NEW SYSTEMS FOR HETEROGENEOUS CATALYTIC EPOXIDATION

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ABSTRACT

Epoxides are very useful key intermediates in the construction of synthetically challenging molecules. Owing to their strategic importance in organic synthesis, novel polymer-supported iminium salts were investigated for the catalytic oxidation of unfunctionalised alkenes. A solid-phase methodology was initiated and then developed for the evaluation of several heterogeneous catalysts.

In an initial approach, immobilised iminium salts were prepared by condensation of 2-(bromoethyl)benzaldehyde with commercially available aminomethyl resins. These materials were shown to be able to successfully catalyse the epoxidation of 1-phenylcyclohexene. The epoxidation reactions were performed in a triphasic system using Oxone® as the oxidising agent and 25 mol% of the catalyst. For all the resin type employed, namely NovaSyn TG, NovaGel, ArgoGel or PEGA, complete conversion of the alkenes to their respective epoxides was obtained. Some polymeric catalysts were also assayed in the epoxidation of several olefinic substrates, but disappointing results were obtained. The synthesis of a chiral resin-bound iminium salt derived from (L)-tyrosinol was achieved, unfortunately it was revealed to be inactive as a catalyst. The alternative oxygen source, tetraphenylphosphonium monoperoxysulfate, was investigated in the epoxidation of 1-phenylcyclohexene mediated by solid-supported iminium salts. Unlike for the homogeneous catalyst, these oxidations did not afford satisfying results with any of the polymer-bound salts assayed.

In an alternative approach, the heterogenisation of the iminium catalysts was envisaged *via* reactions of a polymer-bound (bromoethyl)benzaldehyde precursor with diverse chiral amines. For this purpose, a five step synthesis starting from the bromomethylphenyl acetic acid was implemented. This provided a resin-anchored substituted isochroman, which is yet to be further derivatised to the corresponding benzaldehyde and condensed with an amine.

To conclude, this work reports the first immobilisation of iminium bromide salts on various resin structures, and their efficient application as epoxidation catalysts for 1-phenylcyclohexene. Nevertheless, further optimisation is needed for this newly developed system to represent an attractive strategy for asymmetric catalytic epoxidations.

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ABBREVIATIONS

Å	Angström
acac	Acetylacetonate
AG	ArgoGel
AIBN	2,2'-azobisisobutyronitrile
aq.	Aqueous
atm	Atmosphere
BINAP	Bis(diphenylphosphino)-binaphthyl
BOC	*Tert*-butyloxycarbonyl
b.p.	Boiling point
°C	Degrees Celsius
ca.	Circa
Cbz	Carbobenzyloxy
conc	Concentrated
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DME	Dimethoxyethane
DMF	*Dimethylformamide*
DIPEA	Diisopropylethylamine
DVB	Divinylbenzene
EBHP	Ethylbenzene hydroperoxide
EDTA	Ethylenediaminetetraacetic acid
ee	Enantiomeric excess
eq	Equivalent
Et_3N	Triethylamine
EtOH	Ethanol
$Eu(hfc)_3$	Europium tris[3-heptafluoropropylhydroxymethylene) -camphorate]

FT-IR	Fourier Transformation-Infra Red spectroscopy
GC/MS	Gas chromatography/Mass spectroscopy
h	Hour
HCl	Hydrochloric acid, Hydrogen chloride
He	Helium
H_2O_2	Hydrogen hydroperoxide
HPLC	High pressure liquid chromatography
Im	Imidazole
J	Coupling constant
M	Molar
MAS	Magic angle spinning
*m*CPBA	*meta*-Chloroperbenzoic acid
MeCN	Acetonitrile
MEM	Methoxyethoxymethyl
MHz	Mega Hertz
m.p.	Melting point
M.S.	Molecular sieve
m/z	Mass to charge ratio
NCA	*N*-carboxy anhydride
NMO	4-methyl morpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
PBI	Polybenzimidazole
PCMS	Poly(chloromethylstyrene)
pd	Pentane-2,4-dione
PD	Poly(dihydroterephthalaldehyde ethylenediamine)
PEG	Polyethylene glycol
PEG-PS	Polyethylene glycol-polystyrene
PG	Protecting group
PGMA	Poly(glycidylmethacrylate)

Ph	Phenyl
PhIO	Iodosylbenzene
PM	Polymethacrylate
PPNO	4-phenyl-pyridine *N*-oxide
PS	Polystyrene
psi	Pounds per square inch
*p*TsOH	*para*-toluene sulfonic acid
quat	Quaternary
r.t.	Room temperature
s.m.	Starting material
TBAB	Tetra-*n*-butyl ammonium bromide
^{t}BHP	*tert*-Butyl hydroperoxide
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane
TIPS	Triisopropylsilane
TLC	Thin layer chromatography
Tol	Tolyl
TPPP	Tetraphenyl phosphonium monoperoxysulfate
Tr	Trityl
v/v	Volume per volume
w/w	weight per weight
	Polystyrene backbone
	Non-polystyrene backbone
	NovaSyn TG resin
	NovaGel resin
	ArgoGel resin
	PEGA resin

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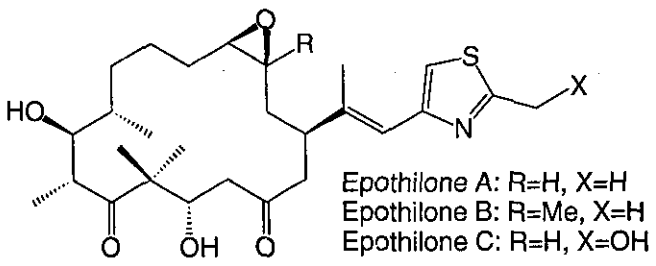
Note: The numbering system of the Figures, Schemes and Tables are independant in each chapter. In addition, the numbering of the compounds in chapter 1 and 2 are not related (unless specified).

Chapter 1: INTRODUCTION

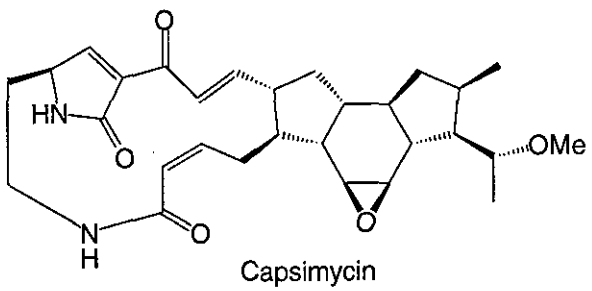
1.1) Scope of the study

1.1.1) Introduction to epoxides

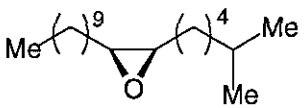
Epoxides, also known as oxiranes, are widely found in numerous natural products: the anti-cancer epothilones,[1] the antibiotic capsimycin,[2] and the insect pheromone disparlure[3] (Fig. 1) are just a few examples of the diverse variety of chiral molecules where epoxide moiety plays a key role in the biological activity.



Epothilone A: R=H, X=H
Epothilone B: R=Me, X=H
Epothilone C: R=H, X=OH



Capsimycin



Disparlure

Figure 1: Examples of natural products containing chiral epoxides

Furthermore, epoxides are versatile building blocks for the construction of challenging molecules.[4] Their usefulness as key intermediates can be explained by their high reactivity associated with the strain of the three membered ring. Driven by the relief of that strain, epoxides are prone to ring-opening, which is achieved by attack of a wide range of nucleophiles. This reaction is one of the most well-studied in organic chemistry.[5] Therefore, the synthesis of epoxides, particularly asymmetric synthesis, has been attracting extensive interest, not only by means of traditional homogeneous processes, but increasingly by heterogeneous methods.[6-9] Indeed, several assets of solid phase organic synthesis have motivated the adaptation of solution phase reactions to solid phase chemistry.

1.1.2) Introduction to solid phase synthesis

Following the success of Merrifield's approach to the synthesis of polypeptides in 1963,[10] the use of insoluble polymeric supports has attracted considerable attention.[11] However, it is only in the last few years that the field of solid phase synthesis for small organic molecules has received much greater interest.[12] Indeed, conducting polymer-supported organic reactions imparts several valuable avantages which can be outlined as follows:[13-23]

- Polymer-supported products can be isolated and purified by simple filtration and washing, thus easily removing soluble by-products and excess reagents.
- Reactions which exhibit poor chemoselectivity can often be directed by attachment of the appropriate component to the solid support to give only the desired product.
- Resin-bound toxic or hazardous compounds can be handled safely without risk to users or the environment.

Nevertheless, some inconveniences arise from the utilisation of this technology:

- Reaction monitoring can cause difficulties compared to solution phase organic synthesis: solid phase reactions are generally more difficult to monitor, for

example, because the techniques of following the reaction by TLC, GC or HPLC are not appropriate.

- Characterisation of the reaction products is not simple: due to the interference of the polymer backbone and the low loading commonly used, conventional IR and NMR spectra are difficult to interpret and are often ambiguous.[24] New techniques of analysis using expensive equipments are necessary (eg. MAS-NMR, single bead FT-IR microspectroscopy)

However, owing to the many advantages offered by solid phase synthesis, numerous asymmetric syntheses employing solid supports have been reported.[25-34] The attractive features of polymer-supported asymmetric reactions can be summarised as follows:[35]

- Isolation of the chiral product free of the chiral catalyst or auxiliary is simplified.
- The chiral catalyst or auxiliary can be recovered easily for possible reuse.
- The use of expensive polymer-supported chiral catalysts may become practical if the polymer-supported species can be efficiently recycled.
- Flow systems can be considered to carry out automated asymmetric syntheses using polymer-supported chiral reagents and catalysts.
- Since crosslinked polymers are insoluble and non-volatile, polymer-supported reagents are odourless and non-toxic.

The asymmetric epoxidation of alkenes is central to many of the recent developments in the stereoselective synthesis of chiral molecules, and attention in several laboratories has therefore focused on a number of heterogeneous asymmetric alkene epoxidation catalysts.[6-9]

As the field of asymmetric reactions on solid supports has met an exponential growth in the last decade, the following introduction does not cover all possible types of heterogeneous supports used in epoxidations. Since the research work discussed in chapter two involves only the utilisation of insoluble polymeric resins, neither inorganic supports (eg. silica, surface modified mesoporous molecular sieve such as MCM-41), nor

soluble polymer supports (eg. polyethylene glycol, etc.) are described. Only insoluble polymer-supported epoxidation reactions are reviewed in this introduction.

