Asymmetric Epoxidation of Electron-Deficient Olefins

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Abstract: This paper focuses on the latest developments in asymmetric epoxidation of electron-deficient olefins since the review by Porter and Skidmore on chiral ligand-metal peroxide systems, polyamino acid catalysed and organocatalysed epoxidations. Particular attention has been paid to the most recent advances using chiral pyrrolidines as organocatalysts.

Key Words: Asymmetric epoxidation, electron deficient olefins, organocatalysis, dioxiranes, chiral ligand–metal peroxide systems, Juliá-Colonna epoxidation.

Dedicated to Prof. M. Yus on the occasion of his 60th birthday.

1. INTRODUCTION

An excellent review on the asymmetric epoxidation of electron-deficient olefins was published in 2000 by Porter and Skidmore [1]. Since then, there have been several important developments in this area, especially the use of chiral pyrrolidines as organocatalysts. This review is an update of the one by Porter and Skidmore.

From the work of Weitz-Scheffer on epoxidation of electron-deficient carbonyl compounds [2] using alkaline H_2O_2, much progress has been made towards the development of an asymmetric variant. The resulting enantiomerically enriched epoxy compounds can be easily transformed into many types of useful chiral compounds [3]. In the mid-1970s, phase-transfer catalysis was investigated by Wynberg *et al.* [4] in a biphasic Weitz-Scheffer epoxidation using chiral ammonium salts derived from *Cinchona* alkaloids. In the early 1980s, Juliá and coworkers developed a new methodology for the asymmetric epoxidation of α,β-unsaturated ketones using polyamino acids which meant a breakthrough for this type of reactions [5]. Several methods for the asymmetric epoxidation of electron deficient alkenes that use chiral ligand-metal peroxide systems have been reported [6]. Prof. Shibasaki *et al.* and Prof. Jackson *et al.* have described different catalyst systems based on organometallic complexes with BINOL [7] and tartrate derivatives [8] respectively. These processes allow the epoxidation of a wide range of electron-deficient olefins with high enantioselectivity. Other methodologies developed for this reaction include the use of chiral alkyl hydroperoxides [9] and chiral dioxiranes [10]. Recently, the use of chiral pyrrolidines as organocatalysts has been reported as a new methodology for asymmetric epoxidation of electron-deficient olefins [11].

This review will not include methods that rely on structural features such as allylic alcohols for the asymmetric epoxidation of an electron-deficient alkene [12]. Many other methods for the synthesis of chiral epoxides from other substrates apart from electron deficient alkenes can be found in an excellent review by Xia *et al.* covering homogeneous and heterogeneous catalytic asymmetric epoxidation [13].

2. CHIRAL LIGAND-METAL PEROXIDES SYSTEMS

Several methods that rely on the use of a chiral ligand coordinated to the metal atom of a metal peroxide have been developed for the epoxidation of electron-deficient olefins. Many of these systems were reviewed by Porter and Skidmore [1]. During the last years only two of them appear to have remained interesting among synthetic organic chemists: the use of tartrates and BINOL **1** as ligands (Fig. **1**).

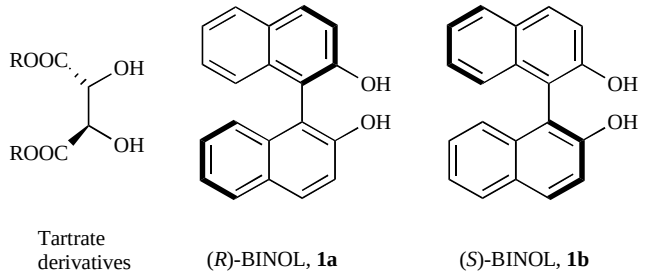
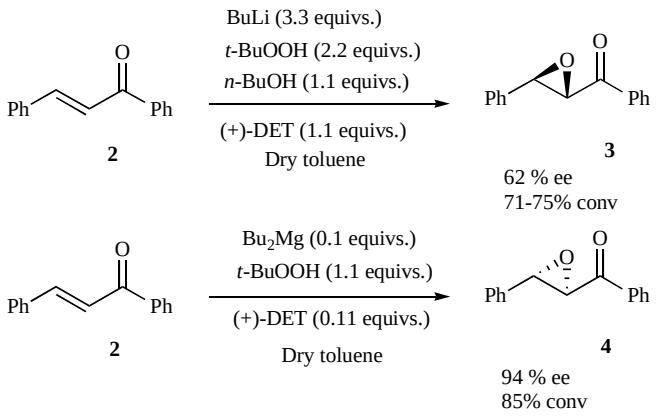


Fig. (1).

2a. Alkyl Tartrate-Metal Peroxides

Jackson *et al.* had previously established that treatment of (*E*)-chalcone **2** with a reagent prepared from lithium *tert*-butylperoxide and a stoichiometric amount of diethyl tartrate (DET) gave the corresponding epoxide **3** in moderate yield and 62% ee, being essential a stoichiometric amount of lithium *tert*-butoxide for the reaction to proceed (Scheme **1**) [8].



Scheme 1.

In contrast, when the magnesium system was explored, it was found that only a catalytic amount of base and chiral ligand were required to effect the epoxidation (Scheme **1**). This reaction was

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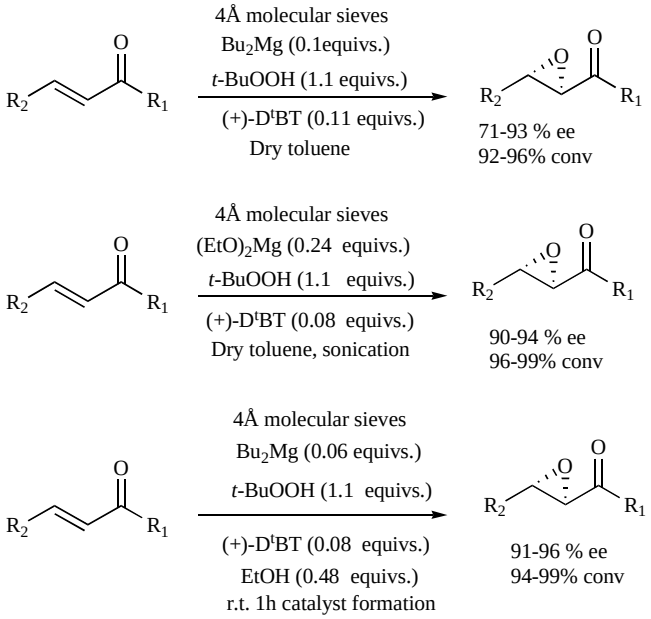
more enantioselective, giving chalcone epoxide **4** in 94% ee and with the opposite absolute configuration to that obtained with the lithium system using the same enantiomer of ligand [14,15]. In order to apply this methodology to aliphatic enones, Jackson added powered activated 4Å molecular sieves to the system. The use of di-*tert*-butyl tartrate (D*t*-BT) as ligand, magnesium ethoxide as base and the introduction of ultrasonication, increased the levels of conversion and enantioselectivity up to 99% and 94% respectively [14, 15]. These authors also found that the addition of a small amount of ethanol could eliminate the need for ultrasonication, allowing a substantial reduction in the amount of base required (Scheme **2**).



Scheme 2.

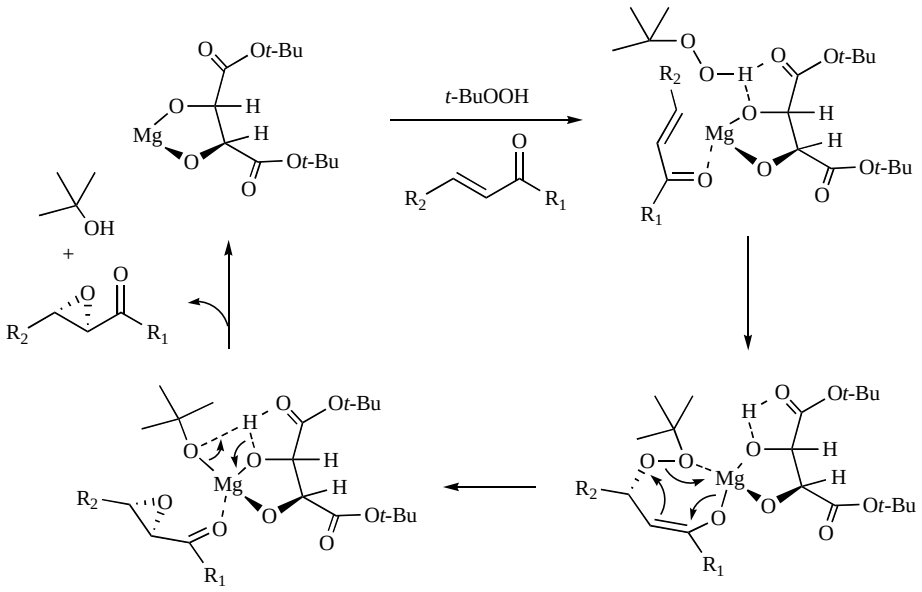
Jackson *et al*. have studied the effect of adding a range of other additives when using dibutylmagnesium as base. Addition of water improved the results, whereas omission of the molecular sieves completely inhibited the reaction. Interestingly, the use of "wet" *tert*-butylhydroperoxide (prepared by extraction of commercial 70% aqueous *tert*-butylhydroperoxide into toluene, without azeotropic distillation) gave similar results, making the work-up easier for large scale operations. When using "wet" *tert*-butylhydroperoxide, the ligand of choice was di-*iso*-propyl tartrate [15] and it was demonstrated that a combination of water and 4Å molecular sieves was optimal for the process. The mechanism proposed by Jackson is depicted in Scheme **3**.

2b. BINOL Systems

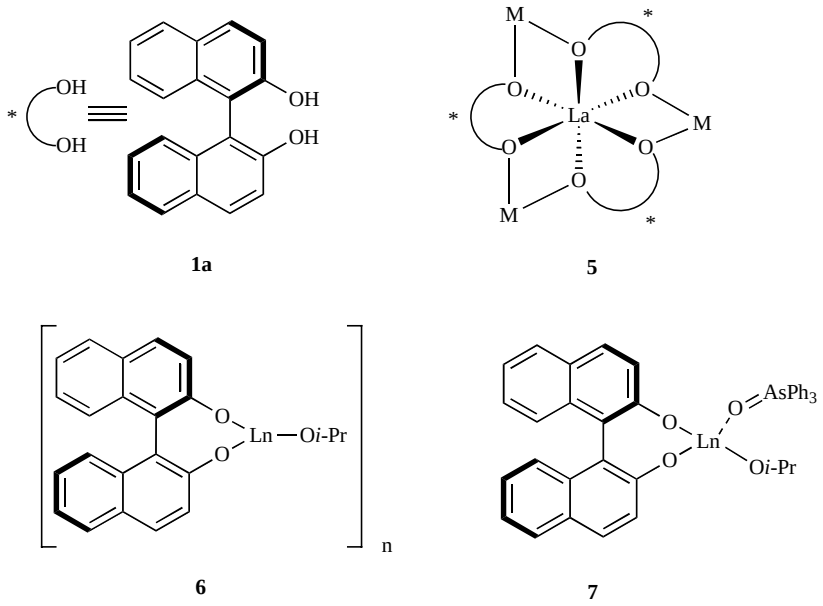
Probably the most general method for the catalytic asymmetric epoxidation of electron deficient olefins uses a combination of lanthanide alkoxides and BINOL derivatives with alkyl hydroperoxides as oxygen source [7]. Shibasaki *et al.* have developed two types of catalyst systems for the asymmetric epoxidation of unsaturated carbonyl compounds. One of them consists of complexes of general form $LnM_3[(R)\text{-BINOL}]_3$ (Ln=lanthanide, M=alkali metal) (**5** in Fig. **2**, where Ln=La) and the other one is alkali-metal-free (**6** in Fig. **2**). In both cases a complex between a lanthanide metal and BINOL is formed [16]. It was found that $LaNa_3[(R)\text{-BINOL}]_3$ (**5** in Fig. (**2**), when M=Na) complex afforded chalcone epoxide in 92% yield and 83% ee with *tert*-butyl hydroperoxide (TBHP) as oxidant, although it did not prove to be general for other enone substrates. On the contrary, the alkali-metal-free catalyst La-BINOL **6** (when Ln=La) gave the epoxidation reaction for a wider range of (*E*)-enones with excellent enantiomeric excesses when cumyl hydroperoxide (CHP) was used as oxidant [7, 16].

The optimization of the reaction revealed that the optimum lanthanide metal depended on the substrate; lanthane was the best one for chalcone-type substrates, whereas ytterbium complexes exhibited better catalytic activity for aliphatic substrates using TBHP as oxidant (Table **1**). These latter complexes were used for the epoxidation of (*Z*)-enones to the corresponding *cis*-epoxides with high enantiomeric excess [16].

Further development has been achieved by Inanaga and coworkers with the use of additives such as triphenylphosphine oxide [17] or derivatives such as *tris*(4-fluorophenyl)phosphine oxide [18]. In this manner, the reaction time was shortened and the chiral lanthanum complex system was stabilised. Addition of $Ph_3As{=}O$ was investigated by Shibasaki and it was found that the catalytic activity was increased even with reduced amounts of catalyst (Table



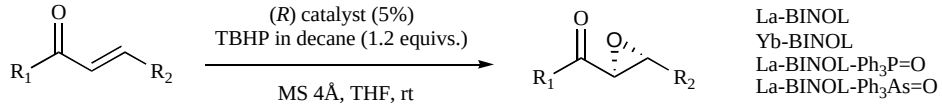
Scheme 3. Catalytic cycle proposed by Jackson for the asymmetric epoxidation of enones promoted by the alkyl-tartrate magnesium system.



1a **5** **6** **7**

Fig. (2).

Table 1. Enantioselective Epoxidation of α,β-Unsaturated Ketones with Different BINOL Complexes

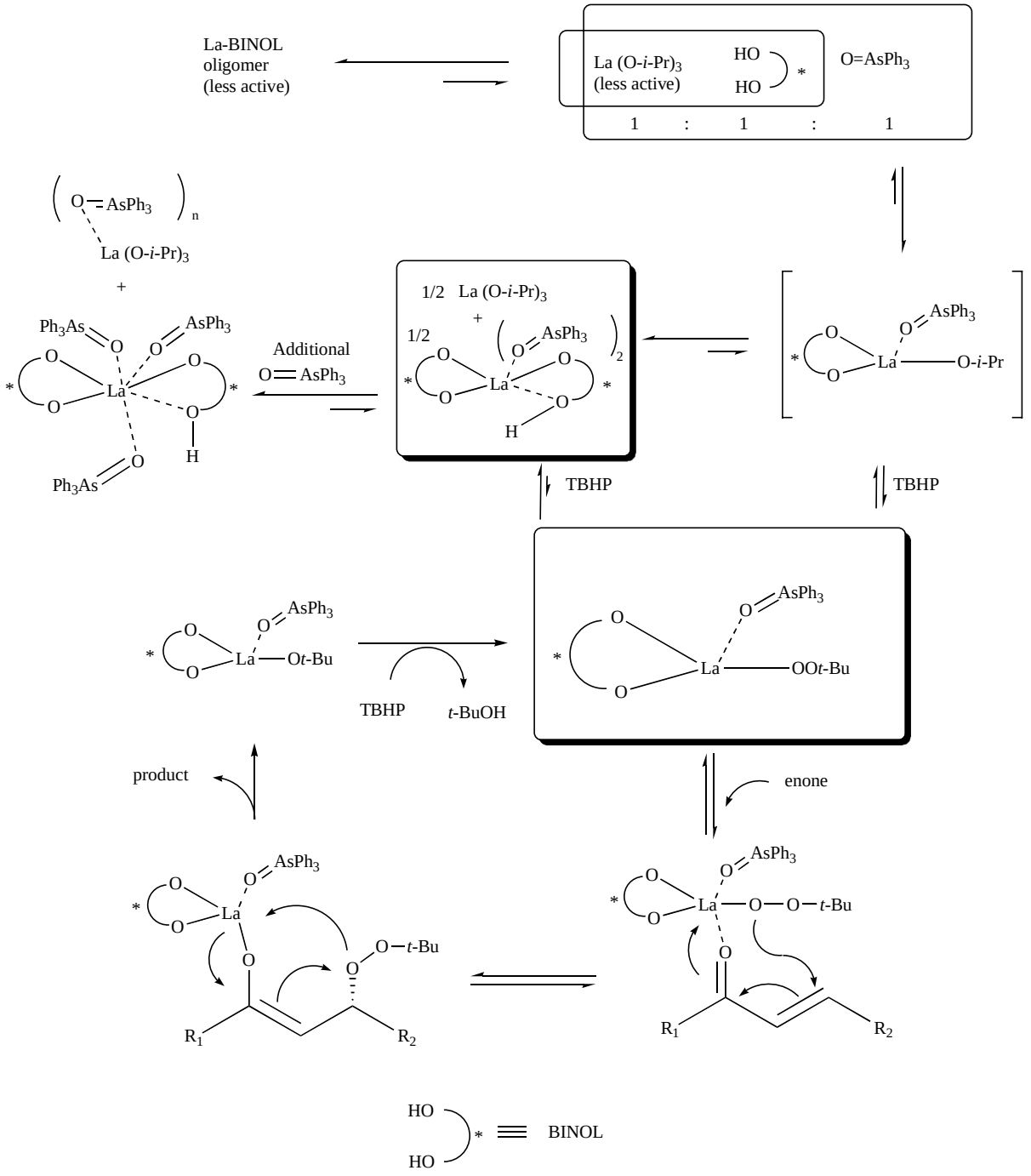


R_1	R_2	Method[a]	Yield (%)	ee (%)
Ph	Ph	A	93	91
		B	99	81
		C	99	96
		D	99	96
o-MOM-C_6H_4Ph	Ph	A	85	85
		D	91	95
t-Bu	Ph	C	89	93
		D	95	94
i-Pr	Ph	A	55	88
		B	82	93
		C	67	96
		D	72	95
Me	Ph	A	83	94
		B	92	94
		C	92	93
		D	92	>99
Me	CH_2CH_2Ph	A	91	88
		C	92	87
		D	98	92
Me	C_5H_{11}	A	71	91
		D	89	95

[a] **A**: La-BINOL, see ref 21; **B**: Yb-BINOL, H_2O (4.5 equivs. to Yb) was added, see ref 22; **C**: La-BINOL-Ph_3P=O, see ref. 23; **D**: La-BINOL-Ph_3As=O, see ref. 19.

