. have reported the use of bovine serum albumin (BSA) as an additive to Weitz–Scheffer

Table 12 Substrates epoxidised under Roberts' conditions

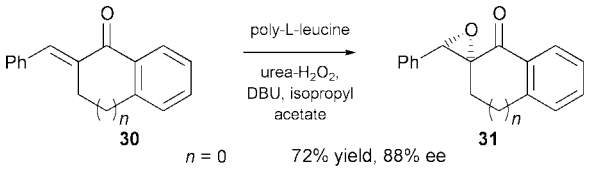
R^1	R^2	Method[a]	Yield (%)	Ee (%)	Ref.
Ph	Ph	A	85	> 95	33
		B	87	94	43
		C	*100*[b]	⩾93	46*a*
Ph	*o*-$O_2NC_6H_4$	A	91	91	47
Ph	*o*-MeC_6H_4	A	94	81	47
Ph	*o*-$MeNHC_6H_4$	A	62	96	47
Ph	*o*-$NH_2C_6H_4$	A	81	> 98	47
		C	85	93	46*a*
Ph	*p*-$NH_2C_6H_4$	A	0	—	47
Ph	2-Naphthyl	A	91	91	44
p-ClC_6H_4	Ph	A	62	62	47
p-ClC_6H_4	*o*-$NH_2C_6H_4$	A	91	> 98	47
Ph	Me	A	70	80	33
Ph	Pr^i	A	56	89	46*a*
		C	78	93	46*a*
Ph	Bu^t	A	76	94	33
		B	94	94	43
p-$MeOC_6H_4$	Bu^t	A	⩾90	⩾96	33
Ph	Bu^i	A	87	96	44
Ph	Pr^n	A	85	94	44
Ph	Et	A	80	82	44
Cy	Ph	A	91	89	33
β-(*E*)-Styryl	2-Naphthyl	A	85	96	48
(*E*)-ClCH=CH	Ph	A	57	86	48
(*E*)-Bu^tO_2CCH=CH	Ph	A	95	90	48
(*E*)-MeO_2CCH=CH	Ph	A	90	90	48
(*E*,*E*)-MeCOCH=CHCH=CH	Ph	A	43	90	48

[a] A = poly-L-leucine, urea–H_2O_2, DBU, THF; B = poly-L-leucine, sodium percarbonate, DME, water; C = poly-L-leucine–SiO_2, urea–H_2O_2, DBU, THF. [b] Italicised values refer to conversion rather than yield.



28 **29**

Scheme 15

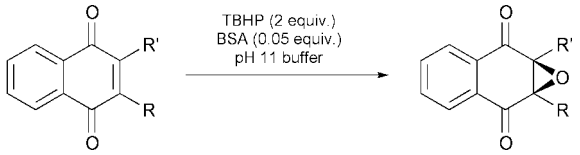


30 **31**

$n = 0$ 72% yield, 88% ee
$n = 1$ 76% yield, 84% ee
$n = 2$ 74% yield, 59% ee

Scheme 16

epoxidations of naphthoquinones.[53] Both the magnitude and the sense of enantioselectivity in the reaction were found to be strongly dependent on the nature of the side chains R and R′ (Scheme 17, Table 13). The best enantioselectivities were obtained using *tert*-butyl hydroperoxide (TBHP) as the oxidant,



Scheme 17

in an alkaline buffer solution (slightly higher ees were obtained in pH 9 buffer than in pH 11 buffer).[53b] Further improvements in enantioselectivity could be obtained by addition of small amounts of isooctane to the reaction mixture.[53c]

Table 13 Epoxidation of naphthoquinones in the presence of BSA[53]

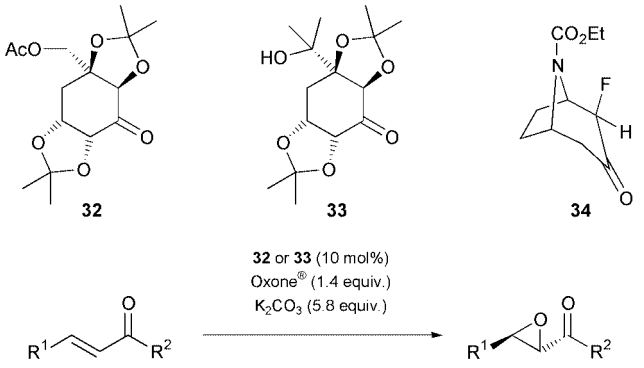
R	R′	Yield (%)	Ee (%)
Me	H	34	20
Bu^i	H	62	77
		56[a]	90[a]
Bu^n	H	35	14[b]
n-C_6H_{13}	H	29	30[b]
n-C_8H_{17}	H	66	100[b]
Cy	H	64	70
Et	Me	22	54[c]

[a] Epoxidation performed in the presence of 5 mol% isooctane. [b] The predominant isomer was the enantiomer of that illustrated. [c] The absolute stereochemistry was not determined.