1.2) Polymer-supported epoxidations using metals

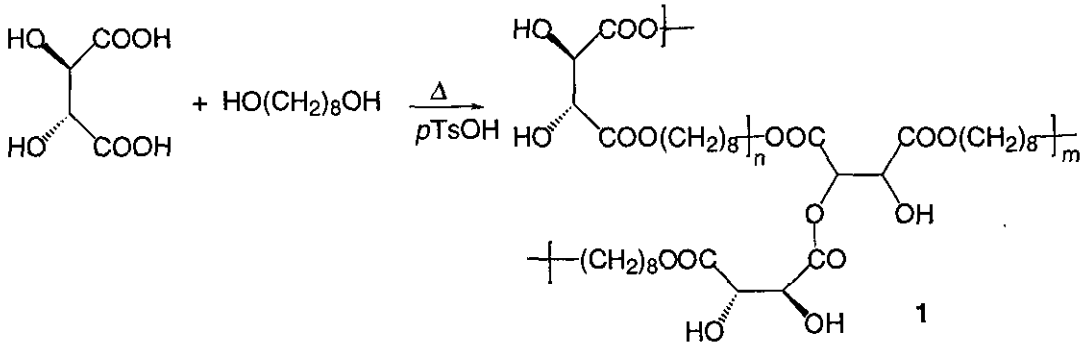
The field of metal complexes as catalysts in organic synthesis is very active, and applications of these complexes in heterogeneous catalysis have been widely investigated.[6] Due to the attractiveness of catalyst recycling, heterogeneous catalysis has been considered as one way of addressing the challenge of finding an efficient metal-catalysed system which can promote oxidations of a variety of substrates without producing harmful by-products. Therefore, in order to immobilise metal complexes for oxidations, crosslinked organic polymer supports have been functionalised to form polymeric ligands which prefigure metal catalysts with high activity combined with good selectivity and reproducibility. The metal-catalysed epoxidations can be divided into two sections: asymmetric and achiral reactions.

1.2.1) Polymer-supported Sharpless epoxidation

Sharpless' titanium tartrate ester-based asymmetric alkene epoxidation is a very important organic synthetic method in academic laboratories. It is therefore not surprising that the polymer-supported analogues of the Sharpless system have been keenly investigated.

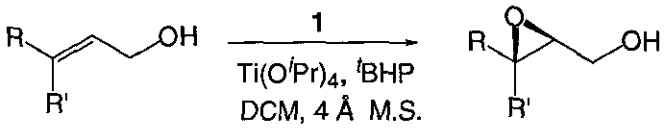
It was Farrall who first immobilised a single tartrate ester moiety on a 1% crosslinked polystyrene resin and utilised it as a catalyst in the epoxidation of geraniol.[36] The epoxide was produced in 60-70% yield and with 50-60% ee. A few years later, Sherrington investigated the heterogenisation of the Sharpless epoxidation. The study began with the synthesis of linear soluble poly(tartrate ester) ligands, which were used as homogeneous catalysts with titanium tetraisopropoxide and *tert*-butyl hydroperoxide (^{t}BHP) as the oxidant.[37] These attempts led to the synthesis of branched/crosslinked poly(tartrate ester)s as depicted in Scheme 1.[38] It is noteworthy that branched polymers

have a degree of branching from 3 to 15%*, and are generally soluble in DMSO but insoluble under the epoxidation conditions, while crosslinked polymers have a degree of branching > 15% and are insoluble in any hot solvents.



Scheme 1: Synthesis of heterogeneous poly(tartrate ester) ligands

Epoxidation of (*E*)-hex-2-en-1-ol (**2**) under the conditions shown in Scheme 2 using both branched and crosslinked polymeric catalysts gave lower yields (32-72%) and enantioselectivities (26-87% ee) than the homogeneous counterpart (85% yield, 94% ee).



2 : R = C_3H_7, R' = H
3 : R = Ph, R' = H
4 : R = C_8H_{17}, R' = H
5 : R = $(CH_2)_2CH(Me)_2$, R' = Me

Scheme 2: Epoxidation conditions for (*E*)-allylic alcohols

Substrates such as (*E*)-cinnamyl alcohol (**3**), (*E*)-undecen-1-ol (**4**) and (*E*)-geraniol (**5**) were also tested for epoxidation with the poly(tartrate ester)s, but the isolated yields and the asymmetric induction were disappointing. The crosslinked polymeric ligand provided poorer enantiomeric excesses (ees) (14-40% ee) than the branched equivalent (60-90% ee) for these alkenes. Hence, the enantioselectivity of the epoxidation is dependent on the level of branching/crosslinking. With the (*Z*)-allylic alcohols, the reaction required at least a

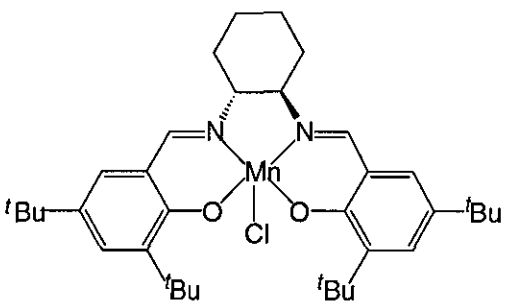
* The degree of branching/crosslinking was calculated by integration from ^{1}H NMR

week to achieve significant conversion (*ca.* 50%), and the enantioselectivities were moderate (38-86% ee) under the same conditions as used for (*E*)-allylic alcohols.[39] The epoxidation of homoallylic alcohols also revealed a lack of substrate reactivity.[40] Indeed, some substrates were reacted from 1 to 21 days, and provided low yields of epoxides (20-52%). Additionally, the enantioselectivity was markedly lower (38-60% ee) than with allylic alcohols. The extension of the carbon chain in the substrate by one methylene group may involve a more flexible titanium complex, thus resulting in poorer asymmetric induction.[40] Nevertheless, the rigid environment of the polymer-supported ligand seemed to some extent to compensate, allowing an improvement over homogeneous tartrate esters (6-48% ee).

Since this work, relatively few attempts have been made to prepare polymer-bound catalysts for Sharpless epoxidation. This can probably be explained by the poor results of the heterogeneous approach, as well as the relatively low cost of soluble tartaric acid diesters and the excellent results of the well-developed homogeneous system. This led to the investigation of other immobilised systems, particularly the Jacobsen-Katsuki epoxidation.

1.2.2) Polymer-supported epoxidation using Jacobsen's catalyst

An important methodology for enantioselective alkene epoxidation has been developed largely through the work of both Jacobsen and Katsuki using chiral (salen) catalysts, such as **6**.[41,42]



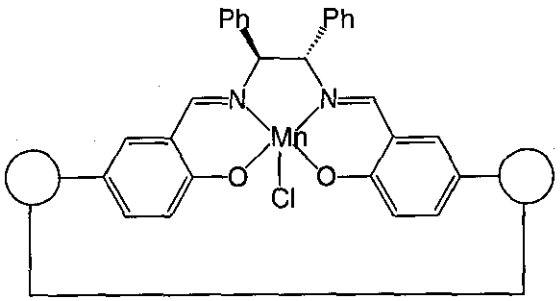
6

Although this epoxidation system is widely used, the soluble catalysts are relatively costly and rather unstable in contact with oxidants, thus preventing recycling. With the

heterogeneous approach, the work-up of the reactions would be facilitated while the recovery and reuse of the expensive chiral catalysts would be the two invaluable assets. The advantages offered by solid phase chemistry, especially polymer-supported chiral auxiliaries/catalysts has encouraged numerous attempts of the immobilisation of chiral manganese (salen) catalysts.[43-52] To synthesise these polymer-anchored salen catalysts, two general methods exist and have been evaluated. The first route involves the synthesis of monomers bearing chiral catalyst moieties, followed by their co-polymerisation with suitable crosslinking monomers. The second approach uses pre-formed resin matrices, which undergo chemical modifications of the accessible functional groups to produce covalent attachment of the complex. Both methods are discussed below.

1.2.2.1) Polymer-supported Jacobsen's catalyst: First strategy

The first strategy for heterogenisation of the chiral manganese (salen) complexes consisted of co-polymerising the monomer containing the catalyst species with a crosslinking monomer. This route was applied by Dhal for the preparation of the manganese catalysts **7** and **8** using polydimethacrylate as the crosslinking monomer.[43]



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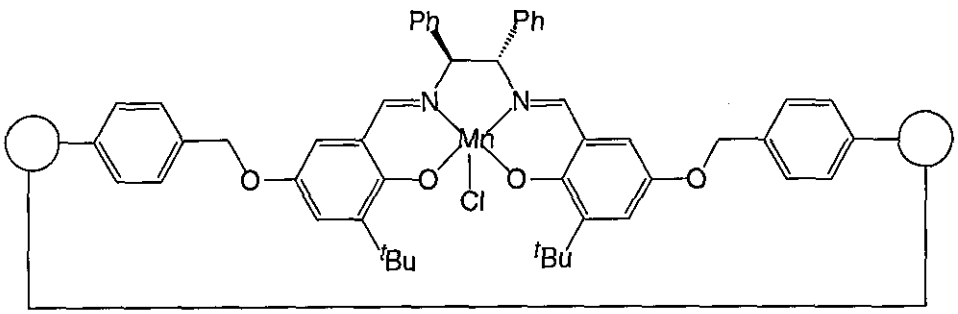

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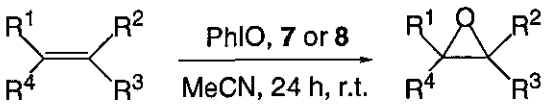
Epoxidations of several olefins were performed using the polymeric catalysts **7** and **8** under conditions similar to the corresponding homogeneous system (Scheme 3).

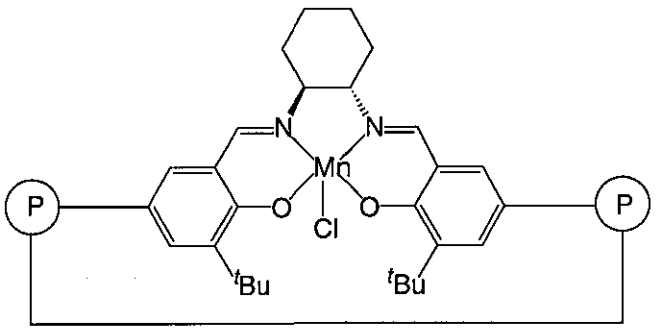


Alkenes used: styrene, (*E*)-stilbene, indene, 1,2-dihydronaphthalene

Scheme 3: Epoxidation conditions for various alkenes using Dhal's catalysts

Conversions of alkenes to epoxides were satisfactory (55-76%) and comparable to the results with soluble catalysts; but low enantiomeric excesses (2-30%) were obtained with both insoluble resins.

Other epoxidation attempts were made by Salvadori with a similar polymerised salen system.[44] The chiral manganese(III) salen complex was incorporated in a polystyrene/DVB (divinylbenzene) co-polymer and furnished the catalysts **9** and **10**.