1) [19]. This multifunctional asymmetric catalyst generated from La(O-*i*-Pr)$_3$, BINOL and Ph_3As=O as additive was used in the synthesis of biological active compounds such as (+)-Decursin, a protein kinase C (PKC) activator (Fig. **5**) [20].

Shibasaki *et al.* have suggested that the active species in the catalyst solution generated from La(O-*i*-Pr)$_3$, (*R*)-BINOL and Ph_3As=O in a ratio 1:1:1 is **7** (Fig. **2**). These authors have proposed a mechanism for the asymmetric catalysed epoxidation of enones using these conditions (Scheme **4**) [16, 19, 20b].



Scheme 4. Mechanism proposed by Shibasaki for the asymmetric epoxidation of enones promoted by La(O-*i*-Pr)$_3$, (*R*)-BINOL and Ph_3As=O system.

Various groups have investigated how the introduction of different substituents in the BINOL ligand affects the effectiveness of the catalyst. Shibasaki *et al*. developed ligand 3-(hydroxymethyl)-BINOL **8** (Fig. **3**), which provided better results than BINOL itself [21-23]. Qian and de Vries synthesized a series of 6,6´-disubstituted BINOLs **9a-g** (Fig. **3**) [24, 25] and tested them in the epoxidation of chalcone derivatives using CHP as oxidant. Best results were obtained with the catalyst prepared from Yb(O-i-Pr)$_3$ and 6,6´-diphenyl-BINOL in a ratio 1:1, increasing the enantiomeric excesses with respect to those produced with BINOL catalyst without additives [25]. These authors also described the use of La(O-*i*-Pr)$_3$-(*S*)-6,6´-dibromo-BINOL and Gd(O-*i*-Pr)$_3$-(*S*)-6,6´-diphenyl-BINOL for the asymmetric epoxidation of chalcone derivatives using CHP as oxygen source . Yields in the range 81-95% and ees of up to 95% were obtained. Kumaraswamy *et al*. described the synthesis of a novel enantioenriched-Ca complex using $CaCl_2$ and the potassium salt of (*S*)-6,6´-diphenyl-BINOL. This catalytic system mediated the epoxidation of chalcone derivatives obtaining yields in the range 60-82% and ees in the range 22-80% [26].

Sasai and coworkers have developed several complexes with polymeric supported BINOL ligands in order to facilitate the recovery and reuse of catalysts. The heterogeneous catalysts generated from Yb-(O-*i*-Pr)$_3$ or La-(O-*i*-Pr)$_3$ were found to promote the epoxidation of chalcone and benzalacetone in high yield and ee up to

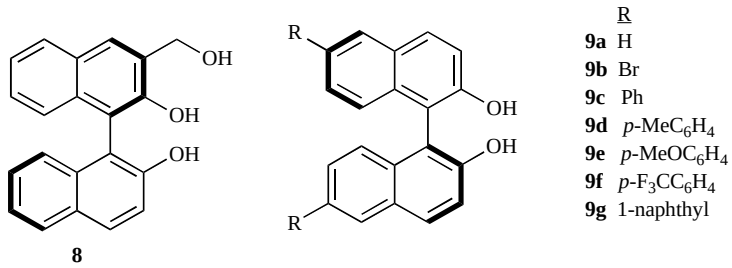


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Fig. (3).

89% [27]. These authors have also described the use of polymer-supported lanthanoid-BINOL complexes in this reaction [28]. Further development has been achieved by Shibasaki and Matsunaga in the design and application of linked-BINOL chiral ligands in bifunctional asymmetric synthesis [29].

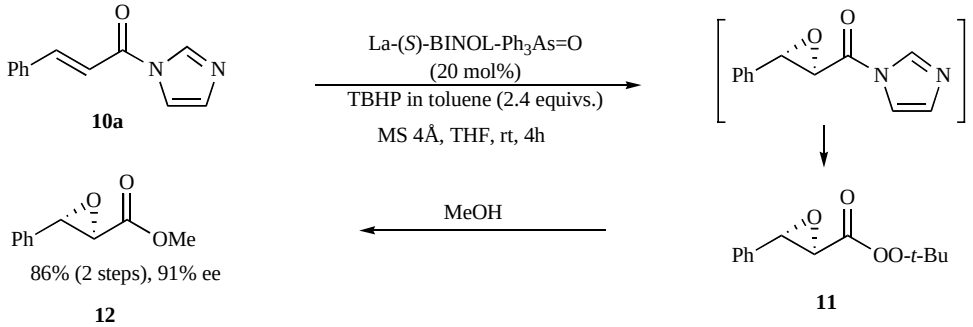
Inanaga *et al.* have investigated the optimization of the epoxidation reaction conditions and they have developed a highly practical method for the enantioselective epoxidation of α,β-unsaturated ketones [30]. The use of a chiral lanthanum complex self-organized *in situ* from La-(O-*i*-Pr)$_3$, (*R*)-BINOL, triarylphosphine oxide and alkyl hydroperoxide (1:1:1:1) mediated the epoxidation of aryl and alkyl enones with high enantioselectivities (up to >99% ee). A remarkably high asymmetric amplification was observed in the epoxidation of chalcone, which strongly suggests the formation of a μ-type dinuclear complex as the active catalyst [31].

In order to broaden the scope of these reaction conditions to the epoxidation of other electron-deficient olefins, Shibasaki *et al.* have developed a methodology for the synthesis of α,β-epoxy esters using imidazolides [32], acylpyrroles [33], amides and ester surrogates [32c]. In this manner, cinnamic acid imidazolide **10a** was oxidized using TBHP as oxidant and La-BINOL-Ph$_3$As=O (10% mol) as catalyst to afford peroxy ester **11**, which was then transformed into the methyl ester **12** by treatment with MeOH (Scheme **5**) [32a].

In the figure below there are several of the ester surrogates which have provided good results (Fig. **4**) [32c].

The addition of 3-6 equivs. of Ph$_3$P=O to the lanthanide BINOL complex also enhanced the rate of the reaction and when the oxidant was changed from TBHP to CHP, the corresponding epoxy esters were obtained with higher selectivity, although with a remarkable decrease in reactivity. Interestingly, this methodology has been applied not only to aryl enones but also to alkyl enones functionalized with a C-C double bond or a ketone, without overoxidation.

As β-alkyl substituted substrates gave slightly lower enantioselectivity than β-aryl substituted ones, Shibasaki *et al.* changed the central metal in the complex and tested the effect in the epoxidation reaction. It was found that Pr-BINOL-Ph$_3$As=O (1:1:1) was the best catalyst system for the epoxidation of this type of substrates, whilst La-BINOL-Ph$_3$As=O (1:1:1) was the catalyst of choice for β-aryl type substrates [20c, 32c, 34]. Although α,β-epoxy amides can be synthesized from the corresponding α,β-epoxy peroxy esters, Shibasaki *et al.* reported the first example of a general direct catalytic asymmetric epoxidation of α,β-unsaturated amides. A wide range of β–aryl and β-alkyl-substituted amides were successfully epoxidised using Sm as metal, TBHP as oxidant in presence of 4Å molecular sieves and Ph$_3$As=O as additive (Table **2**) [34].



Scheme 5.

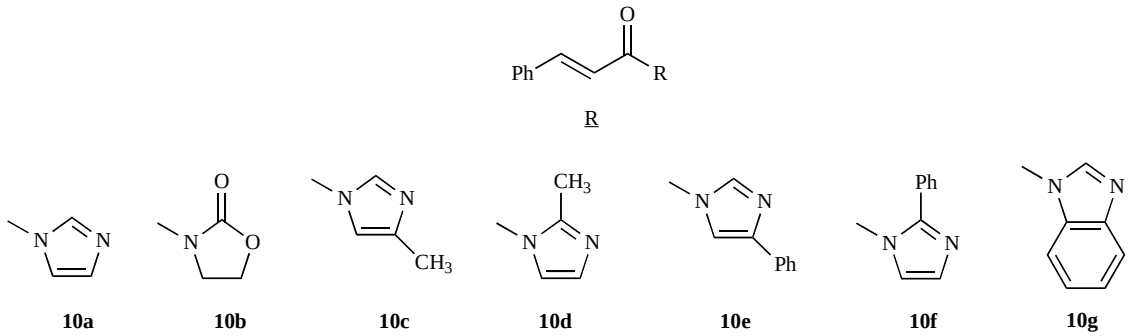
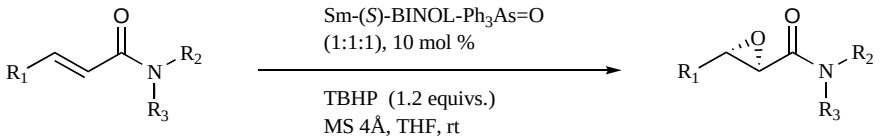


Fig. (4).

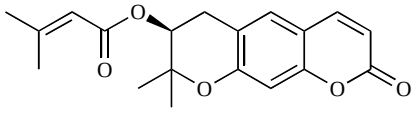
Table 2. Shibasaki *et al.* Sm-(*S*)-BINOL-Ph_3As=O Epoxidation



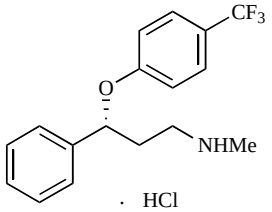
R_1	NR_2R_3	Method[a]	Time (h)	Yield (%)[b]	e.e. (%)[c]
$Ph(CH_2)_2$	CH_3NH	A	8	99	>99
		A[d]	24	94	>99
		A[e,f]	24	91	97
$Ph(CH_2)_2$	BnNH	A	6	97	>99
		A[d]	24	82	99
$Ph(CH_2)_2$	AllylNH	A	4	95	98
$Ph(CH_2)_2$	*c*-HexNH	A	11	97	>99
$Ph(CH_2)_2$	*t*-BuNH	A	22	91	99
$Ph(CH_2)_2$	$(CH_3)_2N$	A	3	96	99
$Ph(CH_2)_2$		A	4	94	>99
$Ph(CH_2)_4$	CH_3NH	A	8	81	>99
C_3H_7	BnNH	A	9	94	94
c-Hex	BnNH	A	12	90	>99
Ph	CH_3NH	A	24	89	>99
		B	18	95	99
		B	9	92	97
Ph	BnNH	B	18	91	>99
Ph	$(CH_3)_2N$	B	9	96	>99
4-F-C_6H_4	CH_3NH	B	20	94	99
4-Me-C_6H_4	CH_3NH	B	21	89	>99

[a] **A**: TBHP in decane was used. MS 4Å were not dried; **B**: TBHP in toluene was used. MS 4Å were dried for 3h at 180ºC under reduced pressure.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] 5 mol% of Sm-(*S*)-BINOL-Ph_3As=O (1:1:1) was used.
[e] Ph_3P=O (30 mol%) was used as additive.
[f] Dy was used as the central metal.

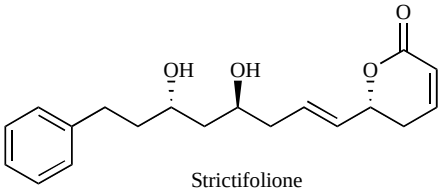
This methodology was employed for the synthesis of several natural compounds such as Strictifolione [35], (*R*)-Fluoxetine [32d], which is an interesting compound due to its biological properties and β-aryl-α-hydroxy amides, which can be used for the synthesis of the neuropeptide Antho-RNamide (Fig. **5**) [34].



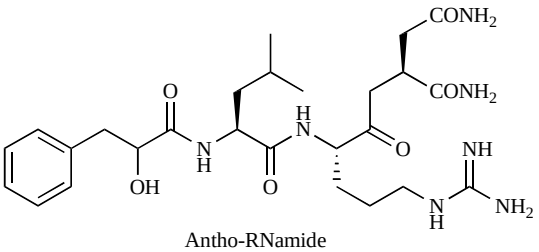
(+)-Decursin



(*R*)-Fluoxetine



Strictifolione



Antho-RNamide

Fig. (5).

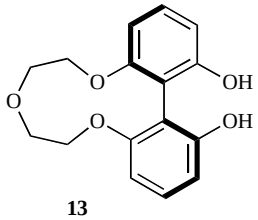
Under the aforementioned reaction conditions, the epoxidation of α,β-unsaturated esters proved to be sluggish. Thus, Shibasaki *et al.* developed a series of new chiral ligands that were effective in the asymmetric epoxidation of this type of compounds. It was found that best results were obtained when using Y as metal, **13** as ligand and $Ph_3As=O$ as additive (Table **3**).

Although excellent results were afforded for aryl and alkyl α,β-unsaturated esters (Table **3**) [36], there were some practical problems related with the catalyst loading, turnover frequency (TOF) and the explosive hazard of TBHP as oxidant. In order to solve them, Shibasaki developed a new methodology that uses *N*-acylpyrroles as α,β-unsaturated ester surrogates, a $Sm(O\text{-}i\text{-}Pr)_3$/(*R*)-$H_8$-BINOL **14** complex to promote the epoxidation and CHP as the oxidant. This catalytic system successfully mediated the epoxidation reaction with as little as 0.02% mol of catalyst and a high TOF ($> 3000h^{-1}$) (Scheme **6**) [33b].

Very recently Shibasaki, Matsunaga and coworkers have demonstrated the utility of anilide as a template to perform asymmetric epoxidation of α-methyl-α,β-unsaturated carbocylic acid derivatives. Epoxides were obtained in 87-99% yield and 78-88% ee using $Pr(O\text{-}i\text{-}Pr)_3$-6,6´-phenyl-BINOL for β-alkyl substrates and $Gd(O\text{-}i\text{-}Pr)_3$-6,6´-I-BINOL for β-aryl substrates (Scheme **7**) [37].

The use of diethylzinc and a chiral alcohol as ligand under oxygen atmosphere for the epoxidation of (*E*)-α,β-unsaturated ketones

Table 3. Shibasaki *et al.* Asymmetric Epoxidation of α,β-Unsaturated Alkyl Esters



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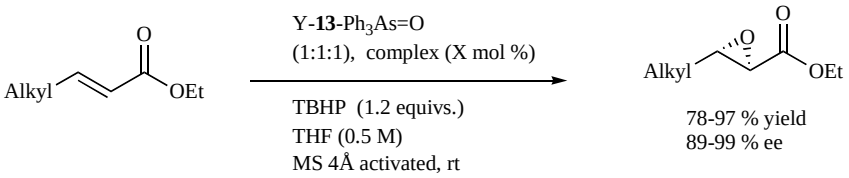
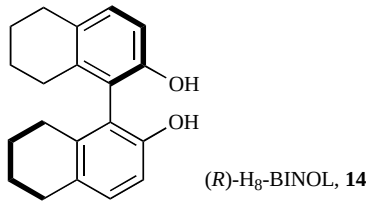
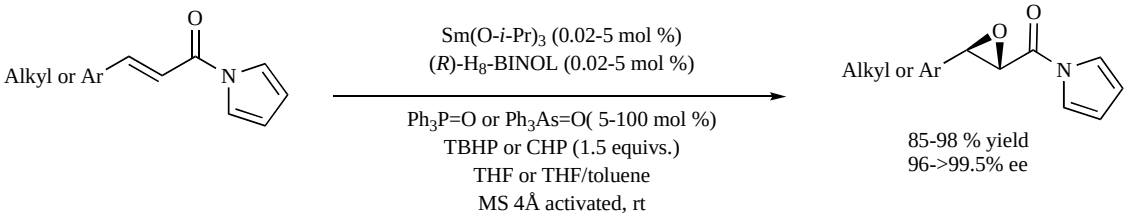


Alkyl	Catalyst (X mol%)	Time (h)	Yield (%)[a]	ee (%)[b]
Ph	10	47	86	91
	5[c]	48	80	86
Ph	10	71	81	93
O, Ph	10	42	78	92
PMBO	10	66	81	96

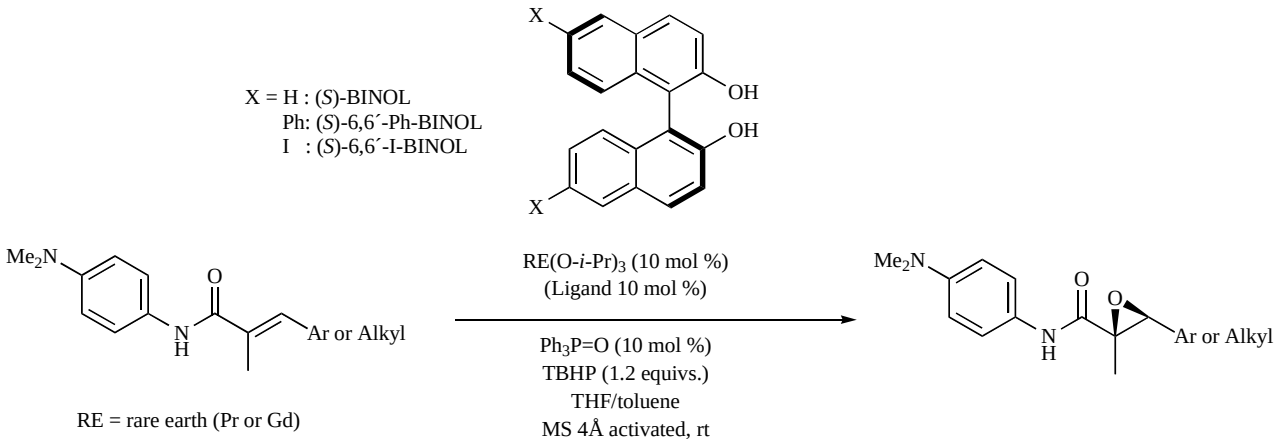
[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] 10 mol % of $Ph_3P=O$ instead of $Ph_3As=O$ was used as additive.



(*R*)-H_8-BINOL, **14**



Scheme 6.



Scheme 7.

and (*E*)-nitroalkenes has been previously reviewed by Porter and Skidmore [1]. Recently, Dötz *et al.* have developed a new system using BINOL and diethylzinc for the epoxidation of substituted chalcones and alkyl-substituted enones [38]. The reaction conditions were optimised as shown in Scheme **8**.