6. Epoxidation with chiral dioxiranes

The first attempts to effect asymmetric epoxidation using chiral dioxiranes were reported by Curci *et al.* in the mid-1980s.[54] It is only recently, however, that chiral ketones, the precursors of the corresponding dioxiranes, have been developed which will allow the epoxidation of a wide range of alkenes with good enantioselectivity.

While chiral dioxiranes can, in theory, epoxidise most classes of olefin, Baeyer–Villiger reaction of the chiral ketone from which the dioxirane is derived frequently competes with epoxidation for unreactive substrates. As a result, only a few chiral dioxiranes have been used successfully to epoxidise electron-deficient alkenes. In particular, the ketones **32** and **33**, derived from (−)-quinic acid, have been developed by Shi and coworkers; on treatment with Oxone® these are believed to generate chiral dioxiranes which then epoxidise the enones shown in Scheme 18 and Table 14, regenerating the chiral ketones.[3,55] An ester, ethyl cinnamate, was also epoxidised with good enantioselectivity, albeit in low yield.



32 **33** **34**

Scheme 18

Table 14 Epoxidation using Shi's chiral dioxiranes[3,55]

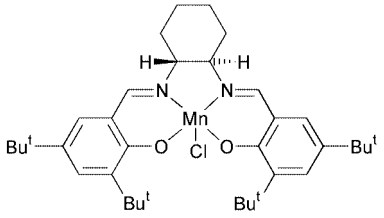
R^1	R^2	Ketone	Yield (%)	Ee (%)
Ph	Ph	**32**	80	94
		33	85	96
Ph	Me	**33**	75	82
Ph	Pr^i	**33**	70	89
Ph	OEt	**32**	34	86
		33	35	89

The tropinone derivative **34**, developed by Armstrong and Hayter[56] as a chiral dioxirane precursor, has also been applied to the epoxidation of an electron-deficient olefin; methyl cinnamate was epoxidised with 33% yield and 64% ee using this catalyst under conditions similar to those employed by Shi and coworkers.[3,55]

7. Miscellaneous methods

Among the numerous substrates which have been epoxidised using manganese–salen catalyst **35** are several electron-deficient alkenes. A series of (*Z*)-cinnamate esters has been studied by Jacobsen *et al.*; on epoxidation with sodium hypochlorite in the presence of **35**, both *cis*- (**36**) and *trans*-epoxides (**37**) are obtained (Scheme 19, Table 15).[57] Two general trends can be extracted from these data: the presence of electron-donating groups (R^1) on the aromatic ring minimises the extent of 'leakage' to the *trans*-epoxide **37**, but gives the lowest enantiopurity in the *cis*-product **36**; and for a given R^1, increasing the bulk of R^2 increases the enantioselectivity.

Furthermore, various isoflavones have been epoxidised by Lévai *et al.* using catalyst **35** and its enantiomer (Scheme 20, Table 16);[58] in this case, although good ees were obtained for certain substrates, the yields are disappointing.



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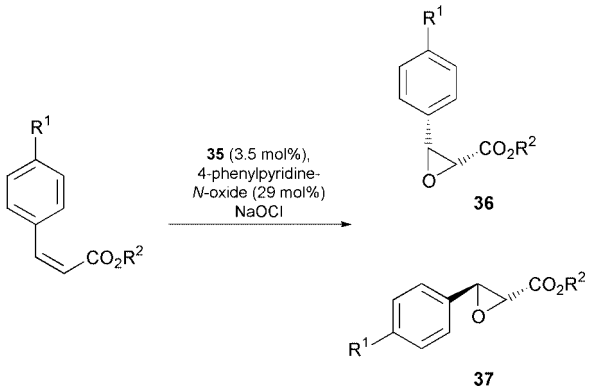
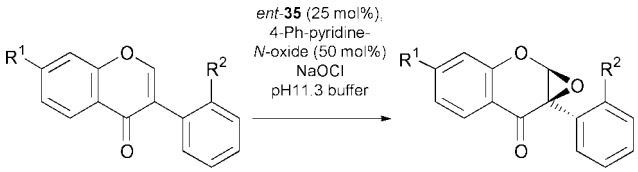


Scheme 19

Table 15 Epoxidation of cinnamate esters using Jacobsen's catalyst[57c]

R^1	R^2	*cis* **36**:*trans* **37**	*cis* **36** Ee (%)	*trans* **37** Ee (%)
OMe	Me	11.7:1	72	66
Me	Me	7.0:1	79	41
H	Me	5.7:1	85	62
CF_3	Me	1:1.25	79	55
NO_2	Me	1:3.7	91	53
H	Et	—	92	—
H	Pr^i	—	96	—

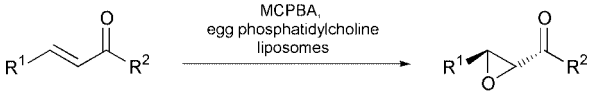


Scheme 20

Table 16 Epoxidation of isoflavones using Jacobsen's catalyst[58]

R^1	R^2	Yield (%)	Ee (%)
H	H	25	65
OMe	H	26	77
OMs	H	23	56
OMe	OMe	30	90
OMs	OMe	31	94

An isolated report by Kumar and Bhakuni in 1996 outlined the use of MCPBA localised in a chiral liposomal bilayer as a reagent for asymmetric epoxidation.[59] Five electron-deficient olefins were oxidised with moderate to good enantioselectivity using this reagent, with esters displaying higher ees than ketones (Scheme 21, Table 17).