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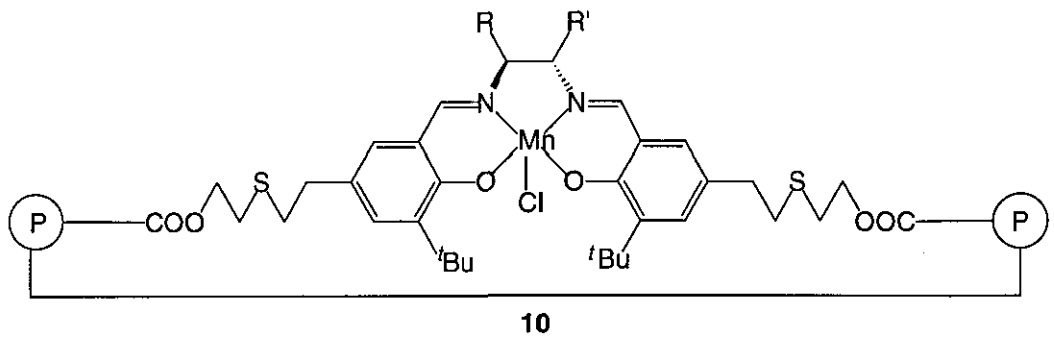
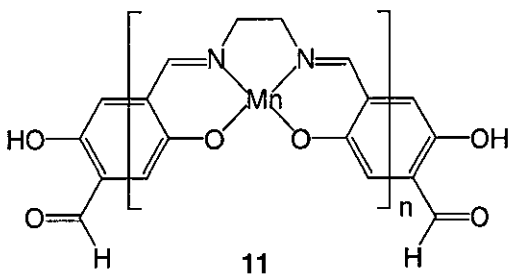


10

R and R' = $-(CH_2)_4-$
R = R' = Ph

Subsequently, the oxidations of styrene, (*Z*)-β-methylstyrene and indene were effected with *m*CPBA/NMO as oxidising agents in acetonitrile. This solvent appeared, among several solvents tested, to give the best combination in terms of reactivity and insolubility of the polymeric catalysts. The epoxidations were rapid (0.25-1 hour) and, importantly, the catalyst could be recovered cleanly. The chemoselectivity and activity of the heterogeneous complexes remained comparable to the soluble system, however, enantioselectivities were low to moderate (10-60% ee). The efficiency of the catalyst **10** containing a spacing group between the polymeric chain and the acive metal site was compared to the "non-spaced" catalyst **9**. It was found that **10** always provided higher enantioselectivities than **9**. This meant that when the catalytic centre was further from the polymeric chain, the influence of the surrounding polymeric chain was remarkably reduced.

Recently there has been a growing interest in the synthesis and characterisation of polynuclear manganese complexes.[45] To overcome the limitation of a low number of active metal sites in polymer-supported systems, Krishnan and Vancheesan prepared polynuclear manganese Schiff base complexes having a large number of active metal centres.[46] The Schiff base polymer, poly(dihydroxyterephthalaldehyde ethylenediamine) (PD) was synthesised from 2,5-dihydroxyterephthalaldehyde through condensation polymerisation with ethylenediamine in DMF. The schiff base PD was then used as a polynucleating ligand to form the polynuclear manganese(II) complex **11**, and the manganese(III) complex **12**.



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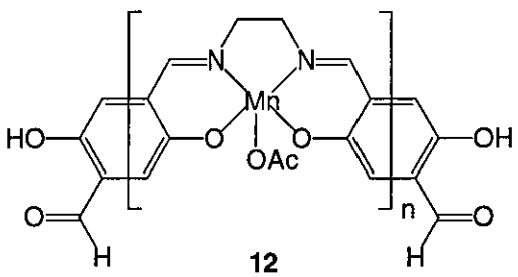


12

Epoxidations of several alkenes using these polymeric catalysts and 30% aqueous hydrogen peroxide showed good selectivity (*ca.* 90%), but resulted in low conversions (11-57%), due to the catalytic decomposition of hydrogen peroxide in a competitive

parallel reaction (Fig. 2). The alkene substrate and hydrogen peroxide compete to react with the oxomanganese intermediate. Furthermore, manganese complexes in the presence of a base are prone to catalyse the dismutation of hydrogen peroxide (Fig. 2). These factors were not favourable for the development of an efficient epoxidation system using these catalysts.

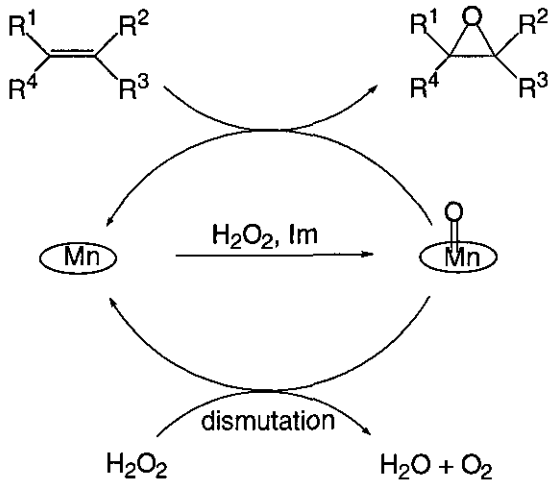


Figure 2: H_2O_2 involved in competitive reactions

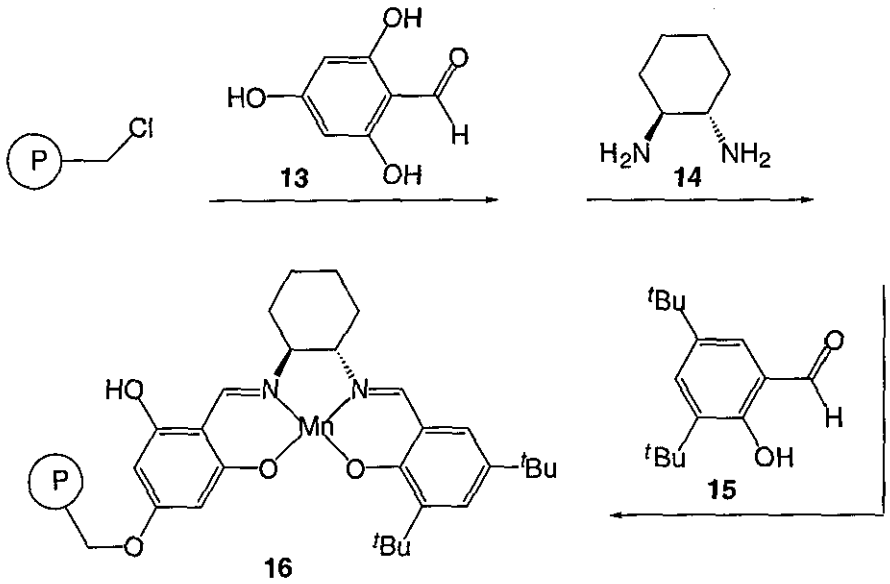
The studies mentioned so far have described the incorporation of a homogeneous salen ligand into a matrix by polymerisation of monomers containing a pre-formed complex. The problem of this strategy is the formation of inaccessible catalytic sites within the polymer, due to the rigidity of the complex. To overcome this inconvenience, a different route was examined to prepare and assess the polymer-bound Jacobsen's catalyst.

1.2.2.2) Polymer-supported Jacobsen's catalyst: Second strategy

The second pathway to the chiral manganese(III) salen catalyst is based upon the covalent attachment of the salen complexes to readily available polymers.

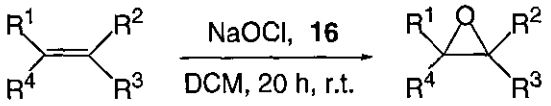
In their efforts to improve the enantioselectivity of asymmetric reactions using heterogeneous metal catalysts, Angelinos and Laibinis decided to tether the salen complex by chemical modifications of the surface of a polymer resin particle.[47] The first building block, 2,4,6-trihydroxybenzaldehyde (**13**), was attached covalently to pendant

chloromethyl groups on the surface of a commercially available polystyrene/DVB co-polymer. The successive organic building blocks, *trans*-1,2-diaminocyclohexane (**14**) and 3,5-di-*tert*-butylsalicylaldehyde (**15**), were added in a stepwise manner to produce the desired manganese complex immobilised on the resin (**16**) (Scheme 4).



Scheme 4: Pendant Jacobsen's catalyst by Laibinis

Upon epoxidation of alkenes using sodium hypochlorite (NaOCl), the enantioselectivities observed with these heterogeneous catalysts (9-46% ee) were lower than those provided by the homogeneous system (70-80% ee).



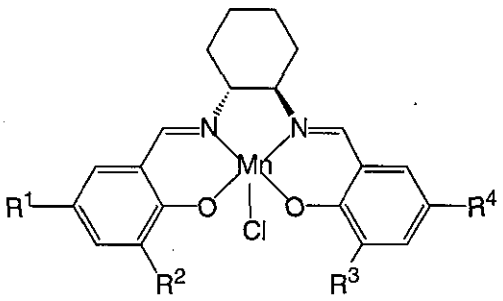
Alkenes used: styrene, (*Z*)-β-methylstyrene
1,2-dihydronaphthalene

Scheme 5: Epoxidation conditions using Laibinis catalysts

These results were nevertheless better than those of the catalysts **7**, **8**, **9** and **10** that used two attachment points of the ligand to the support.[43,44] However, these polymeric complexes exhibited a large decrease of enantioselectivity upon recycling and a

degradation of the manganese catalyst due to the oxidation of the ligand. For these reasons this supported system was not suitable for asymmetric epoxidations.

At the same time, Sherrington was also working on the immobilisation of Jacobsen's catalysts.[48] Polystyrene and polymethacrylate-based, porous and non-porous resin manganese catalysts were synthesised (Table 1) and tested in asymmetric epoxidation of 1-phenylcyclohexene, 1,2-dihydronaphthalene and indene using *m*CPBA/NMO as the oxidising system.