Dötz *et al.* found that chalcone derivatives with electron-donating substituents such as methyl or methoxy in the *para* position of the the β-phenyl ring were not epoxidised. On the other hand, chalcone derivatives with electron-withdrawing substituents such as Br or NO_2, which enhance the electron deficiency of the double bond, were epoxidised and the ees were increased up to 72%. However, the more striking effect was the change of TBHP for CHP, which increased both the yield and the enantiomeric excess of the reaction. These conditions were very favourable for the epoxidation of alkyl enones and yields in the range 83-99% and enantiomeric excesses of up to 96% were obtained. With both alkyl and arylenones the diastereoselectivity was always more than 99%.

These authors postulated the mechanism depicted in Scheme **9** for this epoxidation [39].

3. POLYAMINO ACID CATALYSED EPOXIDATION

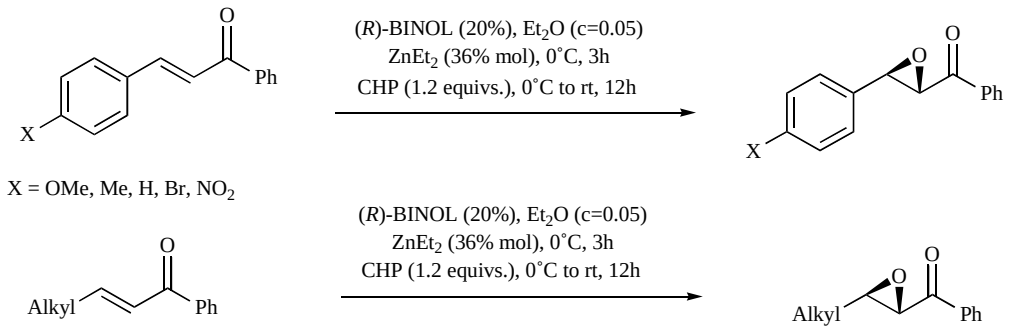
The polyamino acid catalysed asymetric epoxidation of enones was first reported by Juliá and Colonna in the early 1980s [5, 40]. This method consists of a triphasic system comprising an aqueous hydrogen peroxide containing sodium hydroxide, a water inmiscible organic solvent such as hexane or toluene and the insoluble polyamino acid such as polyleucine or polyalanine. The polyamino acid is usually prepared by the polimerization of an amino acid *N*-carboxy anhydride, induced by water or amines. Juliá and Colonna employed a relatively narrow range of substrates; essentially all reported examples were analogues of (*E*)-chalcone (Scheme **10**).

The Juliá-Colonna asymmetric epoxidation has been developed and improved in recent years in several ways [1,41]:

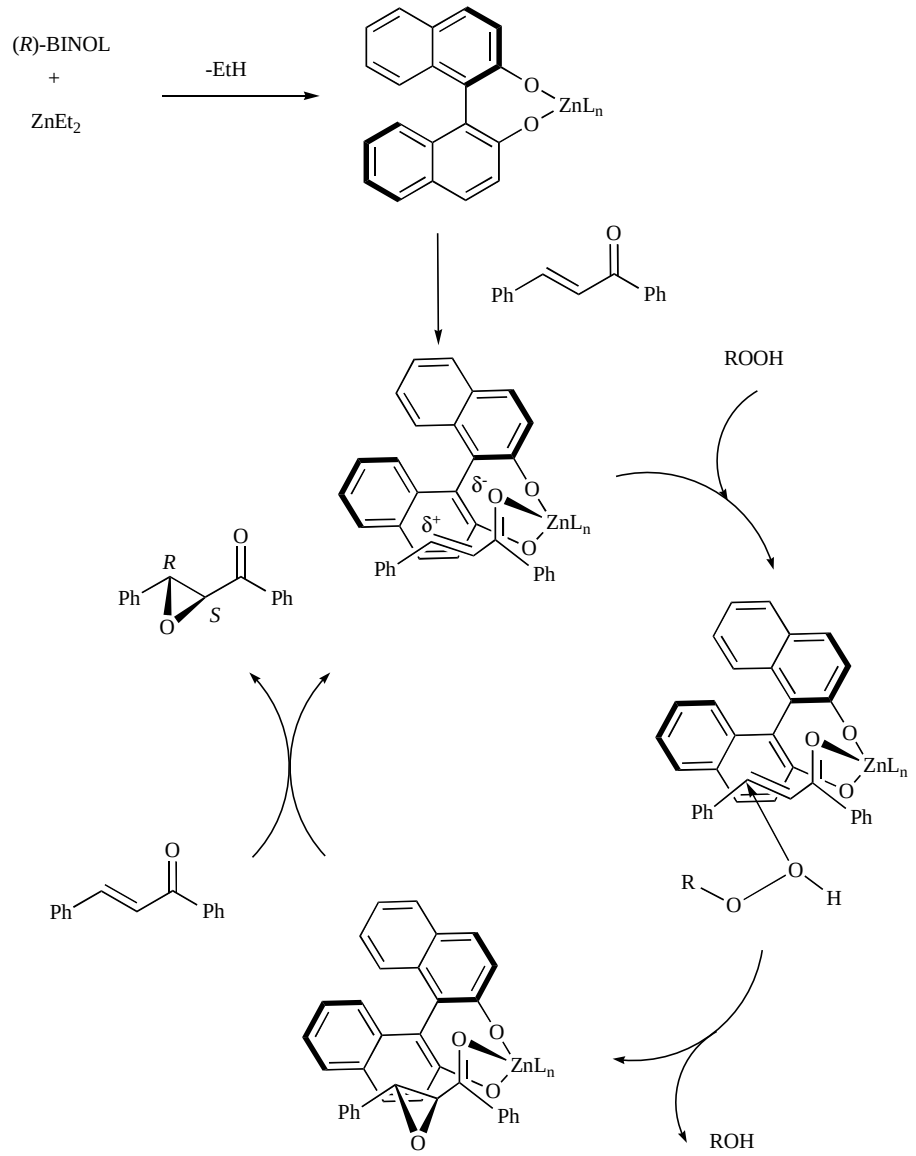
1. Production of the catalyst on a large scale [42].
2. Variation of the triphasic procedure to a new non-aqueous biphasic one by introducing other oxidants such as percarbonate in DME [43] and urea hydrogen peroxide (UHP) with a non-nucleofilic base (DBU) [44].
3. Best recovery and recycling by production of immobilised catalysts [45] and homogeneous catalysts [46], which can be used in membrane reactors [47].
4. Increase of the variety of substrates in the epoxidation reaction. This has given access to a wide range of useful intermediates for the synthesis of many natural products [48] and biologically active compounds [49].

The enantioselective epoxidation of less reactive enones has been performed by Roberts *et al.* after some modifications of the reaction conditions. For example, conformationally-restricted tetralones and analogous compounds (n=0, 2) gave the expected chiral epoxides with enantioselectivities in the range 59-96% ee under biphasic reaction protocol comprising poly-L-leucine (PLL) immobilised on polystyrene, urea-H_2O_2 and DBU in *iso*-propyl acetate (Scheme **11**) [50].

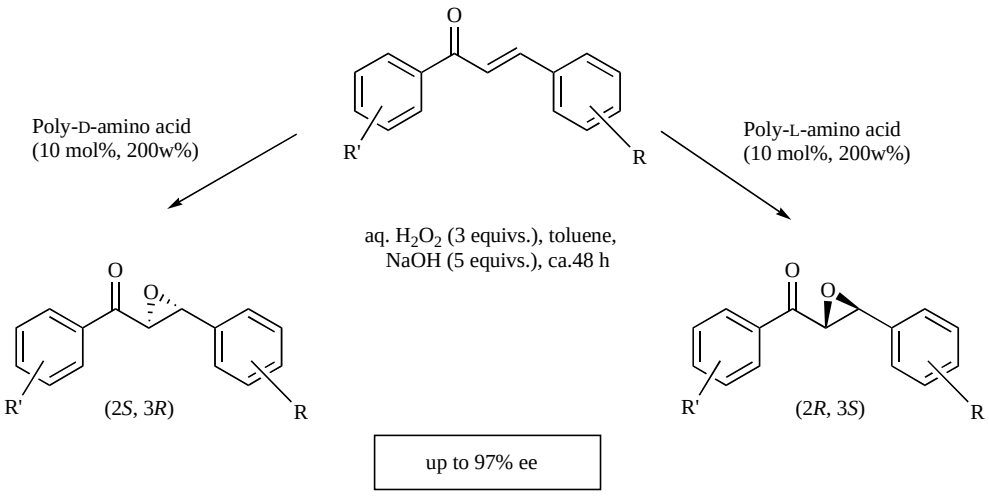
Another significant improvement of Juliá-Colonna epoxidation was introduced by Geller *et al*. It was found that the addition of a phase transfer catalyst (PTC) such as tetrabutylammonium bromide (TBAB) as co-catalyst in the asymmetric epoxidation of *(E)*-chalcone, increased the available concentration of the peroxide in the organic phase. In this manner, the reaction was faster and the expected epoxide was obtained in >99% conversion and 94% ee in only 1.5 hour. The amount of oxidant and base could be reduced



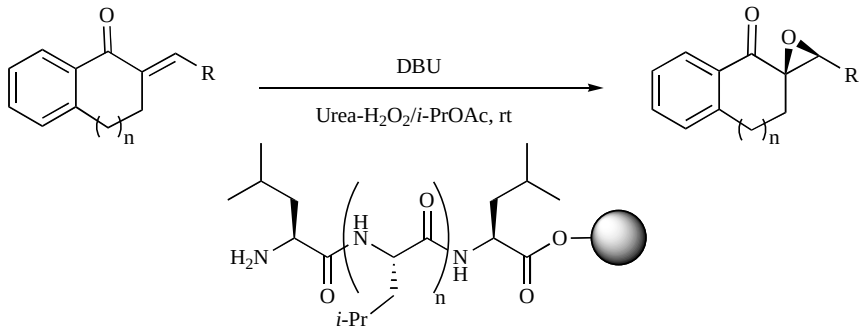
Scheme 8.



Scheme 9. Mechanism proposed by Dötz for the asymmetric epoxidation of enones promoted by (*R*)-BINOL and $ZnEt_2$.



Scheme 10. Enantioselective epoxidation of chalcones (triphasic conditions).



Scheme 11.

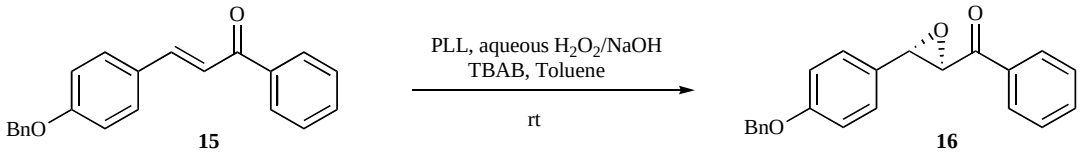
from 30 equivs. to 1.3 equivs. for H_2O_2 and from 4 equivs. to 1.3 equivs. for NaOH [51a]. Moreover, these authors synthesized poly-L-Leucine by polymerization at higher temperatures (ht-poly-L-Leu) and surprisingly, these new catalysts, which did not need a prolonged pre-activation period, led to significantly more active catalysts as compared to the standard material. The combination of ht-poly-L-Leu and TBAB afforded full conversion of *(E)*-chalcone in less than 10 min.

These new triphasic/PTC conditions were successfully scaled-up to a one-hundred gram substrate level. For example, with only 10 w/w% of PLL, epoxy ketone **16** could be obtained from enone **15** in 75% yield and 95.5% ee in large scale (Scheme **12**). However, scaling-up resulted in prolonged reactions times (12-20 hours) even when baffled reactors were used [51b].

In order to test the scope of these new conditions, Geller carried out further epoxidation reactions with substrates other than chalcone (**17**-**21**, Fig. **6**) [51c].

In all cases the reactions were faster and the enantiomeric excesses higher than under previously documented conditions (Table **4**).

Due to the very fast reaction under the triphasic/PTC-conditions, the amount of polyamino acid could be reduced and even with PLL amounts of just 0.1 wt%, a reasonable ee was obtained in the epoxidation of (*E*)-chalcone (61% conversion, 80% ee). Thus, using this catalyst loading, the reaction mixture appeared as a biphasic system and mixing, work-up and catalyst recovery were no limitations any longer. Under these conditions a separate pre-activation of catalyst was not required and the catalyst itself could



Scheme 12.

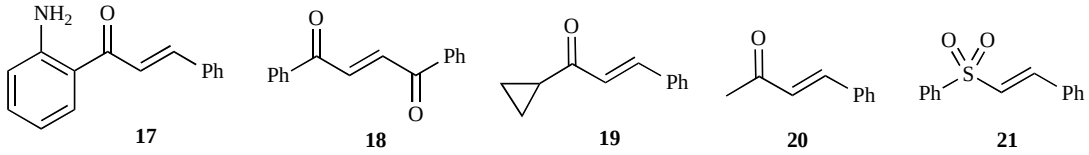


Fig. (6).

Table 4. Comparison of the Triphasic/PTC-Conditions [51c] with other Juliá-Colonna Epoxidation Protocols

Starting Compound	Method[a]	Time	H_2O_2 [equivs.]	NaOH [equivs.]	Conv. (%)	ee (%)
17	A	1 min	5	4.2	97	93
	B	2 h			81	98
18	A	8 min	1.3	1.3	>99	92
	C	15 h			76	76
19	A	5 h	28	4.2	40	90
	C	18 h			85	77
20	A	1 h	5	4.2	64	77
	D	4 h			70	80
21	A	2h	5	4.2	82	68
	E	4 days			61	20

[a] **A**: 11 mol% PLL, 11mol% TBAB, see ref. 51c; **B**: biphasic, see ref. 52a; **C**: triphasic, see ref. 52b; **D**: biphasic, see ref. 52c; **E**: conditions not published, see ref. 50.

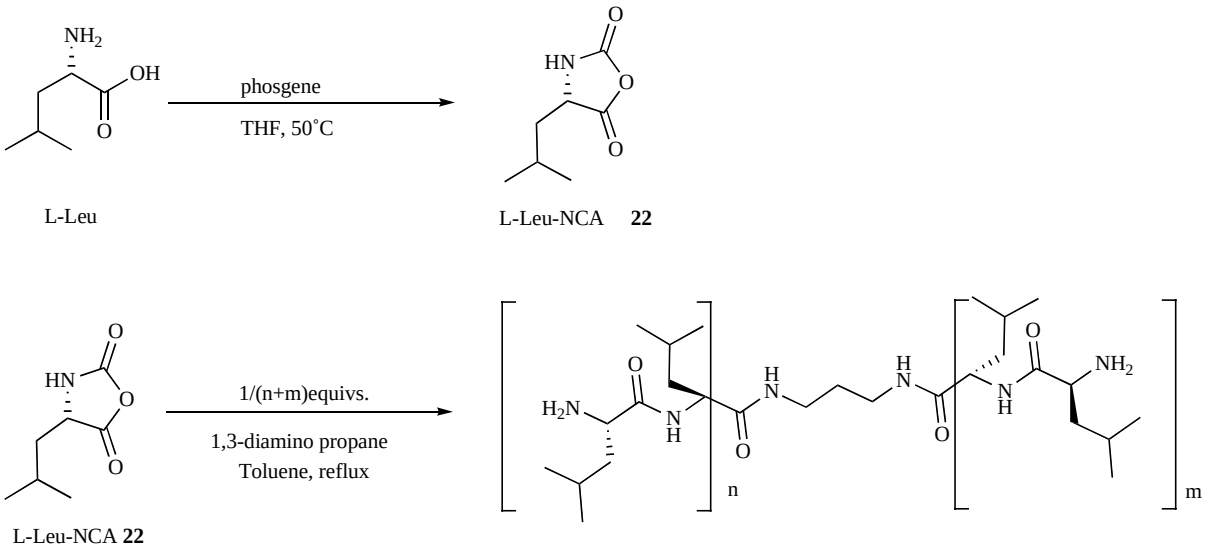
be prepared *via* L-Leu-NCA **22** very fast in a reliable way (Scheme **13**) [53].

Later, Roberts *et al*. expanded the range of substrates epoxidised under Juliá-Colonna conditions to unsaturated ketoesters and vinyl sulfones (Fig. **7**) by using PLL (1 mol%), aqueous sodium hydroxide (5 M, 2 equivs.), hydrogen peroxide (30%, 1.8 equivs.) as oxygen source and Bu_4NHSO_4 (1.5 mol%) in toluene. The corresponding (2*R*, 3*S*) epoxides were obtained with conversions in the 56-100% range, and ees in the 70-95% range. The authors highlighted the fact that, surprisingly, PLL sequesters peroxide from aqueous solution obtaining a polyamino acid/peroxide-containing gel [54].

Besides changing the reaction conditions, the structure of the polyamino acid catalyst was changed in order to improve the initially reported results. Ohkata *et al*. synthesized several PLL derivatives containing α-aminoisobutyric acid (Aib) residues and applied them as catalysts in the epoxidation of (*E*)-chalcone [55a]. It was found that the butyric residues in the mid section of the amino acid oligomer promoted the α-helix formation, which might be important for asymmetric induction in the epoxidation reaction under tri- and biphasic conditions, as previously suggested by Juliá and Colonna. The solubility of the catalyst in organic solvents was also improved and it was shown that the longer the oligomer, the better the enantioselectivity. These authors have also studied the influence of the polymerization degree of PLL in the Juliá-Colonna epoxidation of several substituted chalcones. The corresponding epoxides were obtained with high yield (up to 97%) and enantioselectivities (up to 98% ee) with H-(L-Leu)$_n$OH (n = 15).

The role of the amino acid in the *N*-terminus of the catalyst was studied by Roberts *et al*. It was demonstrated that the residues near to the *N*-terminus of the chain determined the sterochemical outcome of the epoxidation reaction [56]. In order to determinate whether the terminal amine group played a defining role in the action of the peptide catalyst, some R_1-(L-Leu)$_{20}$-R_2 derivatives were prepared and tested in the epoxidation of (*E*)-chalcone. Interestingly, when the reaction was performed with an oligomer having 5 residues of (*R*)-leucine starting from the *N*-terminus, followed by 15 residues of natural (*S*)-leucine, the epoxide antipodal with that obtained using PLL as catalyst was achieved with 85% yield and 45% ee. Thus, only 25% of the residues of the catalyst dictated the stereochemical outcome of the reaction. When the (*R*)-residues in the oligomers were changed, it was shown that the penultimate and one before penultimate residues played a crucial role in the product of the reaction and when these positions were occupied by glycine residues, having no stereocentres, the enantioselectivity dropped down from 88 % ee for H-(L-Leu)$_{20}$-R to 29 % ee for H-(L-Leu)-Gly$_3$-(L-Leu)$_{17}$-R.