Scheme 21

Table 17 Epoxidation using liposomised MCPBA[59]

R^1	R^2	Yield (%)	Ee (%)
Ph	OMe	75	92
m-$MeOC_6H_4$	OMe	70	95
Ph	Ph	65	70
o-ClC_6H_4	Ph	63	68
Ph	*m*-ClC_6H_4	67	62

The groups of Colonna[60] and Takahashi[61] have both reported on the modification of Weitz–Scheffer conditions by the addition of cyclodextrins. Under Colonna's optimised conditions, the ees recorded for the epoxidation of a range of naphthoquinones and chalcone derivatives were below 48%; the highest ee observed by Takahashi and coworkers in the epoxidation of cinnamaldehyde was 2.5%.

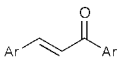
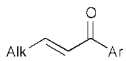
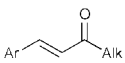
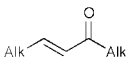
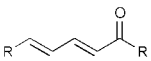
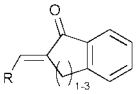
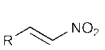
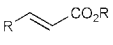
In a related study, Sakuraba and Tanaka have shown that crystalline chalcone–cyclodextrin complexes, when dispersed in water, can be epoxidised by sodium hypochlorite with high yield and *ca.* 30% ee.[62]

8. Summary

It is clear from the above review that no single approach for the epoxidation of electron deficient olefins stands out from the methods discussed. The variation in selectivity observed between the different approaches means that they should all be considered as potential candidates for a given synthetic transformation. In order to aid this selection process Table 18 compares the effectiveness of the different methodologies for the epoxidation of various key classes of olefin. For the sake of clarity, it has not been possible to include all of the methods, and we have chosen to concentrate on a representative selection of the most general and effective. One caveat which should be borne in mind when consulting Table 18 is the tendency for a range of yields or ees to reflect unrepresentative, extreme results, particularly when a larger number of examples has been reported.

Despite the lack of a general method a number of high yielding and highly stereoselective methods exist; with judicious choice the chemist can epoxidise a wide range of electron deficient olefins. This fact, coupled with the potential of epoxides substituted with electron withdrawing groups as synthetic intermediates,[28c] should ensure that these methods gain increasing acceptance amongst the synthetic organic community. Moreover, it seems likely that we will witness many new and interesting developments in this field over the coming years. It remains to be seen, however, whether one single method will be developed to such an extent that it dominates epoxidation of enones in the way that the Sharpless reaction has become the pre-eminent method for the epoxidation of allylic alcohols.

Table 18 Comparison of epoxidation methods for various classes of olefin[a]

Olefin class[b]	Enders[c]	Shibasaki[d]	Jackson[e]	Lygo[f]	Corey[g]	Roberts[h]	Shi[i]
	94% yd 61% ee 1 example	78–93% yd 83–91% ee 2 examples	36–61% yd 81–94% ee 5 examples	77–99% yd 71–89% ee 9 examples	70–97% yd 92–98.5% ee 12 examples	21–98% yd 53–99% ee 18 examples	85% yd 96% ee 1 example
	94–99% yd 82–92% ee 5 examples	81–95% yd 71–94% ee 3 examples	—	79–94% yd 77–90% ee 7 examples	85–90% yd 91–95% ee 3 examples	91% yd 89% ee 1 example	—
	— —	55–83% yd 88–94% ee 2 examples	— —	40% yd 85% ee 1 example	—	70–90% yd 80–96% ee 6 examples	70–75% yd 82–89% ee 2 examples
	99% yd 90% ee 1 example	71–91% yd 88–91% ee 2 examples	—	—	—	—	—
	—	51–80% yd 82–96% ee 5 examples	—	—	—	—	—
	—	—	—	—	—	43–95% yd 86–98% ee 7 examples	—
	62–99% yd 64–99% ee 5 examples	—	—	—	no yd reported 61–76% ee 2 examples	63–85% yd 59–96% ee 8 examples	—
	47–74% yd 37–82% ee 5 examples	—	—	—	—	—	—
	—	—	—	—	—	—	35% yd 89% ee 1 example

[a] Values given are the range reported, yd = yield. [b] Alk = alkyl group. [c] **1**, Et_2Zn, O_2 (refs. 8, 11). [d] **11**, $Ln(OPr^i)_3$, CMHP or TBHP (refs. 13a, 16). [e] (+)-DET, Bu_2Mg,TBHP (ref. 17). [f] **20**, NaOCl (ref. 24). [g] **20**, KOCl (ref. 25). [h] poly-L-leucine, DBU, UHP (refs. 33, 47–49, 63). [i] **33**, K_2CO_3, Oxone® (ref. 3).

Acknowledgements

We thank Professor S. M. Roberts for helpful advice and discussions and JS would like to acknowledge Degussa-Hüls AG for the funding of a Principal Scientist position.

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