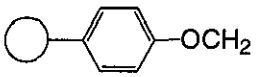
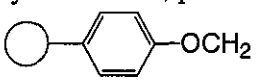
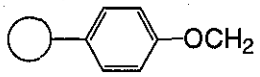
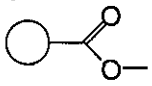
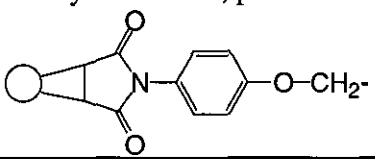
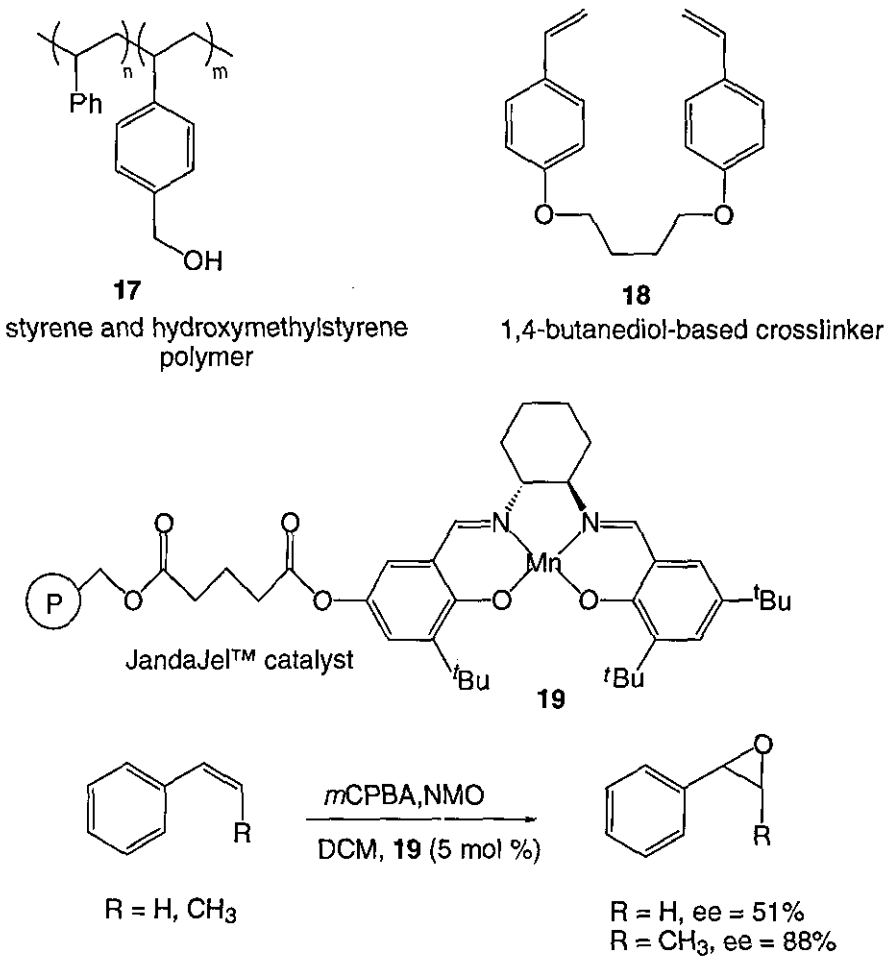
R1	R2	R3	R4
styrene-based, gel 	tBu	H	tBu
styrene-based, porous 	tBu	tBu	tBu
methacrylate-based, porous 	tBu	tBu	tBu
H	methacrylate-based, porous 	tBu	tBu
styrene-based, porous 	tBu	tBu	tBu

Table 1: Sherrington's supported manganese salen catalysts

While the soluble analogues furnished an average of 90% yield and 92% ee, the polymeric catalysts yielded 30-61% of epoxides and 6-60% ee. The reduced activities of the supported entities and also the decrease in epoxide enantioselectivity were disappointing. Furthermore, the catalysts could not be recycled without significant loss of activity.

Recently, Janda also published the results of his investigations into asymmetric epoxidation using a heterogeneous Jacobsen's catalyst (**19**).[49] The chiral manganese(III) salen complex was anchored to JandaJel™ resin, which is prepared by co-polymerisation of **17** with the crosslinking agent **18** (Scheme 6).

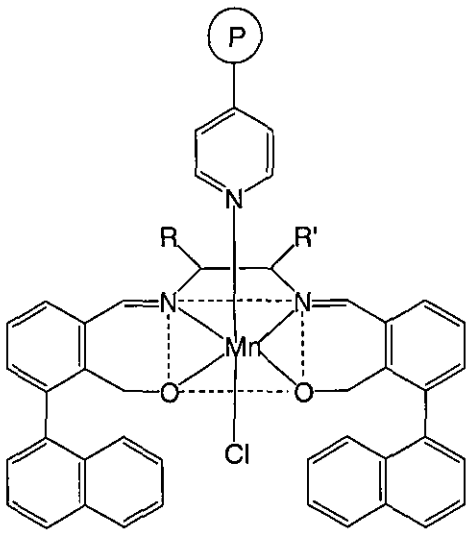


Scheme 6: Alkene epoxidation with JandaJel™ Jacobsen's catalyst

Styrene, (*Z*)-β-methylstyrene and 1,2-dihydronaphthalene were epoxidised using **19** and *m*CPBA/NMO as the oxidant system. The reactions were complete in 15 minutes with JandaJel™ resin, while the polystyrene/DVB resin-bound catalyst required one hour to

proceed to completion. The enantioselectivity was satisfactory, since the epoxides were produced with ees nearly equivalent to those achieved using the commercial soluble Jacobsen's catalyst. Moreover, the JandaJel™ immobilised complex could be recycled three times before any significant decrease in enantioselectivity was observed, whereas the polystyrene catalyst lost activity with each use. This encouraging result requires further study to improve recycling and asymmetric induction.

In the above examples, the ligands were tethered to the polymer support by attachment to the benzene ring of the salen derivative. As an alternative to this approach, a pre-formed manganese complex was axially coordinated to a pyridine-containing polystyrene resin, giving the polymer **20**.[50]

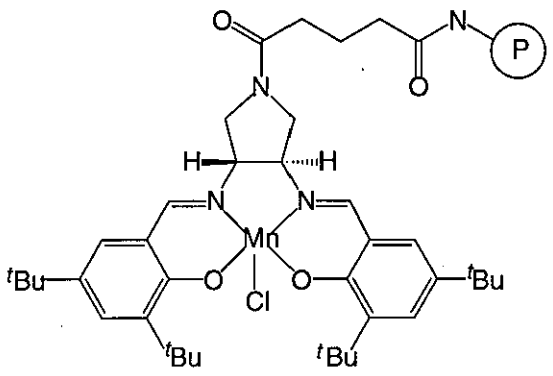


20

a) R = R' = -$(CH_2)_4$-
b) R = H , R' = CH_3
c) R = R' = C_6H_5

Kureshi assessed these pyridine-linked catalysts in the enantioselective epoxidation of various substituted styrenes with iodosylbenzene, however levels of conversion to epoxides and ees were low, at 25-74% and 16-46% respectively.

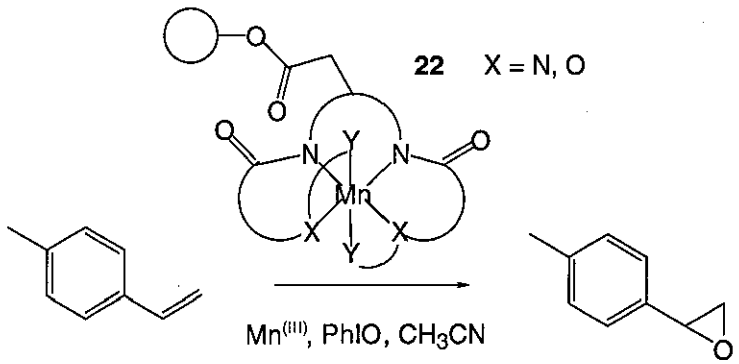
Recently, Song reported the attachment of the catalyst through a pyrrolidine-derived linker.[51] The manganese complex **21** functioned as an effective supported epoxidation catalyst when immobilised on NovaSyn® TG amino resin LL. This resin is constituted of polystyrene grafted with polyethylene glycol (see section 2.1.1.3).



21

In the presence of **21**, dimethylchromene was converted to its epoxide in 85% yield with 92% ee using *m*CPBA/NMO as the oxidant system. In general, the activity and enantioselectivity were slightly lower than with the homogeneous analogues. The reactions with *m*CPBA/NMO provided faster reactions and higher enantioselectivities than those with sodium hypochlorite. Unfortunately, the catalyst **21** underwent partial decomposition under the reaction conditions.

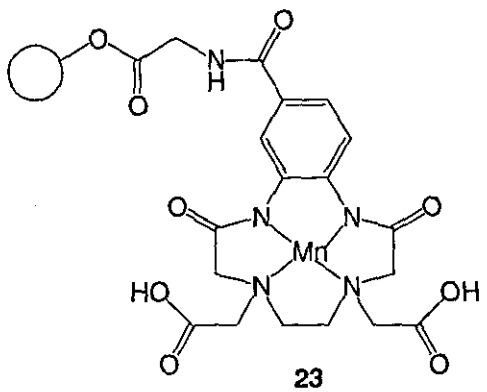
In an exploration of polymer-supported metal catalysts for oxygen atom transfer, Sames and Havranek applied a screening methodology to investigate manganese complex catalysts.[52] The solid supports, either TentaGel® or macroporous polystyrene, were attached to the complex through the diamine functionality (**22** in Scheme 7).



Scheme 7: Resin-bound diamide ligands for Mn(III)-catalysed epoxidations

A stepwise evolutionary process combining design and parallel screening of solid-bound manganese complexes was developed. The study was composed of successive generations

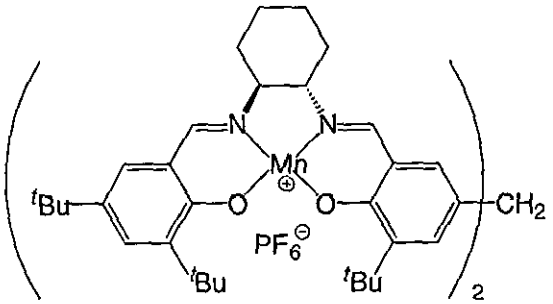
of ligand libraries, which were all screened for epoxidation using iodosylbenzene as the oxidant. In this work the oxidation was not asymmetric and, in this sense cannot be compared to the previous examples. Nevertheless, this method allowed the evaluation and improvement of essential properties of the catalyst, namely selectivity, turnover rates and catalyst stability, which led to the third generation of ligands. This third screening provided the cyclic catalyst **23** which yielded 98% of epoxide in two minutes.



23

1.2.2.3) Polymer-supported Jacobsen's catalyst: Third strategy

Another potentially attractive strategy consists of trapping the manganese (salen) catalyst in a suitable polymer matrix. Vankelecom described the occlusion of Jacobsen's catalyst in an elastomeric polydimethylsiloxane membrane.[53] The activity and enantioselectivity of this system for the epoxidation of various alkenes was similar to that of the homogeneous analogue. In addition, the catalyst membrane could be regenerated by simple washing and reused twice without loss of activity or selectivity. The asset of this new method of heterogenisation lies in the preservation of the structure of the chiral manganese complex without any additional chemical bonding, the complex being maintained in the elastomer network only by steric restrictions. Unfortunately, there was a problem of manganese leaching upon recycling. In their efforts to improve the retention of the catalyst in the membrane, the same group also synthesised **24**, a dimeric form of the catalyst linked at the *para* position of the benzene rings.[54]



24

It appeared that the dimer was as active and enantioselective as the homogeneous Jacobsen's catalyst with substrates such as 1-phenylcyclohex-1-ene, 1,3-cyclo-octadiene and (*E*)-β-methylstyrene. However, traces of manganese leaching were still encountered. Although the dimer proved to have a much lower degree of leaching compared to the Jacobsen's catalyst, the dimeric system was dependent on the combined effect of swelling of the membrane and the solubility in the solvent used.