There are several ways to solubilise the polyamino acids. One of them is their incorporation to a soluble polymer. Following this criteria, Roberts *et al*. bonded PLL to polyethylene glycol (PEG) giving a THF-soluble catalyst for the Juliá-Colonna epoxidation [57] which afforded excellent enantioselectivities (up to 96% ee) in the epoxidation of (*E*)-chalcone, even with short chain length of PLL. FT-IR studies have revealed that PLL chains attached to diamino-PEG, predominantly adopt an α-helical structure in organic solvents as long as the chain length exceeds four residues, which is the minimum number required to form one helical turn.



Scheme 13. Synthesis of L-Leu-NCA **22** and polymerisation to poly-L-Leu.

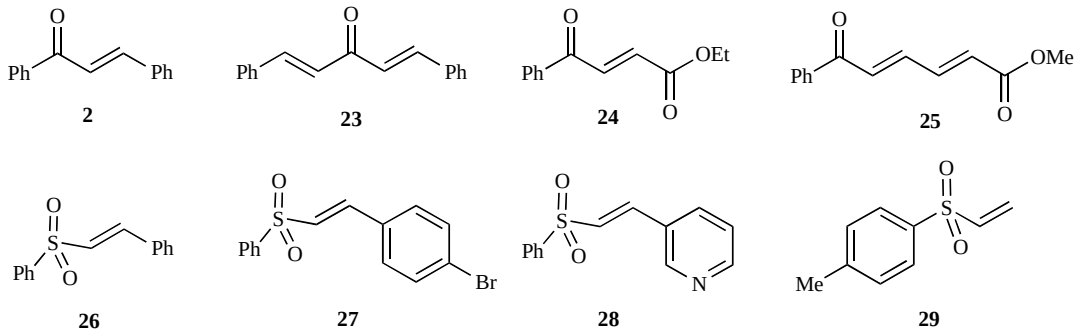
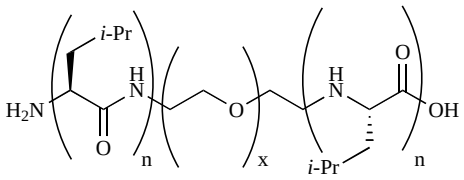


Fig. (7).



30

Fig. (8).

It was shown by Tsogoeva and coworkers that the activity of the aforementioned polymer as catalyst could be increased by enlarging the PEG chain. So, with x and n values about 453 and 8 respectively (Fig. **8**, **30**), using NaOH as base and UHP as the oxidant, the expected (2*R*, 3*S*) epoxide was obtained from (*E*)-chalcone with high enantioselectivity (94% ee) and a conversion over 99% after 15 minutes [58]. These authors also synthesized another soluble polymer obtained by polymerisation of aminomethylstirene and subsequent attachment to the corresponding leucine oligomer (Fig. **9**, **31**).

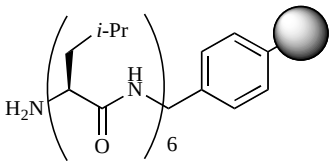


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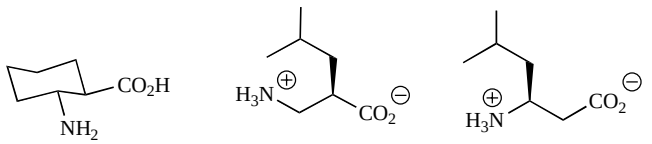
Fig. (9).

This catalyst was used in the epoxidation of (*E*)-chalcone under previously mentioned conditions and the expected (2*R*, 3*S*) epoxide was obtained in 92% yield and 97% ee after 60 minutes. These THF-soluble catalysts have been used in a continuous membrane reactor, maintaining the same activity after 28 residence times [59].

Other soluble catalysts have been constructed using NH_2-PEG-OMe as the support system by Kelly *et al*. Its secondary structure could be determinated by circular dichroism and it was found that the rate and ee of the epoxidation reaction were correlated with the helicity of the polypeptide and both of them increased with increasing chain length [60]. For example, H-[(L-Leu)$_{15}$]-NH-PEG-OMe is mainly the α-helical conformer and it has proved to be an excellent epoxidation catalyst in the epoxidation of (*E*)-chalcone. The expected (2*R*, 3*S*) epoxide was obtained in 97% ee at a conversion over 95%.

Berkessel and coworkers have also carried out studies about correlation between conversion, ee and helicity of the catalyst. Series of L-Leu 1-20 mers, peptides carrying 1-5 *N*-terminal Gly residues, and oligomers of (*S*)-β^3-Leu **34** and (1*R*,2*R*)-2-aminocyclohexane-carboxylic acid **32** (Fig. **10**) were synthesized on TentaGel S NH_2 and were tested in (*E*)-chalcone epoxidation. It was found that five L-Leu were enough to catalyse the Juliá-Colonna epoxidation of (*E*)-chalcone with 96-98% ee. On the other hand, it was confirmed that none of the β-oligomers from **33** and **34** showed catalytic activity (≤1-2% conversion after 24 h) [61].

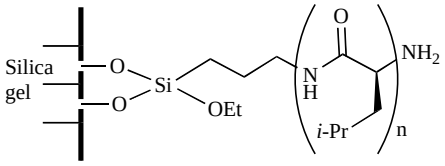


32 **33** **34**

Fig. (10).

Molecular modelling and experimental studies suggested that the catalytic active zone consisted of the *N*-terminal triad of an α-helical segment, since the carbonyl oxygen atom of the enone substrate is H-bonded to the NH groups of the amino acids at the *N*-terminus and at the third residue. Furthermore, the hydroperoxide nucleophile is delivered by the NH group of the second residue. Consequently, the sense of the helicity in the peptide catalyst determines the sense of induction in the epoxidation reaction. Again, it was shown that as little as four amino acids were enough to form an α-helix and only one helical turn was needed for obtaining efficient catalysts.

In order to solve the problems derived from handling the gel catalyst, Tang and coworkers grafted the PLL to silica gel functionalized with primary 3-aminopropyl groups (AMPSi), obtaining the silica grafted PLL **35** [62] (Fig. **11**). When this catalyst was used in the epoxidation of (*E*)-chalcone, the enantioselectivity increased with the degree of polymerization of the poly-L-Leucine, reaching 93% ee and 90% yield when *n* = 45. However, the enantioselectivity was not affected by changing the reaction conditions, such as oxidants and solvents. Attempts to recycle the catalyst were made and it was shown that if the catalyst was washed with MeOH after the reaction, it could be reused 10 times while retaining its activity and selectivity.

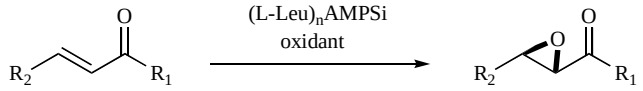


35

Fig. (11).

The epoxidation of various (*E*)-α,β-unsaturated ketones was also examined using the silica-grafted PLL **35**. All the olefins tested afforded the corresponding epoxides in good yields and enantioselectivities (Table **5**). Electron donating groups such as MeO, significantly decreased the enantioselectivity of the asymmetric epoxidation, while electron-withdrawing ones had little effect on it. Ortho-substituents lowered both the yields and enantioselectivities of the reactions catalised by the silica-grafted PLL **35**.

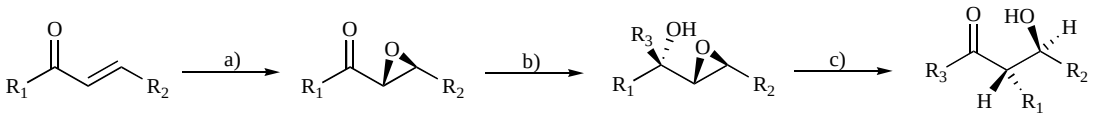
Table 5. Enones Epoxidised Using the (L-Leu)$_n$AMPSi Catalyst[a]



R_1	R_2	Yield (%)	ee (%)
Ph	Ph	94	93
Ph	*p*-$MeOC_6H_4$	80	82
Ph	*p*-$NO_2C_6H_4$	80	92
Ph	*o*-$MeOC_6H_4$	54	70
Ph	*o*-$EtOC_6H_4$	50	73
Ph	*p*-ClC_6H_4	90	92
o-$MeOC_6H_4$	Ph	70	80
p-ClC_6H_4	Ph	88	93

[a] 1.0 mmol substrate, 0.06 mmol catalyst, 1.6 mmol sodium percarbonate, 2 ml DME, 2 ml H_2O, rt, 2 h.

Roberts *et al*. reported the synthesis of epoxy *tert*-alcohols from (*E*)-enones using this kind of catalysts under biphasic-conditions in a two step approach consisting of Juliá-Colonna asymmetric epoxidation followed by a Grignard alkylation of the epoxyketone (Scheme **14**) [63].

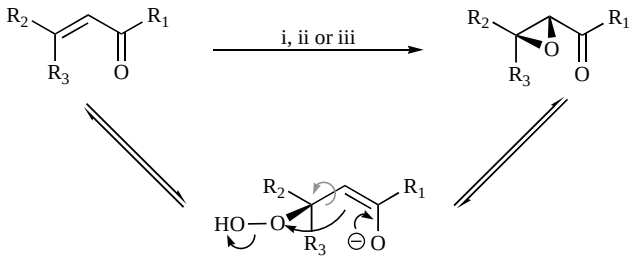


Scheme 14. a) Asymmetric epoxidation; b) Grignard alkylation; c) Yb(OTf) catalyzed arrangement.

Geller *et al*. studied the influence of PTC under biphasic and silica grafted PLL-conditions using unactivated poly-L-Leu, in the epoxidation of (*E*)-chalcone. It was found that the expected (2*R*, 3*S*) epoxide was obtained in only 30 minutes with >99% conversion and 92% ee [51c].

Roberts *et al*. have studied β-analogues of the Juliá-Colonna poly-α-leucine catalysts in order to evaluate their potential as asymmetric catalysts, since β-amino acids form stable helices more easily than the related α-amino acids. However, the orientation of the NH bonds in the β-helix is opposite to that of the α-helix. The peptides from β^2-leucine **33**, and β^3-leucine **34** (Fig. **10**) were synthesized in order to test the influence of this new orientation in the enantioselectivity of the Juliá-Colonna epoxidation of different substituted chalcones (R_1=Ph, *t*-Bu and R_2=Ph, Et). Both catalysts were very inefficient and only after basic treatment of the catalyst derived from β^3-leucine, could the enantioselectivity be improved up to 70% ee [64].

Roberts, Kelly and their coworkers also reported kinetic studies of the Juliá-Colonna reaction [65, 66]. In the Kelly-Roberts model, enone binding is carried out by the NH groups of two adjacent amino acids, whereas the third one is involved in the binding/delivery of the hydroperoxide. These three NHs implicated in catalysis do not need to include the *N*-terminus, but may as well be derived from residues 2, 3 and 4. In these studies Roberts, Kelly *et al.* indicated that the reaction proceeded *via* a fast reversible addition of hydrogen peroxide anion to form a racemic enolate, followed by slow intramolecular stereo selective nucleophilic displacement of hydroxide to form the final non-racemic epoxide (Scheme **15**). Thus, the role of the catalyst is the stabilisation of the initially formed enolate through the oxi-anion hole formed by the amidic groups located near to the *N*-terminus of peptide. This stabilisation is higher for one of the two enantiomeric enolate intermediates, favouring kinetic resolution of the racemic mixture.



Scheme 15. *Reagents and conditions*: (i) Weitz-Scheffer, (ii) Juliá-Colonna triphasic system, (iii) Juliá-Colonna biphasic system.

The Juliá-Colonna epoxidation has been used by Lauret and coworkers in the synthesis of the structure claimed for Puetuberosanol. It was found that the natural product did not have the reported structure (Scheme **16**) [67]. Also the synthesis of a protected galactonic acid derivative has been carried out using the Juliá-Colonna epoxidation of some unsaturated enones possessing a stereogenic centre at the γ-position [68].

4. PHASE TRANSFER CATALYSIS

The use of chiral onium salts and crown ethers as effective phase-transfer catalysts has been widely studied for enantioselective carbon-carbon or carbon-heteroatom bond-forming reactions under mild biphasic conditions [69].

Regarding the asymmetric epoxidation of enones, the most common used phase transfer reagents are alkylated *Cinchona* alkaloids and recently also chiral azacrown ethers.

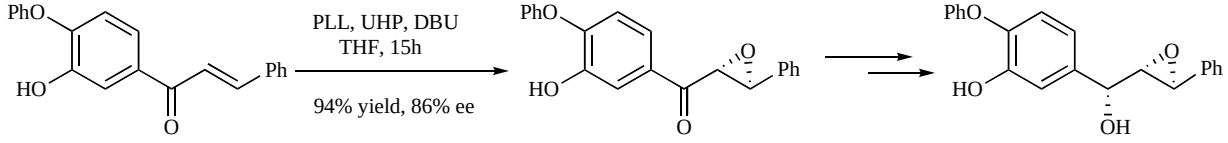
In the mid-1970s, Wynberg and coworkers first investigated the use of phase transfer catalysis (PTC) in a biphasic Weitz-Scheffer epoxidation using phase transfer catalysts derived from quinine and quinidine [4]. Since then, a large number of papers of PTC epoxidation of enones have appeared, due to its practical advantages and synthetic versatility [1].

Continuing with their investigations on asymmetric epoxidation of enones and naphtoquinones, Arai, Shioiri and coworkers reported again the epoxidation of (*E*) and (*Z*)-enones promoted by chiral PTC reagents derived from cinchonine or quinidine (**41 a-f**) in the presence of H_2O_2 as oxidant (Scheme **17**, Table **6**) [70].

The dependency of the enantioselectivities on the substituents on PTC structure, especially the secondary alcohol and benzyl moieties, was studied. Electron donating groups on C-4 position of the benzyl ring such as MeO gave significant lower ee than electron withdrawing groups, and regioisomers with the substituent in C-3 instead of C-4 proved to be ineffective for asymmetric induction in the epoxidation of enones. It was also shown that the *N*-(α-naphthylmethyl)quinidinium salt **38** (Fig. **12**) acted as an effective PTC for the asymmetric epoxidation of 2-substituted naphtoquinones **42**, obtaining the corresponding epoxides **43** with enantioselectivities in the 64-76% ee range (Scheme **18**).

Interestingly, higher enantioselectivities (up to 84% ee) were afforded when using the deaza derivative **39** (Fig. **12**) as PTC [71]. This type of chiral quaternary salts derived from cinchonine, in particular *N*-benzylcinchoninium chloride **40** (Fig. **12**), has been used by Barrett *et al*. for the asymmetric epoxidation of the naphtoquinone Palmarumycin CP_1 using TBHP as oxidant to obtain the desired epoxide **45** in good yield (81%) and excellent enantioselectivity (>95% ee) (Scheme **19**) [72].

Lygo and coworkers, also continuing with their investigations in this field using sodium hypochlorite as oxidant and *N*-anthracenylmethyl derivatives of cinchona alkaloids catalysts such as **46** (Fig. **13**), found that the asymmetric epoxidation of a variety



36 **37** Puetuberosanol

Scheme 16. Synthesis of the structure proposed for Puetuberosanol.

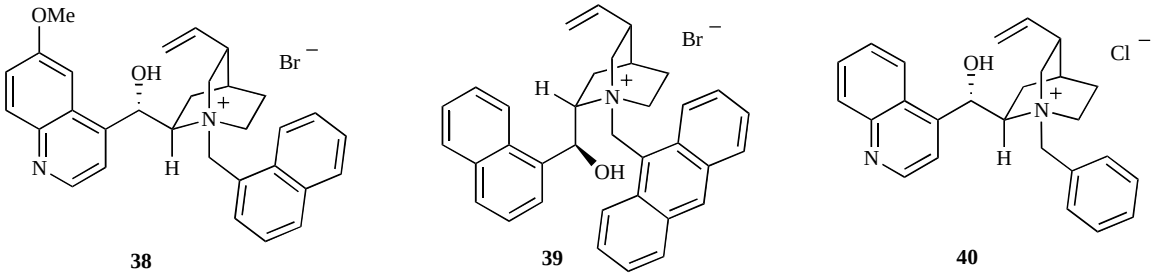
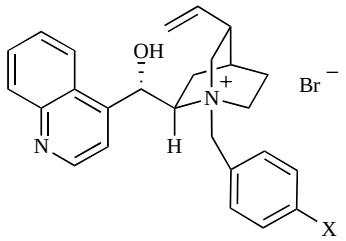
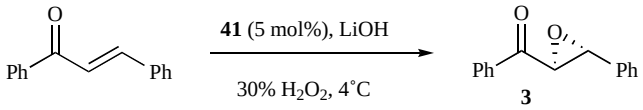


Fig. (12).

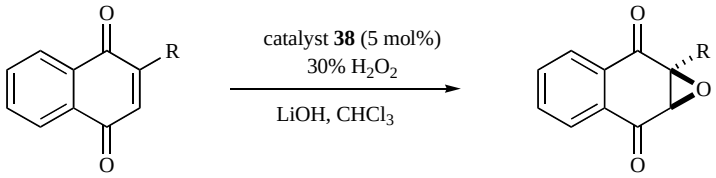


41a (X = H)
41b (X = Cl)
41c (X = I)
41d (X = OMe)
41e (X = NO_2)
41f (X = CF_3)



72% yield, 1% *ee* with **41a**
68% yield, 65% *ee* with **41b**
97% yield, 84% *ee* with **41c**
70% yield, 4% *ee* with **41d**
61% yield, 72% *ee* with **41e**
72% yield, 73% *ee* with **41f**

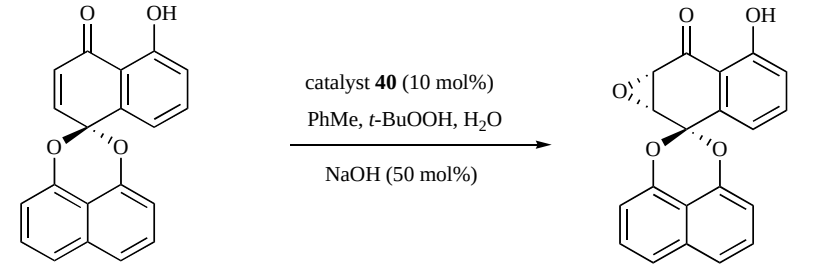
Scheme 17.



42a (R = *c*-Hex)
42b (R = *i*-Pr)
42c (R = Ph)

60% yield, 64% ee **43a** (R = *c*-Hex)
93% yield, 70% ee **43b** (R = *i*-Pr)
47% yield, 76% ee **43c** (R = Ph)

Scheme 18.



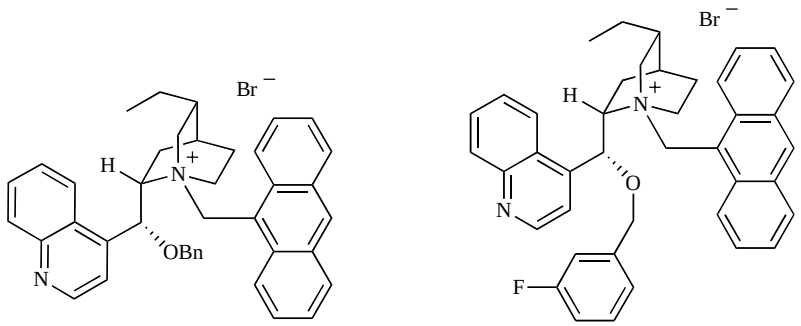
Palmarumycin CP1 **44**

45 (81% yield, >95% ee)

Scheme 19.

of α,β-enones proceeded with only 1 mol% of this catalyst (Table **6**) [73a].

The only exceptions were substrates with enolizable R_1 substituents, so it has been suggested that enolization competes with epoxidation in these cases. Tri-substituted chalcones (with a methyl group either in α or in β-position) did not undergo epoxidation under standard reaction conditions, so it seems that further substitution in the alkene is not tolerated. Interestingly, (*Z*)-α,β-chalcone



46 **47**

Fig. (13).

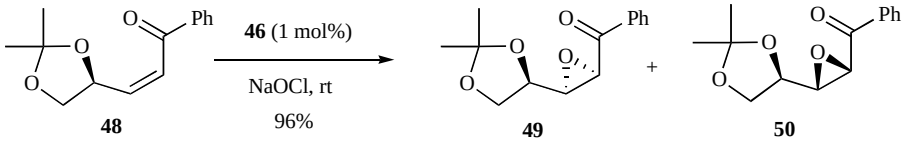
was converted under the same optimized conditions into the corresponding *cis*-α,β-epoxychalcone, which is very unusual for Weitz-Scheffer epoxidations, as the two-step mechanism allows for bond rotation prior to ring closure and the stereochemical information is lost [73c]. PTC epoxidation of (*Z*)-enone **48** produced the corresponding *cis*-epoxides **49** and **50** (Scheme **20**), in contrast with the Juliá-Colonna-Roberts procedure which is reported to give only *trans*-epoxides from the corresponding (*Z*)-enones [1]. This fact has also been observed by Dorow and coworkers, who have used this type of *N*-anthracenylmethyl cinchona alkaloid derived catalysts and potassium hypochlorite as oxidant at low temperature for the asymmetric epoxidation of α,β-unsaturated sulfones. It was shown that the ether moiety of the dihydrocinchonidine salts had a significant effect on both the enantioselectivity and conversion. Catalyst **47** (Fig. **13**) which contains the 3-fluorophenyl methyl ether, was the most effective one [74].

Lygo and coworkers also investigated the one-pot conversion of allylic alcohols into α,β-epoxyketones, as it was known that secondary alcohols could be oxidized to the corresponding ketones using NaOCl and PTC conditions. Combining increased catalyst loading (5 mol%) with slow addition of the substrate, a series of allylic alcohols **51** were transformed into the corresponding α,β-epoxyketones **52** with moderate to good yields although with lower enantioselectivities to those obtained by direct epoxidation of the corresponding enones (Scheme **21**) [73b,c].

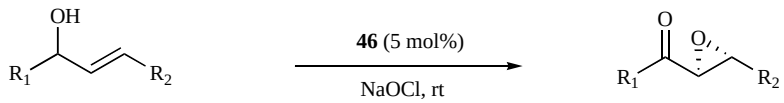
Liang *et al.* successfully tested trichloroisocyanuric acid (TCCA) as a safe, inexpensive, and mild oxidant for the asymmetric epoxidation of enones with *N*-anthracenylmethylcinchonidinium derivative **46** as PTC [75a]. When KOH was used as inorganic base to release hypochlorite from TCCA, this system proved useful for the epoxidation of a wide range of substituted chalcones either in liquid-liquid [75a] or solid-liquid [75b] biphasic systems, achieving high diastereoselectivities and good to high enantioselectivities (Table **6**). Liang also used this procedure for the one-pot Claisen-Schmidt condensation-asymmetric PTC epoxidation, leading to α,β-epoxyketones with enantioselectivities comparable to that of the PTC epoxidation of enones [75c].

Adam and coworkers have reported the use of optically active hydroperoxides under phase transfer catalysis conditions using cinchona-derived catalysts in an attempt to prove if synergic effects of the chirality in the hydroperoxide and in the PTC could enhance the enantioselectivity of the epoxidation reaction [76a]. Only for the conformally rigid *s-cis*-enone **55**, good ee values of up to 95% were achieved either by racemic hydroperoxides **53** and **54** or achiral cumyl and *tert*-butylhydroperoxides using PTC **41f** (Scheme **22**). Better results were obtained in the asymmetric epoxidation of isoflavones **57** using **41f** as the catalyst and cumyl hydroperoxide (CHP) as oxidant [76b]. Isoflavone epoxide **58a** was obtained almost quantitatively and with excellent enantioselectivity even when the catalyst loading was reduced to 1 mol% (Scheme 23). However, the kinetic resolution of the racemic hydroperoxides was very poor in all cases, suggesting that this reagent is only weakly bound to the phase transfer catalyst and so the hydrogen-bond aggregation of the isoflavone and the PTC is the dominating factor in the enantiofacial differentiation.

Bakó and coworkers have found that chiral monoaza-[15] crown-5 compounds derived from D-glucose **59**, D-galactose **60**, D-mannose **61** and D-mannitol **62** (Fig. **14**) are useful catalysts in the phase-transfer-catalysed asymmetric epoxidation of chalcones with TBHP [77]. It was observed that yields and enantioselectivities were significantly affected by the type of monosaccharide; glucopyranoside-based catalysts **59** promoted the formation of the



Scheme 20.

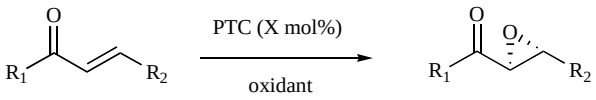


51a ($R^1 = R^2 = Ph$)
51b (R^1 = 3,4-$(OCH_2O)C_6H_3$; $R^2 = Ph$)
51c (R^1 = *p*-FC_6H_4; $R^2 = Ph$)

52a: 66% yield, 79% ee
52b: 63% yield, 87% ee
52c: 95% yield, 84% ee

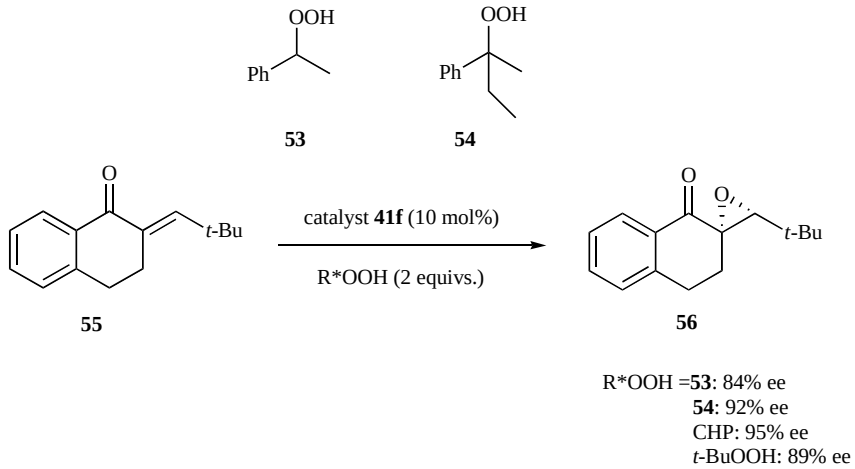
Scheme 21.

Table 6. Comparison of Arai [70], Lygo [73] and Liang [75] Epoxidation of Enones

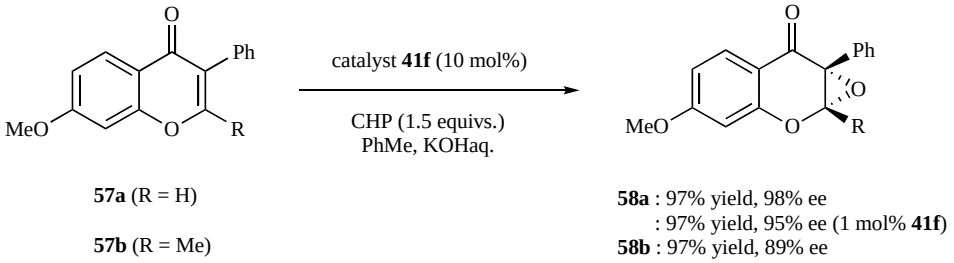


R_1	R_2	Method[a]	Yield (%)	ee (%)
Ph	Ph	A	97	84
		B	98	86
		C	90	89
		C[b]	90	87
p-FC_6H_4	Ph	B	94	87
		C	79	88
Ph	*m*-MeC_6H_4	A	100	92
3,4-$(OCH_2O)C_6H_3$	Ph	B	95	92
Ph	3,4-$(OCH_2O)C_6H_3$	B	94	92
Ph	*p*-$NO_2C_6H_4$	C	83	96
p-$NO_2C_6H_4$	Ph	B	85	86
p-$NO_2C_6H_4$	EtO_2C	B	74	86

[a] **A**: catalyst **41c** (5 mol%), 30% H_2O_2, LiOH (3 equivs.), *n*-Bu_2O, 4ºC. See ref. 70; **B**: catalyst **46** (1 mol%), NaOCl (2 equivs.), PhMe, rt. See ref. 73; **C**: catalyst **46** (10 mol%), TCCA (0.7 equivs.), 50% KOH aq. (3 equivs.), 0ºC. See ref. 75.
[b] **B**: solid KOH (6 equivs.) was used (non-aqueous system).



Scheme 22.



Scheme 23.

(2*R*,3*S*) isomer of the corresponding epoxyketone, while the lariat ethers incorporating a mannose unit **61** led to the formation of the (2*S*,3*R*) isomers. The best enantioselectivity (92% ee) was obtained using catalysts **59** with *N*-γ-hydroxypropyl substituent, thus showing that the *N*-substituents in the crown ring strongly affect the asymmetric induction.

Another example of asymmetric epoxidation of chalcones catalyzed by azacrown ether-type phase transfer catalysts is the one reported by Hori and coworkers. In this case, the PTC of choice was the C_2-symmetry chiral PTC (*S*,*S*)-**63n**, derived from (*S*)-BINOL (Fig. **15**) [78]. In the presence of hydrogen peroxide as oxidant, good yields and enantioselectivities in the range 22-83% ee

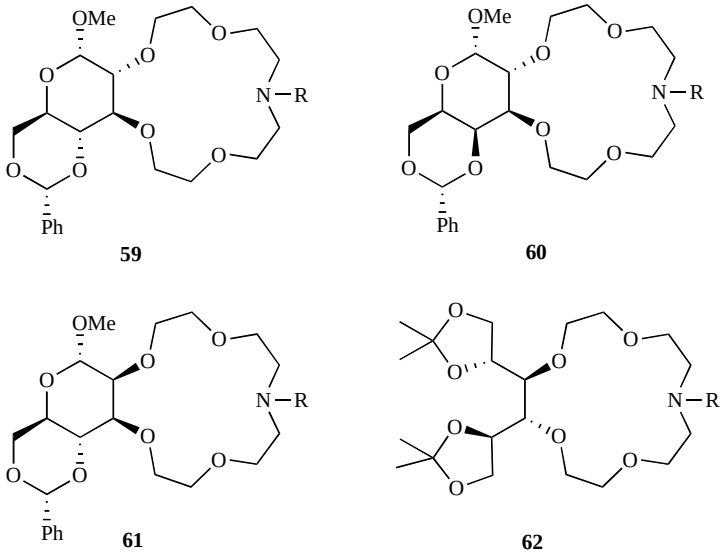
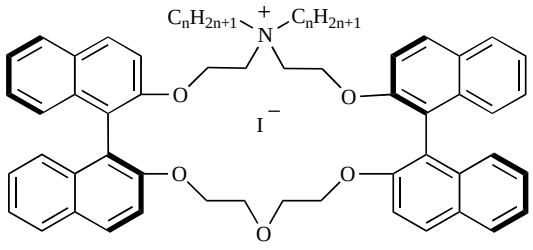


Fig. (14).

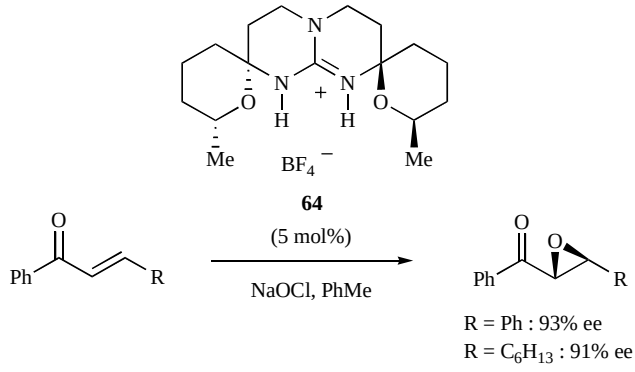
were obtained. As in the aforementioned method, this reaction depended on the length of the carbon chain on the nitrogen atom and also on the bulk of the base used.



(*S*,*S*)-**63n**

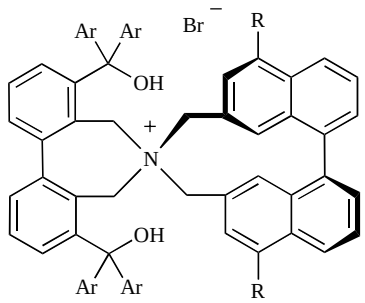
Fig. (15).

Murphy *et al.* have synthesized several tetracyclic C_2-symmetric guanidium salts **64** (Scheme **24**) from (*S*)-malic acid and have used them in several asymmetric transformations including the asymmetric epoxidation of chalcone derivatives using sodium hypochlorite as oxidant [79]. Only two examples were reported, although in both of them, good enantioselectivities (93% and 91% ee) were achieved (Scheme **24**).



Scheme 24.

The design of new *N*-spiroammonium salt catalysts **65** (Fig. **16**) by Maruoka and coworkers has shown a significant improvement in phase transfer catalysed asymmetric epoxidation of enones. This chiral quaternary ammonium bromide with dual functions allows highly enantioselective epoxidation of a variety of α,β-unsaturated ketones using sodium hypochlorite as oxygen source [80]. Catalyst **65b** proved to be the most effective one for epoxidation of aryl ketones and virtually complete stereochemical control was achieved for β-benzylidene-α-indanone (Table **7**). Interestingly, the substrates having an alkyl substituent either on the double bond or on the carbonyl carbon were also epoxidised with high enantioselectivities using catalyst **65a**. In all cases, (α*S*,β*R*) epoxides were obtained. Citing X-ray diffraction analysis of catalysts **65**-PF_6, Maruoka suggested that this high asymmetric induction could be due to recognition of the catalyst by the enone substrates through hydrogen bonding interaction as well as the chiral molecular cavity. Maybe the main drawback of this procedure is the length of reaction; even relatively reactive substrates such as chalcone and simple derivatives require at least 24 hours for complete conversion.

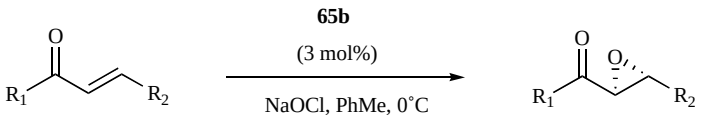


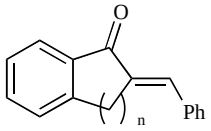
65a : (Ar = 3,5-Ph_2-C_6H_3, R = H)
65b : (Ar = R = 3,5-Ph_2-C_6H_3)

Fig. (16).

Recently, Jew *et al.* have demonstrated that the use of novel meta-dimeric catalysts, derived from cinchona alkaloids **66** (Fig. **17**), with hydrogen peroxide as oxidant and a surfactant, gave epoxidation of a range of enones with almost quantitative yields and ees of 97-99% [81]. Interestingly, the use of surfactants dramatically increased not only the rate of the reaction (five times), but also the enantioselectivity of phase transfer catalytic epoxidation. The best results in terms of both yield (95%) and enantioselectivity (>99% ee) were obtained with the surfactant Span 20 and with the

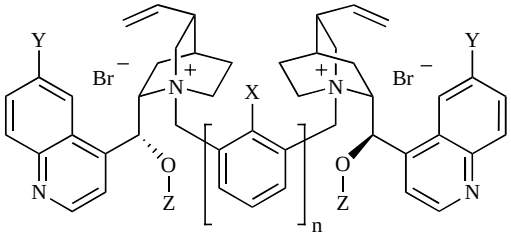
Table 7. Catalytic Asymmetric Epoxidation Using Maruoka´s Catalyst 65



R_1	R_2	Yield(%)	ee(%)
Ph	Ph	99	96
Ph	*p*-ClC_6H_4	99	96
Ph	*p*-$MeOC_6H_4$	83	96
p-ClC_6H_4	Ph	99	93
t-Bu	Ph	87	89
t-Bu[a]	Ph	99	92
t-Bu[a]	*c*-Hex	80	96
t-Bu[a]	*n*-Hex	80	91
			
n = 1		91	99
n = 2		98	96

[a] Catalyst **65a** was used.

dimeric catalyst **66e** (Table **8**). However, the substrate scope of this process is still limited to aryl-substituted enones.