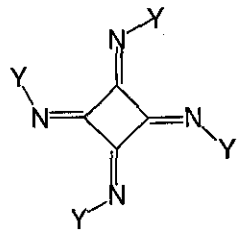
Due to the instability of the Jacobsen's catalyst, attention has turned to a related system, the metalloporphyrins. However, this approach is not yet asymmetric.

1.2.3) Polymer-supported epoxidation using metalloporphyrins

Synthetic metalloporphyrins have attracted much interest as oxidation catalysts because their structures resemble those of cytochromes P-450, nature's catalysts for oxidation of foreign organic compounds in our bodies. Metalloporphyrins as potential catalysts for enantioselective epoxidations have, therefore, been subject to extensive investigations.[55] Indeed, iron and manganese porphyrin complexes containing bulky ligands have been developed and proved to mediate alkene epoxidations.[56] However, the relatively high costs of the metalloporphyrins and their applicability to only rather limited types of alkenes render their utilisation in synthesis impractical. Therefore, the immobilisation of these expensive catalysts would facilitate their isolation by simple filtration, and permit their recycling. In addition, it may offer improved activity as well as better enantioselectivity. Hence, the current interest in supported metalloporphyrins is directed toward the development of oxidation catalysts that combine the versatility of

homogeneous metalloporphyrins with the advantages of heterogeneous systems. For this purpose, metalloporphyrins have been anchored to both organic polymers and inorganic solids.[57-61]

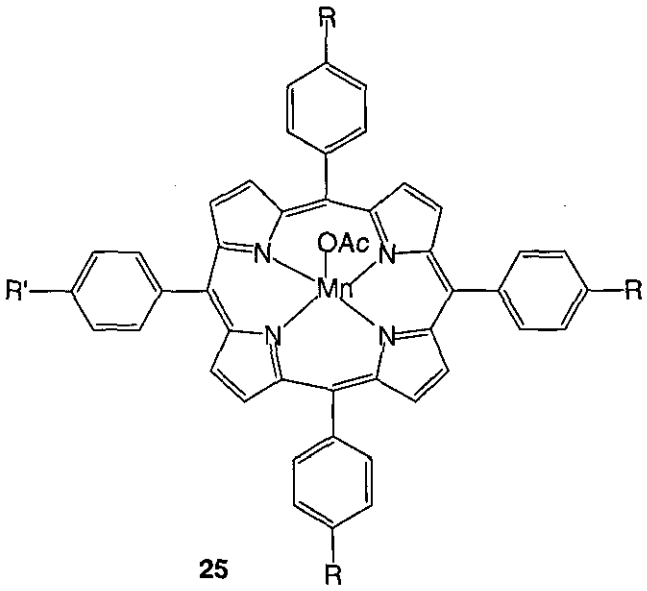
In 1983, Nolte first reported the attachment of (tetraphenylporphyrinato) manganese(III) acetate **25** to a rigid polyisocyanide support **26**.[57] The resulting supported porphyrin **26a** proved to enhance the rate of cyclohexene epoxidation compared to the non-anchored porphyrin catalyst, while **26b** displayed a lower epoxidation rate.



Y = -CH(CO_2H)$CH_2C_6H_4$-OH

26

26a = anchored **25a**
26b = anchored **25b**

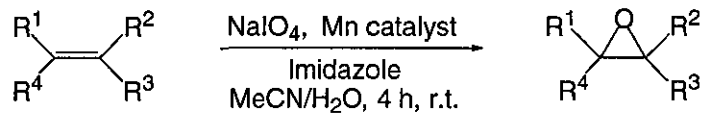


25

25a: R = Me, R' = $O(CH_2)_3Br$ or $O(CH_2)_3O$ after coupling
25b: R = R' = $O(CH_2)_3Br$ or $O(CH_2)_3O$ after coupling

Later, further immobilisations onto inorganic solids were described, but in these cases, the heterogeneous reactions were slower than the homogeneous ones for a wide range of olefins.[58]

A manganese(III) porphyrin has also been tethered on an insoluble poly(4-vinylpyridine) to access a practical and reusable epoxidation catalyst.[59] The immobilised manganese tetra(sulfonato)phenylporphyrin complex catalysed the epoxidation of several alkenes in the conditions shown in Scheme 8.

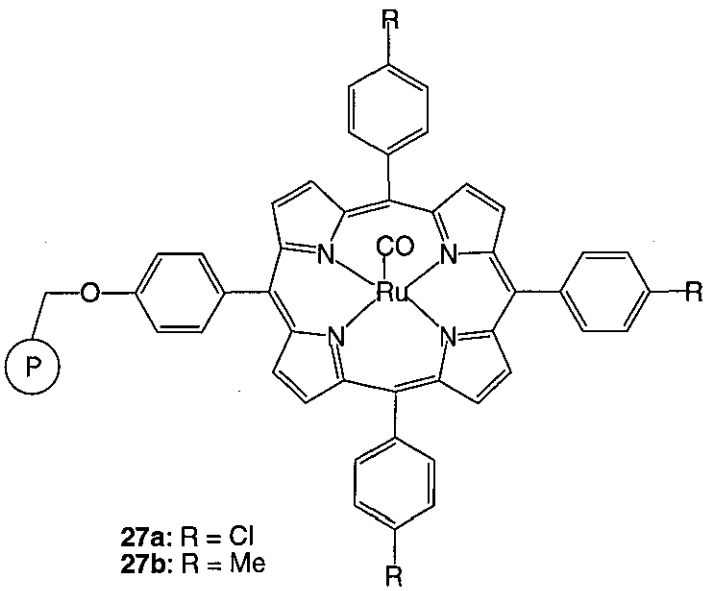


Alkenes used: cyclooctene, cyclohexene, (*Z*)-β-methylstyrene, styrene

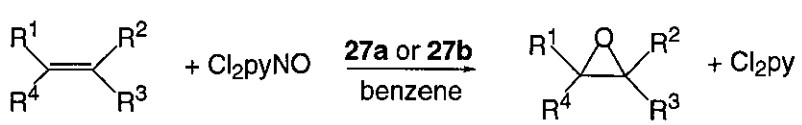
Scheme 8: Alkene epoxidations using manganese porphyrin supported on vinylpyridine

The yields of epoxides were moderate to good (45-95%) and the catalyst remained stable during the reaction. Subsequently, the same group reported that the reaction was more efficient when conducted under ultrasonic irradiation.[60]

Recently, novel ruthenium porphyrins **27a** and **27b** (Scheme 9) were covalently tethered to polystyrene resin and employed in the catalytic alkene epoxidation using 2,6-dichloropyridine *N*-oxide (Cl_2pyNO).[61] The porphyrin **27a**, bearing electron-withdrawing chlorine groups, was found to be a better catalyst than **27b** for the epoxidation of styrene. Moreover, among several reaction solvents such as dichloromethane, or acetonitrile, benzene afforded higher yields of epoxides (56-98%).



27a: R = Cl
27b: R = Me



Scheme 9: Alkene epoxidation using immobilised ruthenium porphyrins

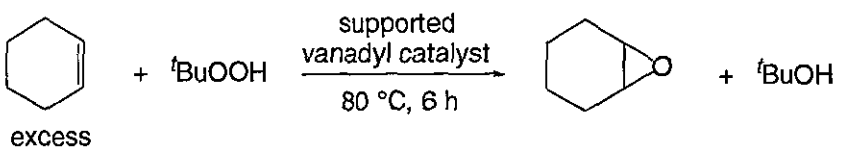
The catalyst **27a** catalysed the epoxidation of various alkenes (66-97% yield), as well as α,β-unsaturated ketones (87, 89% yield), a conjugated enyne (91% yield), a glycal (56% yield) and a protected α-amino alkene (88% yield). This catalyst was reused four times before metal leaching and loss of activity were detected. Nevertheless, chiral versions of these resin-supported metalloporphyrin catalysts have yet to be prepared and assessed in asymmetric reactions to detemine their efficiency as chiral auxiliaries.

In addition to this system, other epoxidation strategies have been attracting interest. Hence, metal complex mediated epoxidation has been evaluated using various other metals and oxidants. Among the latter, the utilisation of alkyl hydroperoxides has been widely reported.

1.2.4) Polymer-supported epoxidation using alkyl hydroperoxides

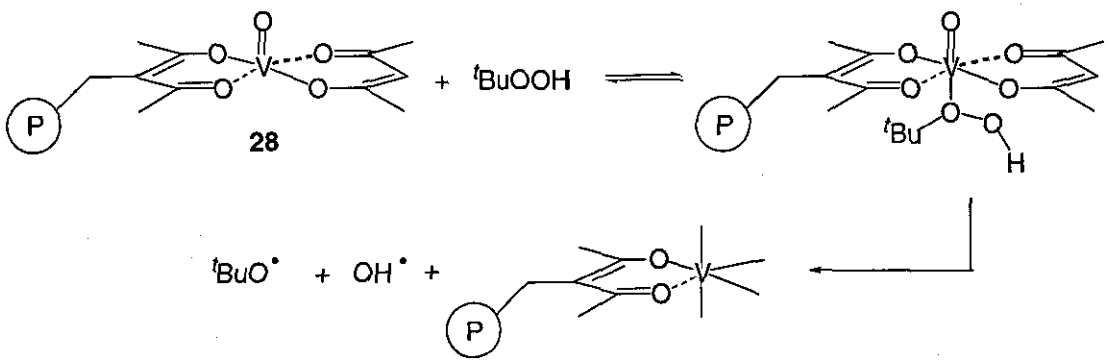
1.2.4.1) Polymer-supported vanadyl catalysts

The incorporation of vanadium ions into insoluble polymers was reported as early as 1977 by Farona and Linden.[62] The general approach to the synthesis of supported vanadyl catalysts involved first the attachment of a ligand such as acetylacetonate (acac), ethylenediamine or pyridine, to a vinyl monomer. The latter was then polymerised to produce the resin beads, and finally the oxovanadium was coordinated to the ligand to provide the immobilised complex. The epoxidation of cyclohexene (Scheme 10) with ^{t}BHP (or ^{t}BuOOH) and these polymer-supported catalysts took place with better conversion than with the soluble model $VO(acac)_2$, under the same conditions. Nevertheless, some oxidant decomposition occurred in competition with the epoxidation reaction.