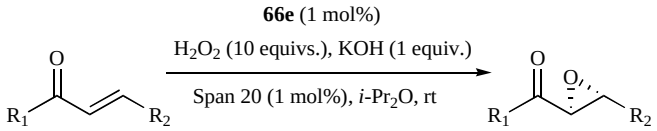


66a	n = 1	X = H	Y = H	Z = H
66b	n = 2	X = H	Y = H	Z = H
66c	n = 1	X = F	Y = H	Z = H
66d	n = 1	X = H	Y = OMe	Z = H
66e	n = 1	X = F	Y = OMe	Z = H
66f	n = 1	X = F	Y = OMe	Z = allyl

Fig. (17).

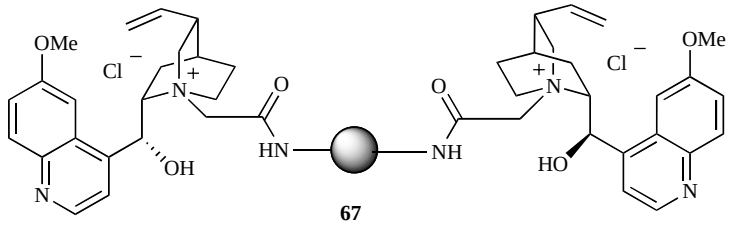
Wang and coworkers have anchored cinchona-derived alkaloids (*via* nitrogen) to long linear PEG chains to afford soluble polymer-supported chiral PTC catalysts for the asymmetric epoxidation of chalcones [82].

Table 8. Catalytic Asymmetric Epoxidation Using Jew´s Catalyst 66e



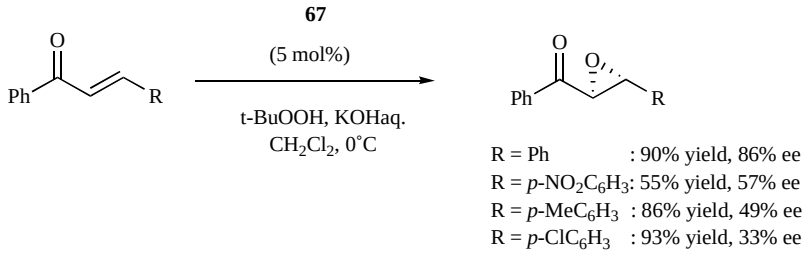
R_1	R_2	Yield(%)	ee(%)
Ph	Ph	95	>99
p-FC_6H_4	Ph	94	98
p-$MeOC_6H_4$	Ph	95	>99
2-naphthyl	Ph	96	>99
Ph	*o*-FC_6H_4	97	>99
Ph	*m*-MeC_6H_4	95	97

Although this could mean a further development of the PTC epoxidation of enones due to the ease of separation, possible recycling, good stability and reduced toxicity, the results obtained were not very encouraging. The best ee (86%) for chalcone was achieved with resin-supported quininium salt **67** (Fig. **18**), but all other chalcone derivatives afforded ees in the 33-57% range (Scheme **25**).



67

Fig. (18).



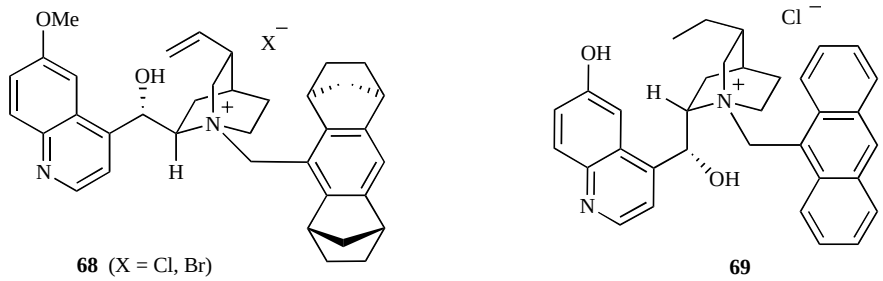
Scheme 25.

Very recently, Berkessel and coworkers have reported a study on systematic structural variations of phase transfer catalysts based on quinine and quinidine with the aim to develop new and highly effective PTCs for the asymmetric epoxidation of 2-methylnaphthoquinone **70** (Vitamin K_3, Scheme **26**) [83]. Among these new catalysts synthesized, the most effective one was **68** (Fig. **19**), which includes further elements of chirality at the quinuclidine nitrogen atom. (2*S*,3*R*) Epoxide was obtained in 86% yield and 79% ee. However, it was found that the best results were achieved with the readily available ammonium salt **69** (Fig. **19**), which afforded the highest enantioselectivity (85% ee at 73% yield for (2*R*,3*S*) epoxide) ever reported for the asymmetric epoxidation of Vitamin K_3 (Scheme **26**).

5. CHIRAL HYDROPEROXIDES

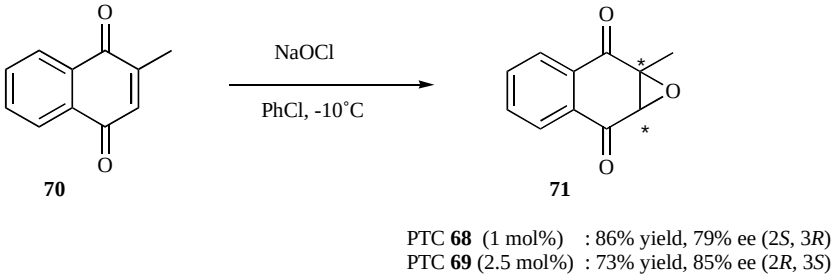
Optically active hydroperoxides are now conveniently available through enzymatic kinetic resolution of racemic mixtures or by derivatization of natural products such as carbohydrates with H_2O_2. However, only recently have investigations on enantioselective epoxidation of α,β-enones mediated by such stereoselective reagents received attention. These chiral oxygen sources have previously been used for the asymmetric oxidation of sulfides and allylic alcohols, which established their potential synthetic value [84,85].

Adam and coworkers reported the first application of optically active *S*-(-)-(1-phenylethyl) hydroperoxide **72** for the enantioselective Weitz-Scheffer epoxidation of α,β-enones [86]. It was observed that, with the same prochiral enone and the same optically active hydroperoxide, the extent and sense of asymmetric induction in the reaction were completely different depending on the type of the base chosen (Scheme **27**, Table **10**). To explain this, a *template effect* made up of the enone substrate, hydroperoxide and base catalyst was proposed. In the template structure, the enantiofacial control is conditioned by the steric interactions between the aggregated species (Fig. **20**). When KOH is used as base, the (α*S*,β*R*) enantiomer of the epoxide is formed due to the lower steric repulsions between the *β*-substituent of the enone and the substituent at the



68 (X = Cl, Br) **69**

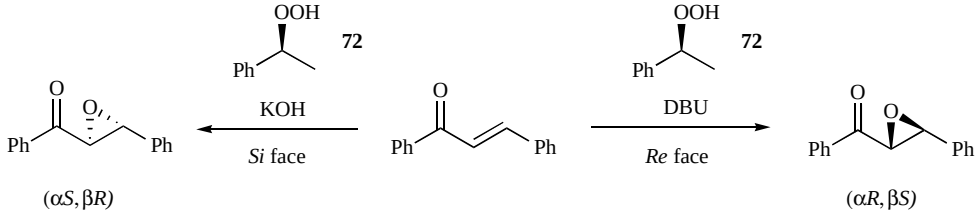
Fig. (19).



70 **71**

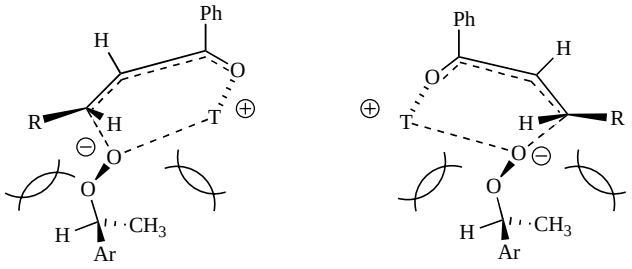
PTC **68** (1 mol%) : 86% yield, 79% ee (2*S*, 3*R*)
PTC **69** (2.5 mol%) : 73% yield, 85% ee (2*R*, 3*S*)

Scheme 26.



Scheme 27.

chirality center of the hydroperoxide anion during the (*Si*)-face attack of the *S-cis* conformation. When the substrate is a conformally fixed *S-cis* enone, an ee value of 90% was afforded with optimized reaction conditions. In the DBU-mediated epoxidation, there is competition between the steric interactions of the hydroperoxide anion with the enone *β*-substituent and the $DBUH^+$ (usually dominant), so the (*Re*)-face attack is favoured and the (α*R*,β*S*) enantiomer of the epoxide is formed in up to 72% ee.



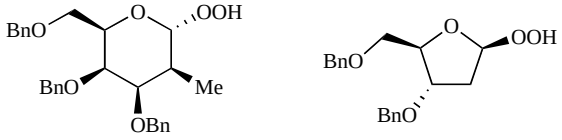
TS-A (*Si* face) **TS-B** (*Re* face)

Fig. (20). Template structures proposed by Adam for the base catalyzed asymmetric Weitz-Scheffer epoxidation of α,β-enones by optically active hydroperoxides, where T^+ (either the K^+ or $DBUH^+$ ions) represents the templating agent.

Taylor *et al.* have synthesized carbohydrate anomeric hydroperoxides (AHPs) and have employed them in the enantioselective epoxidation of quinones and naphtoquinones. The D-pyranose-derived hydroperoxide **73** was the most effective one of a series of screened D-glucose and D-galactose derivatives in the epoxidation of 2-(5-cyclohexylpentadienamido)-1,4-benzoquinone **75** (55% yield and 64% ee) (Scheme **28**) [87a].

Also L-rhamnose-derived **74** gave good enantioselectivity (55% ee), but with opposite sense of stereoinduction to that obtained with **73** [87b]. This fact proved that anomeric purity of the hydroperoxides determined the sense of enantioselectivity. Regarding the naphtoquinones, AHP **74** gave the best ee (78%) for the Vitamin K_3 **70**, although with low yield (32%). For the 2-phenylnaphtoquinone, AHP **73** gave 80% yield and 82% ee (Scheme **29**, Table **9**). Molecular modelling assuming a transition state which involves two species (peroxide and quinine) has failed to explain the observed results, so it has been suggested that the transition state probably involves the base DBU [87b]. However, in this case the mechanism may not be similar to that aforementioned of Adam, as the two systems differ in one important feature: the quinone system has a fixed *S-trans* conformation.

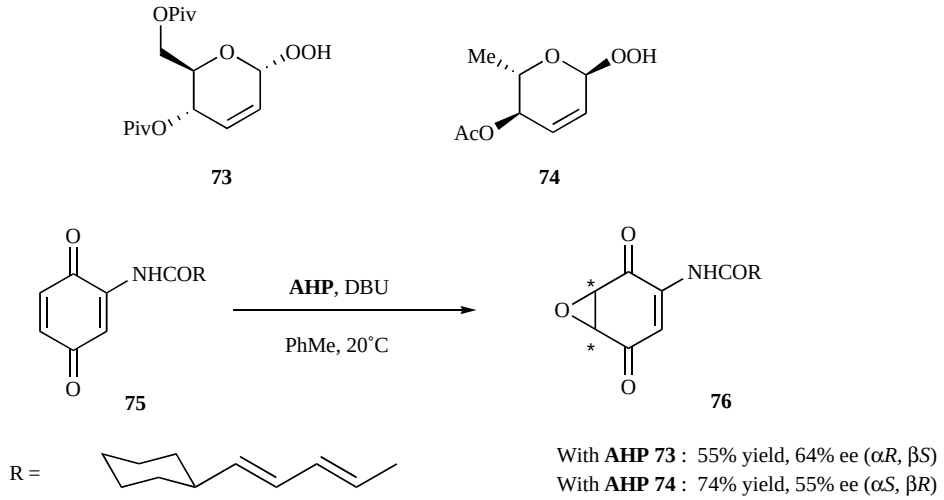
Also Chmielewski and coworkers tested anomeric hydroperoxides derived from 2-deoxysugars such as **77** and **78** (Fig. **21**) in the epoxidation of Vitamin K_3 **70**. However, the best result was an ee of 47% for the (2*R*,3*S*) epoxide with **78** and for the (2*S*,3*R*) epoxide with **77** (Table **9**) [88].



77 **78**

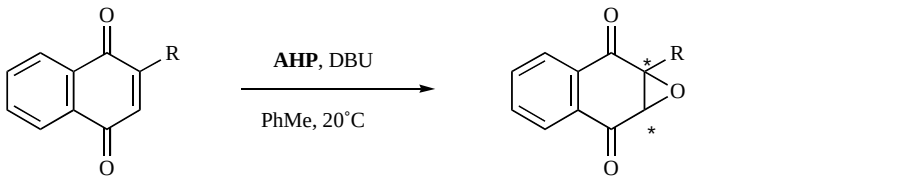
Fig. (21).

A new type of chiral hydroperoxide derived from TADDOL in which one OH group has been replaced by an OOH group was pre-



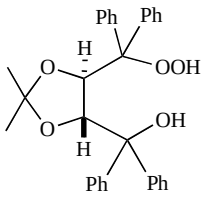
73 **74** **75** **76**

Scheme 28.

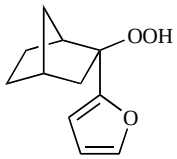


Scheme 29.

pared by Seebach and coworkers. This crystalline TADOOH **79** (Fig. **22**) was tested as a chiral oxidant in the epoxidation of chalcone [89]. Treatment of the hydroperoxide with a sub-stoichiometric amount of *n*-BuLi and reaction with chalcone at low temperature afforded enantioselectivities of up to 98.5% with formation of the (2*R*,3*S*)-epoxychalcone (Table **10**). Comparable results to those observed with the Li peroxide were obtained by using a catalytic amount of LiCl/DBU at 0ºC. In this case, activation of the enone and deprotonation the hydroperoxide occurred at the same time in what has been called *bifunctional catalysis*. The counter ion plays an important role in the mechanism of this reaction, as with *tert*-amines alone, no reaction takes place.



TADOOH **79**



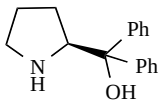
80

Fig. (22).

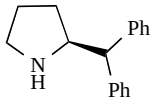
Lattanzi and coworkers have recently reported the tertiary hydroperoxide **80** (Fig. **22**) obtained from (+)-norcamphor and have tested it in the epoxidation of α,β-enones [90]. A series of different substituted (*E*)-chalcones were epoxidised under optimized conditions (*n*-BuLi/THF at -20ºC) with moderate to good yields, although the ees obtained were in the 0-54% range (Table **10**). In this case, no evidence of *template effect* in the control of the asymmetric induction has been found. Actually, when the epoxidation was carried out in the presence of [12]-crown-4 as a Li^+ chelating agent the reaction was accelerated and the epoxide isolated in high yield and with 49% ee, proving that the "naked" sterically demanding hydroperoxide anion is more reactive. Moreover, the (α*R*,β*S*)-epoxides were always preferentially obtained, regardless of the presence of different templating agents (alkaline metal ions or ammonium ion). Lattanzi also carried out the epoxidation of α-substituted naphtoquinones with hydroperoxide **80**. For Vitamin K_3 **70** under best reaction conditions, previously found for chalcones, (2*S*,3*R*)-epoxide was obtained only in 51% ee (Table **9**).

6. CHIRAL PYRROLIDINES

Chiral amines have recently been used as catalysts for many asymmetric transformations [91] of α,β-unsaturated aldehydes [92] and ketones [93]. Recently, Lattanzi and coworkers have reported the use of some amino alcohols as catalysts for the nucleophilic enantioselective epoxidation of α,β-enones [94]. With commercially available α,α-diphenyl-L-prolinol **81** (30 mol%, Fig. **23**) using TBHP as oxidant in hexane, a range of diastereoisomerically pure *trans*-(2*R*,3*S*)-epoxides were obtained starting from (*E*)-α,β-unsaturated ketones (Scheme **30**, Table **11**).



81

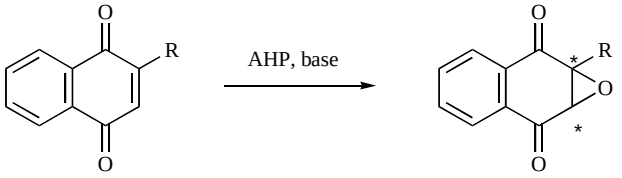


82

Fig. (23).

This protocol could be extended to substrates having an aryl or alkyl substituent either on the double bond or on the carbonyl carbon, leading to moderate to good yields and enantioselectivities of up to 80% ee. When the epoxidation was performed under identical conditions as those mentioned before with catalyst **82** (Fig. **23**) having no hydroxyl group, there was a decrease in both catalytic efficiency and asymmetric induction. This is in agreement with the mechanism proposed by the authors [94], in which the α,α-

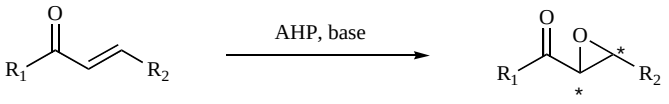
Table 9. Comparison of Taylor [87], Lattanzi [90] and Chmielewski [88] Epoxidations of Naphtoquinones

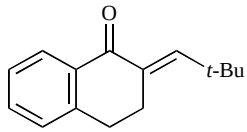
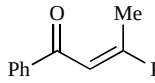


R	Method[a]	Yield (%)	ee(%)	Abs. conf.
Me	A[b]	32	78	2*R*, 3*S*
	B	80	51	2*S*, 3*R*
	C	73	47	2*R*, 3*S*
	C[c]	90	47	2*S*, 3*R*
n-Pr	A	30	69	2*S*, 3*R*
	B	51	20	2*R*, 3*S*
i-Pr	A	67	70	2*S*, 3*R*
	B	32	58	2*R*, 3*S*
Ph	A	80	82	2*S*, 3*R*
	B	78	17	2*R*, 3*S*
Et	A	79	35	2*S*, 3*R*
c-C_6H_{11}	A	65	61	2*S*, 3*R*

[a] **A**: **73** (1.2 equiv.), DBU (1 equiv.), 20ºC. See ref. 87; **B**: **80** (1.1 equiv.), *n*-BuLi (1.2 equiv.), -20ºC. See ref. 90; **C**: **78** (1 equiv.), DBU (1 equiv.), rt. See ref. 88.
[b] AHP **74** was used.
[c] AHP **77** was used.

Table 10. Comparison of Adam [86], Lattanzi [90] and Seebach [89] Epoxidations of Enones



R_1	R_2	Method[a]	Yield(%)	ee(%)	Abs. Conf.
Ph	Ph	A	99	51	(α*S*,β*R*)
		A[b]	84	9	(α*R*,β*S*)
		B	66	43	(α*R*,β*S*)
		C	80	97	(α*S*,β*R*)
Ph	*p*-$NO_2C_6H_4$	A	98	42	(α*S*,β*R*)
		B	98	45	(α*R*,β*S*)
Ph	*p*-$MeOC_6H_4$	A	96	61	(α*S*,β*R*)
		B	30	42	(α*R*,β*S*)
Ph	*p*-MeC_6H_4	A	97	57	(α*S*,β*R*)
p-BrC_6H_4	Ph	A	95	48	(α*S*,β*R*)
		B	65	38	(α*R*,β*S*)
p-MeC_6H_4	Ph	A	98	54	(α*S*,β*R*)
p-$MeOC_6H_4$	Ph	A	97	53	(α*S*,β*R*)
m-MeC_6H_4	Ph	B	67	50	(α*R*,β*S*)
Ph	Me	A	99	44	(α*S*,β*R*)
Ph	*t*-Bu	A	95	75	(α*S*,β*R*)
		A	90	90	(α*S*,β*R*)
		A[b,c]	88	72	(α*R*,β*S*)

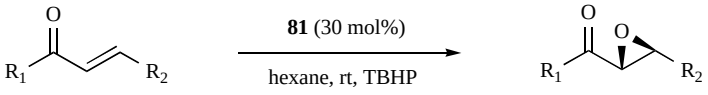
[a] **A**: **72** (1 equiv.), KOH (2-3 equiv.), -40ºC. See ref. 86; **B**: **80** (1.1 equiv.), *n*-BuLi (1.2 equiv.), -20ºC. See ref. 90; **C**: **79** (1.5 equiv.), *n*-BuLi (1.1 equiv.), -78ºC. See ref. 89.
[b] The reaction was carried out with DBU at 20ºC.
[c] (*S*)-(1-(4-chlorophenyl)ethyl) hydroperoxide was used.

diphenyl-L-prolinol acts as a bifunctional catalyst activating both the enone and the TBHP by the hydroxyl and amino groups, respectively (Scheme **31**).

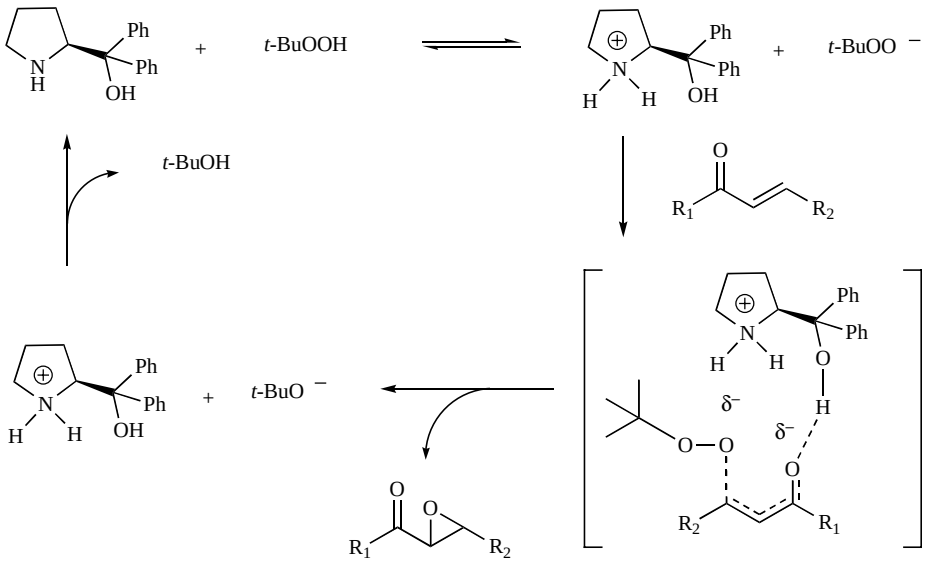
When the basic and hydroxy functionalities of the catalyst were not in the same molecular scaffold, both reactivity and asymmetric induction decreased dramatically, as demonstrated by using pyrrolidine/(-)-TADDOL as the catalytic system. Moreover, the proposed mechanism in which there are no covalent bonds involved in the activation of both reagents by the catalyst, was confirmed by the observation that polar, protic and coordinating solvents such as THF and CH_3CN, which solvate the ion pair, lowered drastically the efficiency and selectivity of the reaction, since the system becomes more flexible.

Further investigation on the stereoelectronic substitution on the phenyl rings of amino alcohol **81**, showed that the electron rich diaryl-2-pyrrolidinemethanols **83** and **84** (Fig. **24**) catalysed the asymmetric epoxidation of a variety of α,β-enones, included aliphatic or enolizable substrates apart from chalcones, with enhanced efficiency [94b-c]. With **84**, the catalyst loading could be reduced to 10% without lowering the ee (up to 90%). This fact was explained in terms of enhanced basicity of the pyrrolidinemethanol compounds supplied by the electron-donating groups on the phenyl rings.

More recently, Zhao *et al.* have investigated the use of polyether dendritic chiral pyrrolidinylmethanol derivatives **85** (Fig. **25**) in the enantioselective epoxidation of enones [95a]. Catalyst **85b** (n = 2) (30 mol%) proved to be the best one when using TBHP as oxidant and in the presence of 4 Å MS (Table **11**). It has been suggested that the mechanism is similar to that reported by Lattanzi [94], with the dendritic catalyst serving also as a bifunctional activator. Good results were obtained with a variety of electron-withdrawing substituted chalcones, although electron-donating substituted chalcones or aliphatic enones did not react. These dendritic catalysts could be easily separated from the reaction mixture by



Scheme 30.



Scheme 31. Catalytic cycle proposed by Lattanzi for the asymmetric epoxidation of α,β-enones promoted by α,α-diphenyl-L-prolinol 81.

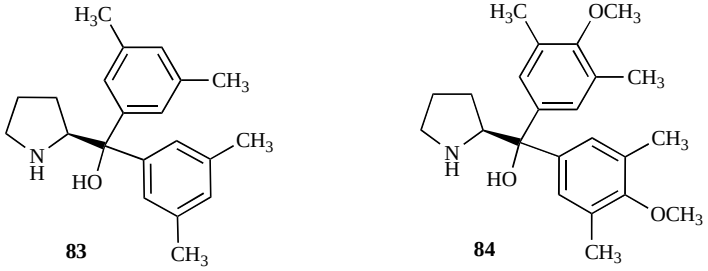


Fig. (24).

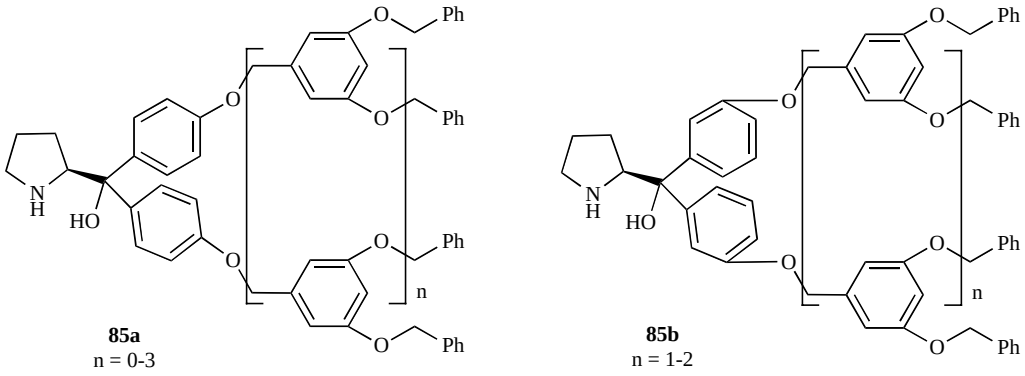


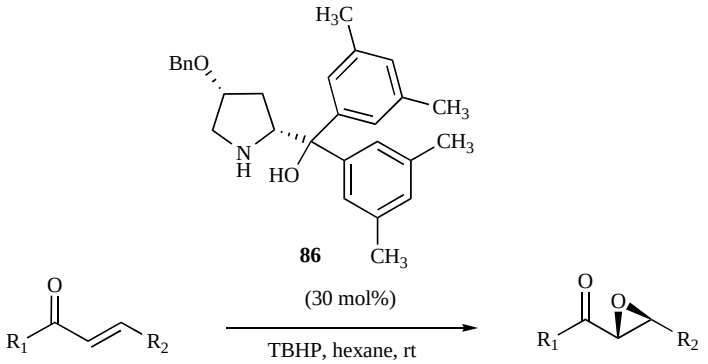
Fig. (25).

precipitation in methanol and so recycling was possible with no loss of activity and enantioselectivity.

Further catalysts for the enantioselective epoxidation of α,β-enones have been investigated by Zhao and coworkers. Very recently, they have reported the synthesis of 4-substituted-α,α-diarylprolinols and showed their high efficiency in terms of yield and enantioselectivity [95b]. It was observed that best results were obtained when the hydroxyl group at the C-4 position was protected, since free C-4 hydroxyl group may compete with the tertiary hydroxyl in the reaction progress. When using *cis*-4-substituted-bis-(3,5-dimethylphenyl)-D-prolinol **86**, moderate to good yields and enantioselectivities up to 96% ee were afforded for a number of substrates with different steric and electronic properties (Scheme **32**). Interestingly, an aliphatic enone was selectively epoxidised with moderate enantioselectivity (Table **11**).

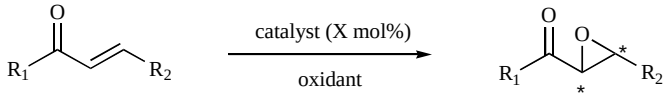
One of the main drawbacks of the organocatalytic asymmetric epoxidation of α,β-enones is the low reaction rate, which is a feature in common with other organocatalytic processes.

Although there are many examples of asymmetric epoxidation of enones by either phase transfer or polyamino acid derivatives catalysis, there is no example of the corresponding reaction with aldehydes. As chiral amines had previously proven to activate α,β-unsaturated aldehydes and ketones towards nucleophilic attack by forming iminium ions [92-93], Jørgensen and coworkers developed



Scheme 32.

Table 11. Comparison of Lattanzi [94] and Zhao [95] Epoxidations of Enones

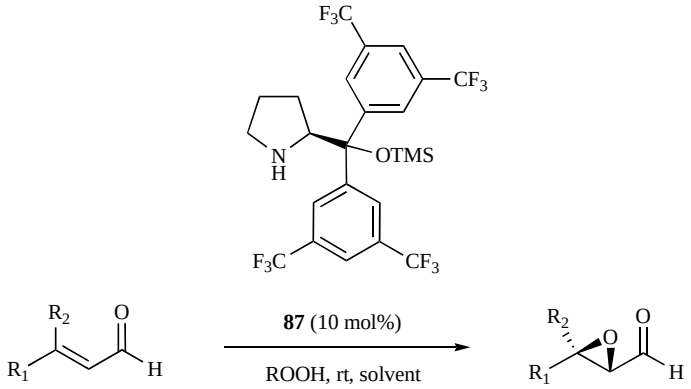


R_1	R_2	Method[a]	Yield(%)	ee(%)	Abs. Conf.
Ph	Ph	A	90	91	(α*R*,β*S*)
		A[b]	93	89	(α*R*,β*S*)
		B	84	74	(α*R*,β*S*)
		C	75	94	(α*S*,β*R*)
p-BrC_6H_4	Ph	A	81	92	(α*R*,β*S*)
p-ClC_6H_4	Ph	B	90	73	(α*R*,β*S*)
		C	80	90	(α*S*,β*R*)
Ph	*p*-$MeOC_6H_4$	A[c]	70	90	(α*R*,β*S*)
		B	trace	nd	
Ph	*p*-MeC_6H_4	A	75	90	(α*R*,β*S*)
		C	72	94	(α*S*,β*R*)
Ph	*p*-ClC_6H_4	A	81	92	(α*R*,β*S*)
		B	90	73	(α*R*,β*S*)
		C	76	96	(α*S*,β*R*)
Ph	*o*-ClC_6H_4	A[d]	70	69	(α*R*,β*S*)
		B	90	56	(α*R*,β*S*)
Furan-2-yl	Ph	A	80	91	(α*R*,β*S*)
		C	78	95	(α*S*,β*R*)
Me	Ph	A	60	87	(α*R*,β*S*)
		B	70	69	(α*R*,β*S*)
		C	49	94	(α*S*,β*R*)
Me	$CH_3(CH_2)_4$	A	70	74	(α*R*,β*S*)
		C	61	72	(α*S*,β*R*)

[a] **A**: catalyst **83** (20 mol%), TBHP (1.2 equivs.), 4ºC. See ref. 94 ; **B**: catalyst **85b** (30 mol%), TBHP (1.2 equivs.), 4A MS, rt. See ref. 95a **C**: catalyst **86** (30 mol%), TBHP (1.3 equivs.), rt. See ref. 95b.
[b] The reaction was carried out at room temperature using 10 mol% of catalyst **84**.
[c] The reaction was carried out at room temperature using 30 mol% of catalyst **83**.
[d] The reaction was carried out at room temperature using 15 mol% of catalyst **84**.

the first organocatalytic asymmetric epoxidation of α,β-unsaturated aldehydes using 2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine **87** as catalyst [96a]. Either H_2O_2, UHP or organic peroxides could be used as oxidants. Good to high yields and diastereoselectivities and high enantioselectivities (up to 98% ee) were obtained for a series of different substituted α,β-unsaturated aldehydes (Scheme **33**, Table **12**). One interesting feature of this reaction is that it proceeds in different solvents, even in environmentally benign water-alcohol solutions. In this case, partial hydrolysis-acetalization of the aldehyde functionality lowered the yield compared to the reactions performed in organic solvents [96b].

The mechanistic proposal for this reaction starts with the formation of the corresponding iminium ion by reaction of the aldehyde with the chiral amine, followed by the nucleofilic attack of peroxide



Scheme 33.

at the β-carbon atom, leading to an enamine. Then the attack of the nucleophilic enamine carbon atom to the peroxide generates the epoxide and the starting amine after hydrolysis (Scheme **34**).

While Jørgensen was developing this investigation, Córdova and coworkers were also studying the organocatalytic asymmetric epoxidation of α,β-unsaturated aldehydes. These authors tested the ability of proline and some other chiral pyrrolidine derivatives and imidazolidinones to catalyze this reaction. However, only comparable results to those obtained by Jørgensen were afforded with catalyst **88** (Fig. **26**) [97a]. When using 10 mol% of this chiral pyrrolidine with either hydrogen peroxide, solid sodium percarbonate (SPC) or TBHP, aromatic, aliphatic and even ester functionalized epoxides were obtained with good diastereoselectivities and enantioselectivities up to 98% ee (Table **12**). Also TMS-protected di(β-naphthyl)prolinol **89** (Fig. **26**) proved to be an excellent catalyst for this organocatalytic reaction [97b]. Moreover, this direct asymmetric epoxidation could be carried out in water alcohol solutions or even in water utilizing H_2O_2 as the oxidant without any apparent loss of enantioselectivity (up to 93%).

Córdova suggested that the high enantioselectivity observed for the asymmetric epoxidation reactions with catalysts **88** and **89** may be due to efficient stabilization of the configuration of the iminium ion intermediate as well as efficient shielding of the *Si*-face of the chiral iminium and enamine intermediates by the bulky aryl groups.

It is interesting to note at this point that the nucleophilic asymmetric epoxidation of α,β-enones and α,β-unsaturated aldehydes are catalysed by structurally and electronically different diaryl-2-pyrrolidinemethanols **81** and **87** respectively, as they proceed *via* two different mechanisms. Actually, Córdova attempted the catalytic asymmetric epoxidation of α,β-unsaturated ketones with different oxidants and **88** as the organocatalyst under optimized conditions, but in all cases the desired epoxide was not obtained.

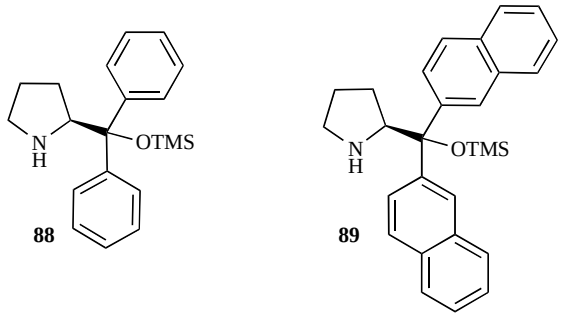
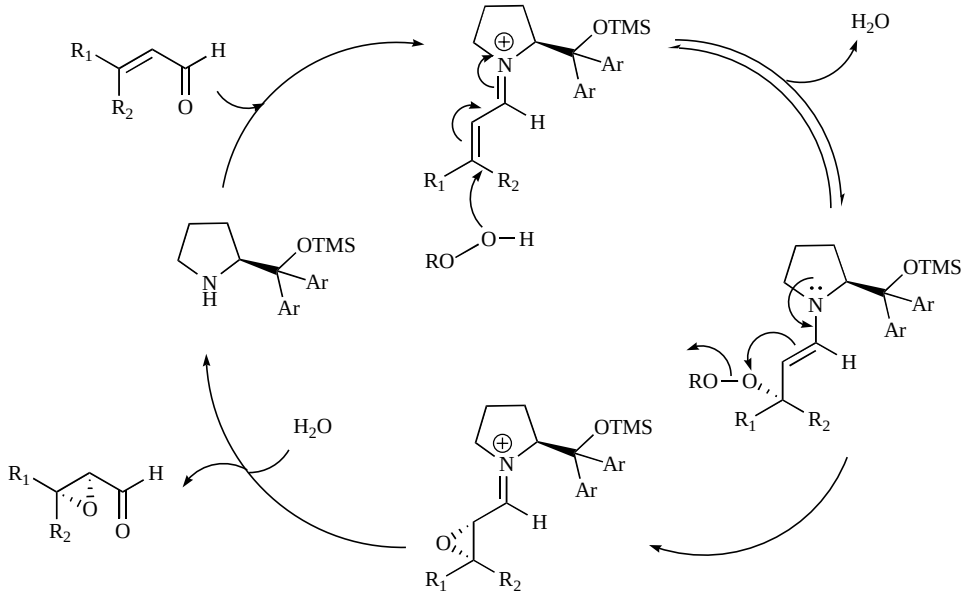


Fig. (26).