Scheme 10: Cyclohexene epoxidation conditions

The yields of epoxides remained low (26%) and the catalysts suffered from significant metal leaching. In a second attempt to synthesise epoxidation catalysts, Farona anchored the oxovanadium(IV) to a sulfonic acid ion exchange resin.[63] The complexes were used in the epoxidation of cyclic and acyclic olefins using ^{t}BHP and afforded better activity and selectivity. To investigate further the results obtained by Farona and Linden, Bhaduri examined the supported $VO(acac)_2$ catalyst **28** for reactions involving ^{t}BHP (Scheme 11).[64]

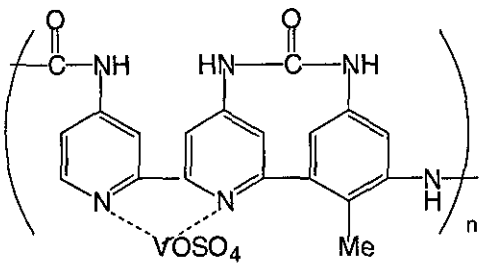


Scheme 11: Reactions involved between vanadyl complex and ^{t}BHP

The catalyst **28** was synthesised by treatment of pentane-2,4-dione with a chloromethylated polystyrene-8% crosslinked DVB co-polymer, followed by the immobilisation of $VO(acac)_2$ in toluene. The resulting polymer-supported complex **28** catalysed the epoxidation of cyclohexene, as well as the homolytic decomposition of ^{t}BHP. This decomposition appeared to be also due to the polymer-chain participation in some additional radical reactions. Although both the homogeneous and the resin-bound reactions underwent oxidative degradation of the catalyst and radical degradation of cyclohexene oxide, (both competing with the selective epoxidation), the supported catalyst permitted superior epoxidation values to the homogeneous analogue. Kinetic studies were undertaken to compare the heterogenous system with the soluble counterpart and highlighted the improved stability of the polymer-bound catalyst. Indeed, the tethering of the complex resulted in a delayed decomposition the metal centre of **28**. As a consequence, the ligand environments around the metal ion were maintained for a longer time, while the homogeneous complex was degraded. Hence, owing to the slower degradation, the

polymeric catalyst remained active longer and gave a higher yield of cyclohexene oxide at the end of the reaction. This study permitted a better understanding of the reaction involved.

Vanadyl catalysts also interested Neckers, who incorporated vanadium transition metal into polar bipyridine-based polyurea matrices, forming, for example, the vanadyl sulfate polymer complex **29**.[65]



29

The activity of these polymer-supported catalysts was evaluated in the epoxidation of a variety of alkenes with ^{t}BHP, but the yields of epoxides were low (15-50%). In some cases, the epoxides were hydrolysed to the corresponding diols in 5 to 30% yield.

When Suzuki studied the epoxidation of allylic alcohols with ^{t}BHP and supported vanadium catalysts, he used crosslinked polystyrene resins containing multidentate functional groups (Fig. 3),[66] because insoluble supported metal complexes tend to become more stable as the dentate number of the ligand increases.[67]

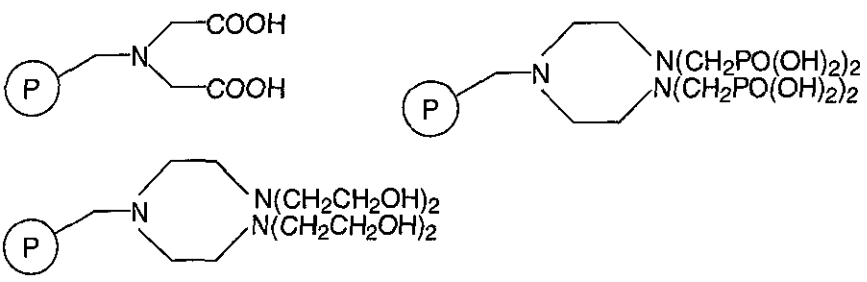
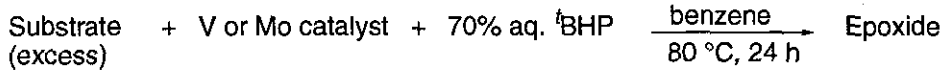


Figure 3: Chelating polymer resins containing multidentate functional groups

The reactivity of these vanadyl complexes was assessed in the epoxidation of cyclohexene and allylic alcohols, and compared to the activity of the corresponding molybdenum complexes under the same conditions (Scheme 12).



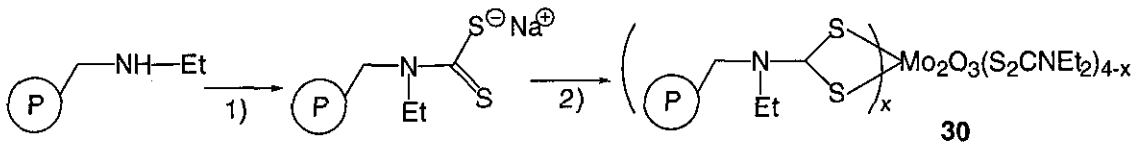
Scheme 12: Epoxidation conditions used by Suzuki

The epoxidation of cyclohexene catalysed by molybdenum gave a high conversion (88%) of the substrate and a better epoxide selectivity in the products (55%), than did vanadium complexes, which gave several by-products, including polymerised compounds. Both vanadium and molybdenum complexes proved to catalyse the decompositon of ^{t}BHP.[68] The vanadium complexes remarkably facilitate the decompositon of ^{t}BHP in the absence of substrate, while in the presence of allylic alcohols the epoxidation proceeds preferentially. An intramolecular oxygen transfer from peroxovanadium(V) complex to an allylic alcohol seems to take place at a much faster rate than the decomposition of the peroxide, perhaps because the olefin is linked *via* a functional group. The epoxidation of cyclohexene, on the other hand, gave very poor yields of the epoxide, perhaps indicating that the decomposition reaction occurs prior to the oxygen transfer to the substrate. With the molybdenum catalysts, the rate of decomposition of ^{t}BHP is much slower, therefore epoxidations of alkenes afford better yields of the desired products. Hence the vanadium catalysed epoxidation is not as successful for simple olefins as it is for allylic alcohol substrates, whereas catalysis by molybdenum complexes is faster and works better for unfunctionalised alkenes, but is less effective for allylic alcohols. For these reasons, the various investigations into asymmetric epoxidation have tended to be focused on the development of polymer-supported molybdenum catalysts.

1.2.4.2) Polymer-supported molybdenyl catalysts

Molybdenum complexes have long been known to be useful catalysts for the epoxidation of olefins,[69] and therefore the preparation of polymer-supported molybdenum catalysts has received much attention. Alkene epoxidation catalysts were first immobilised on carboxylic acid cation exchange resins, [70] and also on anion exchange resins.[71]

In 1983, Bhaduri assessed the polystyrene anchored molybdenum(V) dithiocarbamato-derivative **30** as a catalyst in the conversion of cyclohexene to cyclohexene oxide (Scheme 13).[72] Before the catalytic oxidation of cyclohexene could take place, the prior activation of **30** was necessary to allow the oxidation of Mo(V) to the active Mo(VI).

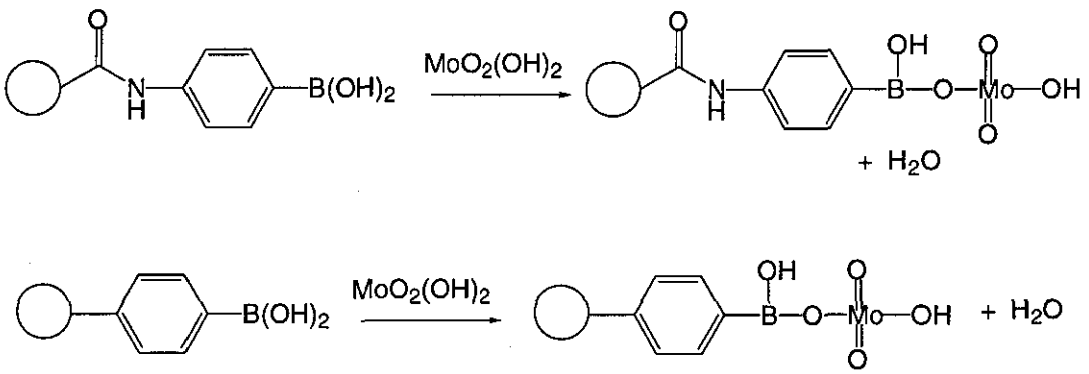


1) CS_2, NaOH
2) $Mo_2O_3(S_2CNEt_2)_4$

Scheme 13: Synthesis of dithiocarbamato Mo(V) complex

The tethered catalyst **30** provided a 20% increase in epoxide yields and a faster epoxidation rate compared to the homogeneous system. As for the vanadyl complex, this is thought to be a consequence of the improved stability of the polymer molybdenum catalyst, and the key role played by the diffusion barrier between the reactants in solution and the supported species, which prevent the rapid oxidation of the ligand environment.

Later, Tempesti reported the immobilisation of molybdenum Mo(VI) on resins containing a boronic acid functionality,[73] which gave the bimetallic B(III)-Mo(VI) catalysts **31** and **32** as illustrated in Scheme 14. Used in the epoxidation of cyclohexene with either ^{t}BHP or ethylbenzene hydroperoxide (EBHP) as oxidants, the resin-bound complexes proved to have an activity and selectivity comparable to the homogeneous bimetallic species.



Scheme 14: Synthesis of the boron-molybdenum complexes

Stamenova described the epoxidation of styrene using EBHP and several vanadium or molybdenum polymer supports, composed of either ethylene/propylene or crosslinked ethylene oxide matrices. Several ligands were employed, and the molybdenum catalyst exhibited higher conversions and selectivities than the vanadium counterpart. However, the epoxide yields were low to moderate (7-70%) and the reactions suffered from significant metal leaching.[74]

It is Sherrington who perhaps made the major contribution to the exploration of heterogeneous molybdenum catalysts.[75-82] Indeed, the synthesis and characterisation of numerous molybdenum catalysts derived from crosslinked poly(chloromethylstyrene) (PCMS), crosslinked poly(glycidylmethacrylate) (PGMA) and crosslinked poly(4-vinylpyridine) (PV-Py) were achieved (Fig. 4),[76] through tethering of the metal centre to the polymeric ligand by ligand exchange with $MoO_2(acac)_2$.

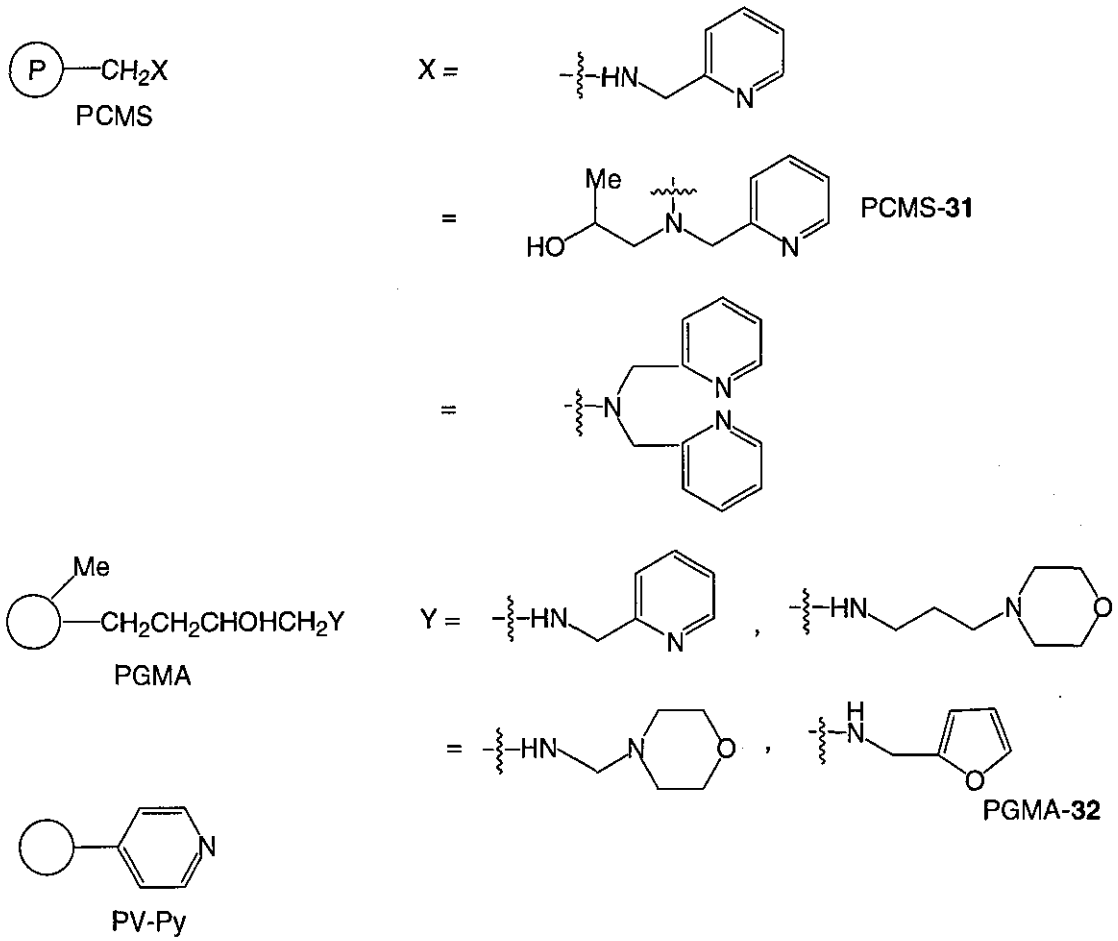
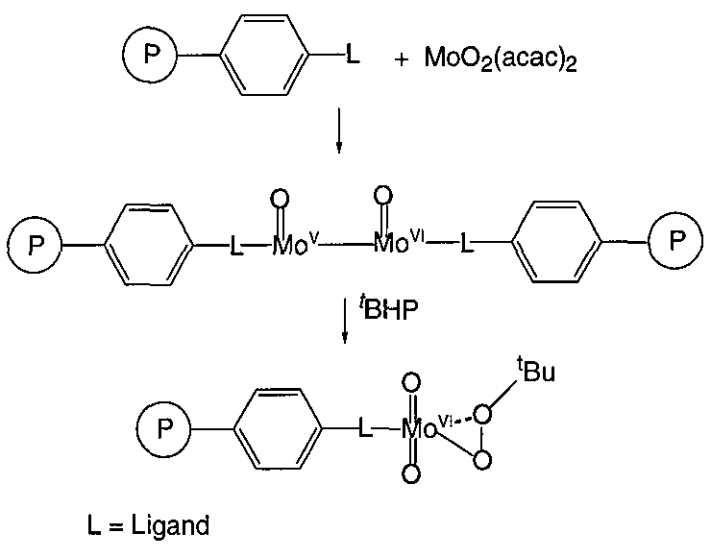


Figure 4: Structures of chelating resins for Mo immobilisation

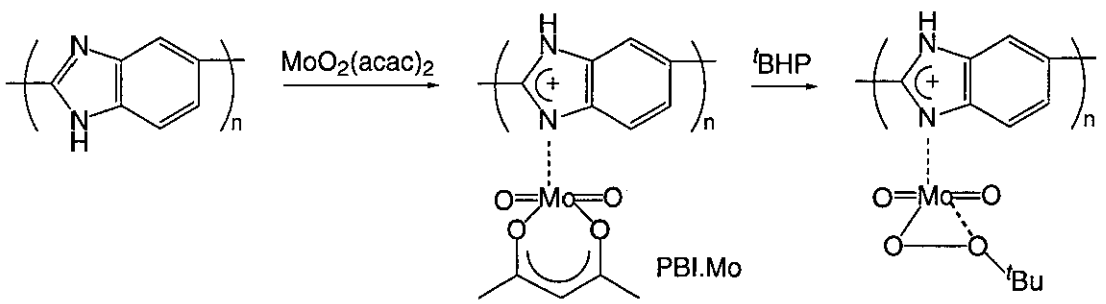
The activation of the resulting complexes by pre-treatment with an excess of ^{t}BHP was required prior to epoxidation of cyclohexene by ^{t}BHP (Scheme 15).



Scheme 15: Preparation and activation of polymer-supported Mo(VI) catalytic centre

The oxidation reactions were then carried out at 80 °C with an excess of alkene relative to oxidant. Each resin bound complex proved to be active, especially the PGMA-based catalysts, which showed slighty better activity over PCMS and PV-Py resins. This result can probably be explained by the higher porosity and polarity of the PGMA resin. Moreover, kinetic studies showed that the catalyst epoxidation rate was strongly dependent on the concentration of ^{t}BHP, and the structure of the ligand was an important factor in producing stable catalysts. In the cases of PCMS-**31** and PGMA-**32** resins (Fig. 4), the molybdenum complexes could be recycled up to nine times. Nevertheless, in all cases significant molybdenum leaching could not be avoided both during the activation period with ^{t}BHP and during epoxidation.

In their efforts to improve the polymer-anchored catalysts, the same group prepared a polybenzimidazole (PBI)-based molybdenum complex.[77-79] The synthesis involved porous polybenzimidazole beads and molybdenyl acetylacetonate, as shown in Scheme 16. The monometallic polybenzimidazole molybdenum complex PBI.Mo did not require activation since ^{t}BHP readily replaced the acac ligand.



Scheme 16: Loading of Mo onto polybenzimidazole

The catalytic activity of the supported complex was evaluated in the epoxidation of propene using ^{t}BHP as the oxygen donor, at 80 °C under a pressure of 400 psi (He). The heterogeneous catalyst afforded better activity and selectivity than the homogeneous analogues, and no molybdenum leaching was observed after ten successive uses of the catalyst. Since the properties and stability of this PBI.Mo complex were promising, Sherrington examined the epoxidation of cyclohexene under similar conditions.[78]

Unfortunately, despite the stability of the resin-bound complex, the activity of PBI.Mo was found to decrease on recycling in epoxidation reactions. Therefore further studies were undertaken with several other polymers containing an imidazole-like moiety (Fig. 5).

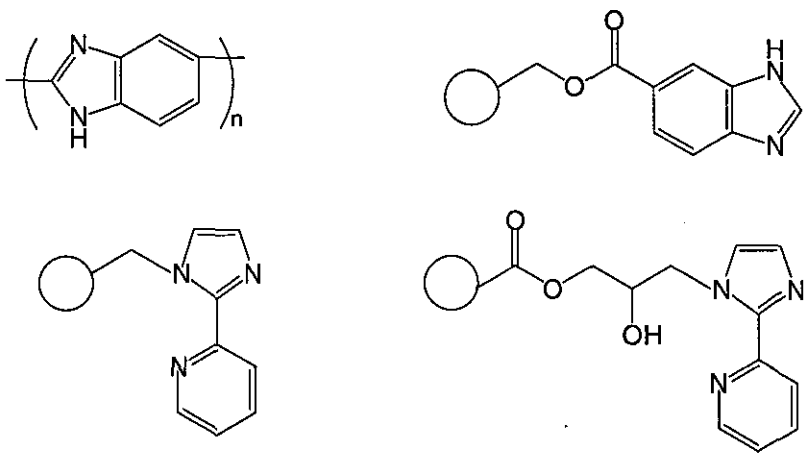
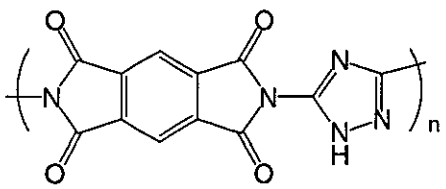


Figure 5: Four imidazole-like resins as potential epoxidation catalysts

Among the various imidazole-derived complexes tested, the PBI.Mo catalyst was the most active, with a yield of *ca.* 90% for the epoxidation of propene. All the polymer-supported molybdenum entities retained their activity over ten consecutive runs. Molydenum leaching was observed during the first three epoxidation reactions, but with further repeated uses, only negligible leaching of the transition metal was observed. This stability seemed to be related to the presence of the imidazole-like ligand, with which the binding of the molybdenum centre seems to be very strong. Overall, the PBI.Mo catalyst provided the best results, giving the best epoxide conversion (although the activity was the poorest in the first run), and molybdenum leaching occurring only in the first run. Hence this complex was also examined in the epoxidation of a wide range of alkenes:[8] cyclohexene, methylenecyclohexane, styrene, 4-vinylcyclohexene, 1,3-pentadienes (50% (*Z*):(*E*)), allyl chloride, allylbromide and allylic alcohol. These reactions were again performed with an excess of alkene with respect to the substrate, to maximise the selectivity towards epoxide. Indeed, some alkenes could undergo allylic oxidation caused by the presence of dioxygen. Hence, in addition to the major epoxide product, cyclohex-2-en-1-ol and cyclohex-2-en-1-one were retrieved from the cyclohexene epoxidation. Nevertheless, these side-products

could not be formed when the reactions were carried out under nitrogen atmosphere. However, these conditions of excess of alkene are not appropriate for multi-step synthesis, for example in the pharmaceutical industry, where it is essential to maximise conversion of alkene precursors for economic reasons. Hence the equimolar epoxidations of cyclohexene, styrene and 4-vinylcyclohexene using ^{t}BHP and PBI.Mo(VI) catalyst were investigated and were achieved at 80 °C over 24 hours.[80] The yields of epoxides were low to moderate (15-70%) due to the decomposition of ^{t}BHP catalysed by the molybdenum when the alkene is not in high concentration in the medium.