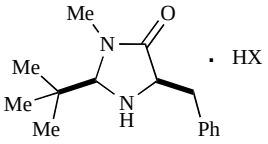
Córdova and coworkers have recently developed organocatalytic one-pot asymmetric tandem epoxidation-Wittig and asymmet-



Scheme 34. Catalytic cycle proposed by Jørgensen for the asymmetric epoxidation of α,β-unsaturated aldehydes promoted by chiral pyrrolidine **87**.

ric cascade epoxidation-Mannich processes to obtain 2,4-diepoxy aldehydes or α,β-unsaturated 4-epoxy aldehydes and 2-keto-4-amino-5-epoxides respectively, in good yields and enantioselectivities [97b].

Another interesting example of asymmetric epoxidation of α,β-unsaturated aldehydes has been reported by MacMillan and coworkers [98]. They used the chiral imidazolidinone salt **90** (Fig. **27**) as iminium activation catalyst in an epoxidation mechanism completely similar to the aforementioned one.



90

Fig. (27).

Optimal levels of reaction efficiency and enantiocontrol (up to 97 % ee) have been accomplished for a variety of enal olefins that incorporate either aryl or alkyl substituents using [(nosylimino) iodo]benzene (NsNIPh) as ambiphilic oxygen source (Table **12**). Strong Brønsted acids such as TfOH or $HClO_4$ as co-catalysts and low temperatures are required to achieve good levels of conversion and enantioselectivity. ^1H and ^{15}N NMR studies have revealed that there is a slow release of monomeric iodosobenzene from NsNIPh using a mild acid as additive. This 'internal syringe pump' effect lowers catalyst depletion derived from some catalytically inactive imidazolidinone oxidation products.

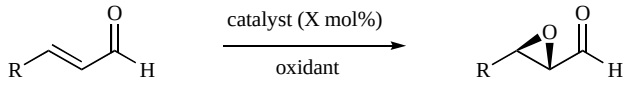
7. CHIRAL DIOXIRANES

Dioxiranes are powerful and versatile oxygen atom transfer reagents [99]. Epoxidation mediated by these oxidants is stereospecific and highly efficient towards both electron-rich and electron-deficient olefins. The general accepted mechanism for epoxidation with these reagents is shown in Scheme **35**.

Dioxiranes are frequently generated *in situ* from Oxone (potassium peroxymonosulfate) and a ketone. This formation takes place in two steps. First, nucleophilic attack of a peroxomonosulfate anion at the carbonyl carbon of the ketone affords the Criegee intermediate, which then breaks down to generate dioxirane with the loss of potassium hydrogen sulfate. The dioxirane transfers one oxygen atom to the olefin to form an epoxide while regenerating the initial ketone. Therefore, in principle, only a catalytic amount of the ketone is required, and the reaction could become a catalytic asymmetric epoxidation if the ketone employed is chiral.

Curci [100], in 1984, was the first to develop this idea, and the area has received considerable attention since then. Several groups have designed different chiral ketones as catalyst for these asymmetric epoxidations. The criteria followed in this design are the following: (1) high catalytic activity of the ketone, (2) high level of

Table 12. Comparison of Jørgensen [96], Córdova [97] and MacMillan [98] Epoxidation of α,β-Unsaturated Aldehydes



R	Method[a]	Yield(%)	dr[b]	ee(%)
Ph	A	80	93:7	96
	A[c]	43	86:14	92
	B	81	93:7	97
	C	92		92
p-ClC_6H_4	A	63	95:5	98
	B	67	83:17	94
p-BrC_6H_4	B	82	87:13	95
	C	93		93
p-$NO_2C_6H_4$	A[c]	56	83:17	90
	B	81	82:18	95
	C	89		97
CO_2R	A (R=Et)	60	90:10	96
	B (R=Et)	89	91:9	98
	C[d] (R=Me)	45		85
CH_2OBn	A	84	96:4	94
	B	61	87:13	91
i-Pr	A	75	98:2	96
n-Pr	B	>90	95:5	93
	B[e]	99	96:4	>95
	C	72		88

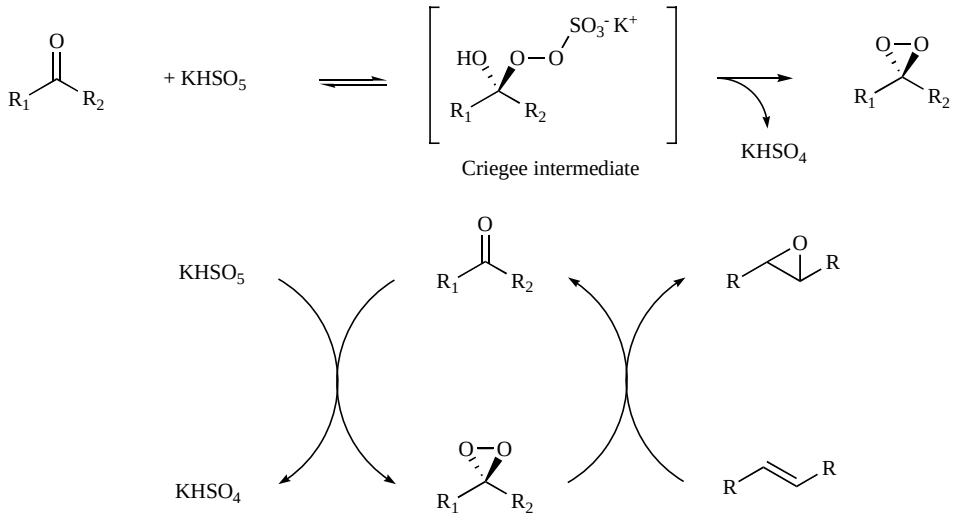
[a] **A**: catalyst **87** (10 mol%), H_2O_2 (1.3 equivs.), CH_2Cl_2, rt. See ref. 96 ; **B**: catalyst **88** (10 mol%), H_2O_2 (1.2 equivs.), $CHCl_3$, rt. See ref. 97 **C**: catalyst **90**· $HClO_4$ (20 mol%), NsNIPh (1.5 equivs.), CH_2Cl_2-AcOH, -30ºC. See ref. 98.

[b] In method **C**, all products are single diastereomers.

[c] The reaction was carried out in EtOH:H_2O (3:1).

[d] Iodosobenzene was used as oxidant.

[e] The reaction was carried out in *t*-BuOH:H_2O (1:1).



Scheme 35. Catalytic cycle for ketone catalyzed epoxidation with Oxone.

stereodifferentiation, (3) stability to Baeyer-Villiger rearrangement, (4) ease of synthesis of the ketone and (5) ease of catalyst recovery.

These ketone catalysts have been extensively applied in the asymmetric epoxidation of unfunctionalized alkenes [101] and excellent results have been achieved in terms of catalyst loading, conversion and enantioselectivity. However, highly enantioselective epoxidation of electron-deficient olefins still remains a challenging problem.

Fig. (**28**) depicts only the catalysts that have been used in the asymmetric epoxidation of electron-deficient olefins.

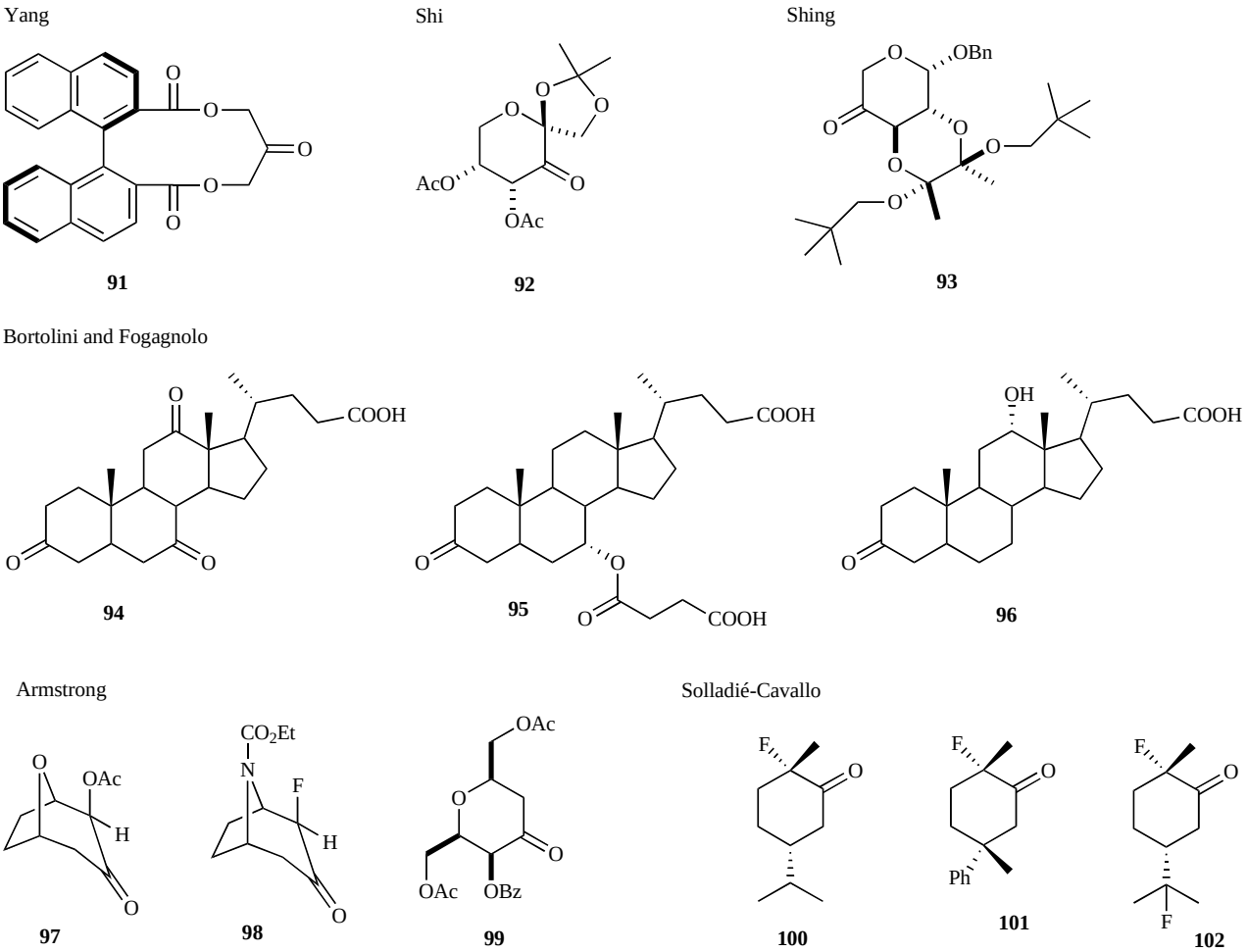
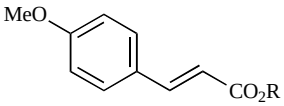
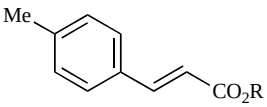
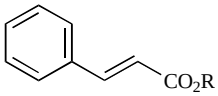
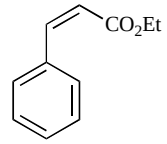
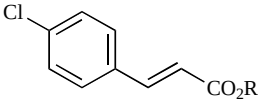
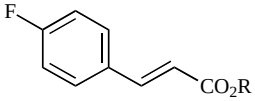
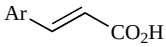
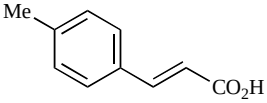
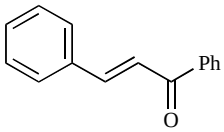
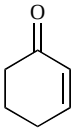


Fig. (28). Chiral ketone catalyst for the asymmetric epoxidation of electron-deficient alkenes.

Some progresses have been achieved since the results reviewed by Porter and Skidmore [1]. New catalysts have appeared, and the epoxidation of cinnamates has received particular attention. Table **13** provides a comparative study of the results attained for several substrates when using different catalysts.

Table 13. Enantioselective Epoxidation of Electron-Deficient Olefins with Ketone Catalysts

Substrate	Cat (mol%)	Yield[a]	ee (%)	Ref.
	R=Me: Yang (5)	89	78	102a
	R=Me: Shing (10)	93	62	104
	R=Me: S-C **100** (30)	82[b]	46	107a
	R=Me: S-C **101** (30)	90[b]	66	107b
	R=Me: S-C **102** (30)	74[b]	60	107b
	R= Et: Yang (5)	85	80	102d
	R=Et: Shi (20-30)	57	90	103
	R=*t*-Bu: Yang (5)	89	77	102d
	R=*t*-Bu: Shing (10)	92	81	104
	R= Me: Yang (5)	95	72	102a
	R= Et: Shi (20-30)	91	97	103
	R= Me: Yang (5)	75	74	102a
	R= Me: A **97** (20)	4[b]	84	106a
	R= Me: A **99** (10)	9	67	106c
	R= Et: Shi (20-30)	73	96	103
	R= Et: A ***ent*-98** (25)	51	64	106b
	R= *t*-Bu: Shing (10)	90	86	104
	Yang (5)	57	26	102d
	Shi (20-30)	84	44	103
	R=Me: Yang (5)	45	73	102d
	R=Et: Shi (20-30)	64	97	103
	R= Me: Yang (5)	74	72	102d
	R=Et: Shi (20-30)	77	96	103
	B & F **94** (100)	>90[c]	<75	105a
	B & F **96** (100)	94	95	105b
	B & F **95** (100)	90	-50[d]	105b
	A **ent-98** (25)	94	54	106b
	A **97** (20)	51[b]	3	106a

[a] Isolated yield;
[b] Determined by
^{1}H NMR; [c] Conversion;
[d] Opposite enantioselectivity was obtained.

Shi ketone catalyst [103] proved to be the best in terms of yield and enantioselectivity. The principal drawbacks of this kind of catalyst is that they are prone to decompose under the reaction conditions presumably *via* Baeyer-Villiger rearrangement. Thus, relatively high loading (20-30 mol%) was needed, although high pH reaction conditions offered better catalytic efficiency.

Catalyst **91** designed by Yang *et al*. [101] was also quite efficient. While Yang has only employed this catalyst and analogues for the asymmetric epoxidation of unfunctionalized olefins, it has been the group of Seki [102] at Tanabe Seikayu Company in Japan that has used catalyst **91** for the asymmetric epoxidation of cinnamates achieving the results described in Table **13**. This method has also been applied to a large-scale asymmetric epoxidation of methyl *p*-methoxycinnamate. After optimization of the reaction conditions, the chiral epoxide was obtained in 87% yield and 78% ee. The chiral ketone can be recovered in 88% yield and the ee of the epoxide was raised to >99% by recrystallization. This chiral epoxide is an intermediate in the synthesis of Diltiazem hydrochloride (Fig. **29**), a drug for the treatment of angina and hypertension.

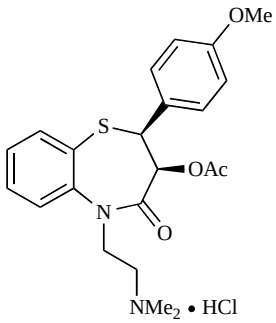


Fig. (29).

Armstrong and coworkers [106] developed several catalysts (Fig. **28**) that have demonstrated to be quite stable under the reaction conditions, but the enantioselectivity achieved is only moderate. The stability of fluorotropinone **98** allowed the development of the first supported and recyclable chiral ketone catalyst [106c]. These authors have also reported some results in substrates other than cinnamates, such as chalcone and cyclohexenone.

Keto bile acid catalyst **96** employed by Bortolini and Fogagnolo [105b] offered promising results in the asymmetric epoxidation of *p*-methylcinnamic acid. The procedure was performed using equimolar concentrations of olefin and catalyst even when they mentioned that this kind of bile acids could be used in catalytic amounts [105a].

The stereochemical outcome of the reaction can be predicted. The two extreme transition state geometries for the epoxidation of alkenes with dioxiranes are spiro and planar (Fig. **30**) and it has been shown that the transformation proceeds mainly *via* a spiro transition state [108]. According to this, a prediction can be made depending on the catalyst structure.

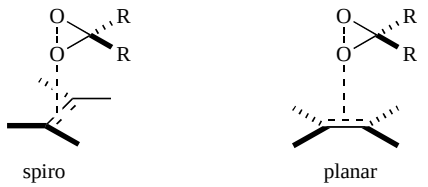


Fig. (30). The spiro and planar transition states for the dioxirane epoxidation of olefins.

7. CONCLUSIONS

This review has summarized the latest developments in the asymmetric epoxidation of electron deficient olefins since the review by Porter and Skidmore on the subject. The resulting chiral epoxides obtained by these methods are important building blocks for the synthesis of enantiomerically pure biologically active compounds. In the field of chiral ligand-metal peroxide systems, many improvements have been achieved by several research groups, mainly by varying the ligand design. In poliamino acid catalysed epoxidations, much progress has been aimed to reduce the catalyst loading and increase recovery and recycling, especially by combination of the poliamino acids with PTC.

Recently, the design of new phase transfer catalysts and the use of other oxidants has improved the PTC methodology applied to the epoxidation of electron-deficient olefins. In organocatalysis by chiral dioxiranes the range of substrates epoxidised is still limited to a small number of examples.

Despite the large number of reports and good results obtained in this field in a relatively short period of time, still many challenges remain. It seems likely that many new advances will appear in this area over the coming years, especially in the field of organocatalysis using chiral pyrrolidines, whose major drawbacks are still low reaction rate and high catalyst loading.

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