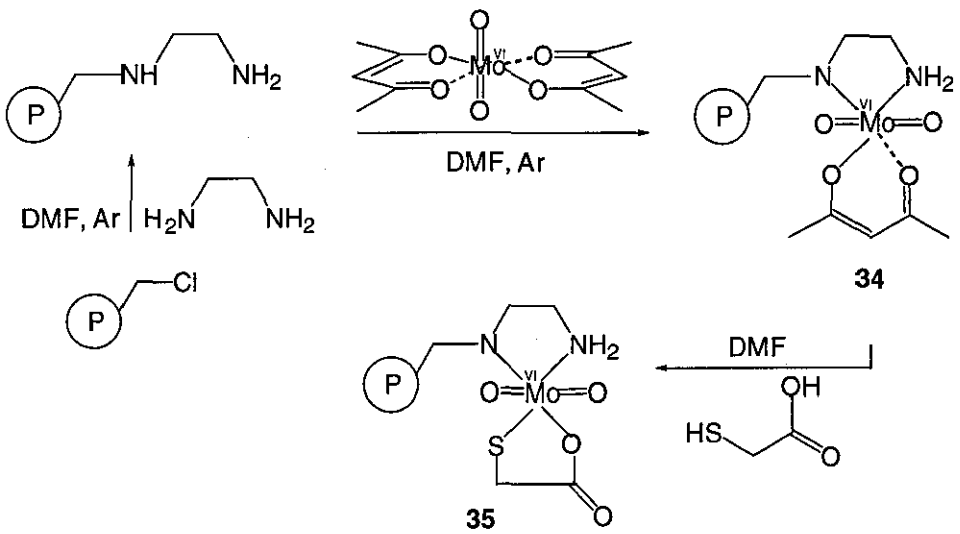
Despite its good stability, the PBI resin was rather expensive and this led to the search for other stable supports. Thus, less expensive polyimide beads containing ligands were synthesised. The 1,2,4-triazole-based polyimide Mo complex **33** was identified as a catalyst for the epoxidation of cyclohexene at 80 °C under 400 psi (He).[81]



33

The crosslinked version of this catalyst proved to be active and was recycled ten times without metal leaching or loss of activity.[8,82]

The development of polymer-supported molybdenum catalysts has also attracted the interests of other groups. For example, Sanz outlined the grafting of a Mo(VI) complex to a 2% crosslinked DVB/polystyrene resin, according to the procedure shown in Scheme 17.[83]



Scheme 17: Synthesis of the immobilised thioglycolic acid Mo catalyst

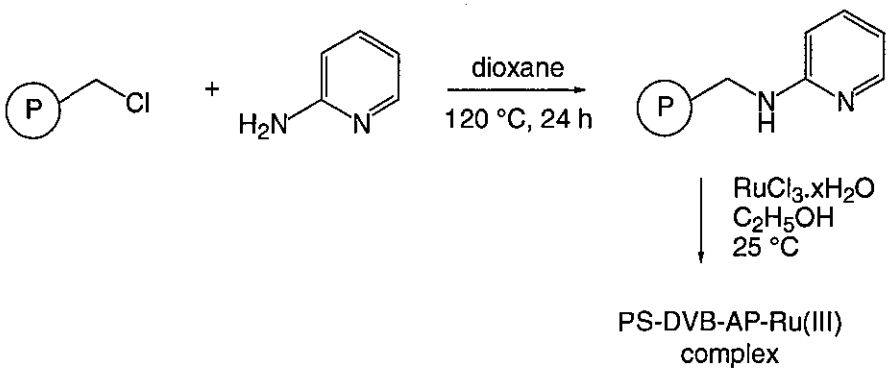
The catalyst **35** was used in the epoxidation of a range of olefins with ^{t}BHP at 80 °C, but the conversion of alkenes was low to moderate (10-78%). The resin **34** (Scheme 17) was also tested as a catalyst for epoxidation under the same conditions, but no epoxide was observed. This result emphasises that the thioglycolic co-ligand in **35** plays an important role in molybdenum complexation and thus in the catalytic activity. This confirms that even "minor" modification of the ligand occupancy can change the properties of the complex.[84] However, in addition to the low conversion, the problem of significant metal leaching during the epoxidation was also noted.

Recently, Kotov published his work on catalytic epoxidation of cyclohexene and other alkenes by ^{t}BHP in the presence of some molybdenum-containing polymeric complexes.[85-87] The stability of the active complexes, based on chelating Amberlite ion exchange resins was evaluated upon repeated use in the epoxidation reactions. The activity of these supported catalysts was also compared to the soluble molybdenyl acetylacetonate $MoO_2(acac)_2$. This investigation revealed that, unlike the homogeneous catalyst, these heterogeneous complexes did not afford quantitative conversion. Nevertheless, the yields of epoxides obtained with these polymer ligands were close to those obtained using $MoO_2(acac)_2$.

1.2.4.3) Other polymer-supported metal catalysts

Although vanadium and molybdenum were most often employed in catalytic epoxidation, some groups have evaluated the activity of other supported metal catalysts.

In 2000, a polystyrene/DVB co-polymer bearing the 2-aminopyridine ligand was condensed with ruthenium(III) salt to form the Ru anchored polymer, which was assessed for epoxidation of (Z)-cyclooctene, cyclohexene and styrene (Scheme 18).[69] The reactions were carried out with ^{t}BHP, and the conversions to the epoxide were rather low (10-50%). Except for (Z)-cyclooctene, the selectivity was disappointing due to the formation of side-products. The cyclohexene substrate gave cyclohex-2-en-1-one as the major product and some cyclohex-2-en-1-ol, while styrene furnished mainly benzaldehyde and some phenyl methyl ketone.



Scheme 18: Preparation of chelating polymeric aminopyridine ruthenium complex

The catalyst was recycled four times, but progressive loss of activity occurred, probably as a consequence of ruthenium leaching from the support.

To complement his studies on molybdenum polymer complexes, Sherrington also investigated the potential of copper, manganese, iron, ruthenium and titanium metal ions in the epoxidation of cyclohexene with ^{t}BHP.[8] The incorporation of the transition metals onto polybenzimidazole resin provided polymeric complexes having catalytic activity with various selectivities. This led to the identification of polybenzimidazole titanium complex (PBI.Ti) as a promising catalyst, as cyclohexene oxide was obtained in 73% yield after epoxidation reaction.

To summarise, the immobilisation of vanadium and molybdenum complexes as epoxidation catalysts is well-documented and will probably be subjected to further development. However, the systems mentioned above showed some limitations, either in loss of activity, usually caused by metal leaching, or selectivity. Furthermore, some reaction conditions remain harsh and cannot be applied to organic synthesis, while some others using an excess of alkenes are disfavoured due to the waste of olefin. Therefore, other polymeric epoxidation systems using different source of oxidants have emerged.

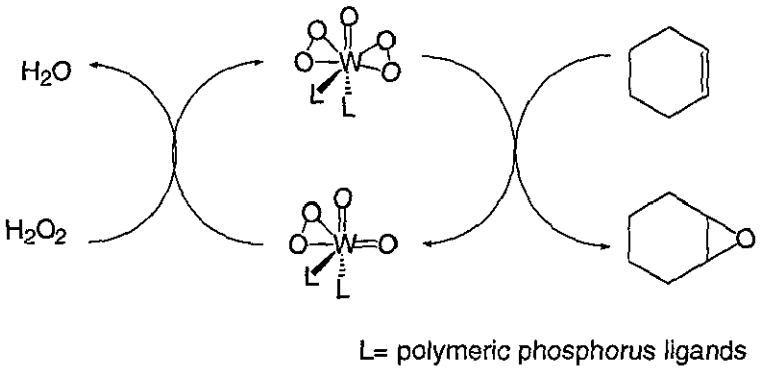
1.2.5) Polymer-supported epoxidation using hydrogen peroxide

Hydrogen peroxide (H_2O_2) is a very good and practical oxidising agent, although its stability is rather limited. The utilisation of H_2O_2 has economic and environmental advantages: it is cheap, widely available and easy to handle. In addition, this oxygen source is much cleaner than alkylperoxides and yields only water as a co-product, thus creating no pollution problems.

1.2.5.1) Polymer-supported tungsten complexes

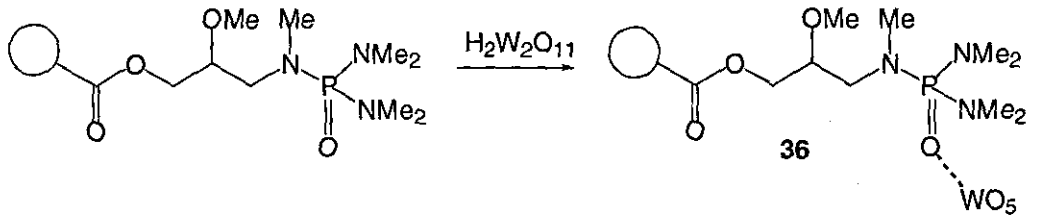
Tungsten (VI) can activate hydrogen peroxide to provide an efficient and selective alkene epoxidation system.[8] However, high concentrations of soluble tungsten oxide give rise to contaminated reaction products. Oxidation reactions using polymeric tungsten derivatives were therefore investigated.

In 1969, Allan and Neogi first reported the preparation of a solid tungsten catalyst by treatment of a quaternary ammonium ion exchange resin with a solution of sodium hydrogen tungstate.[88] More recently, Gelbard developed several tungsten catalysts, which were immobilised onto polystyrene, polybenzimidazole and polymethacrylate co-polymers containing phosphorus(V) ligands.[89] Various organophosphoryl units, including phosphine oxide ($R_3P=O$), phosphonamide ($R(NRR)_2P=O$), and phosphoramide ($R(NR_2)RP=O$), were examined as complexing ligands for tungsten(VI). Each of these was tested in the epoxidation of cyclohexene at 70 °C using 70% aqueous hydrogen peroxide (Scheme 19).



Scheme 19: Catalytic epoxidation with peroxotungstic complexes

Unfortunately, either the oxidations gave a mixture of epoxide and diol, or the metal leaching was too high to allow recycling of the supported catalysts. After many attempts, catalysts with good activity, stability and high selectivity for epoxidation were finally achieved using a polymethacrylate supported phosphotriamide complex **36**. The polymeric ligands were loaded with tungsten pentoxide WO_5 using peroxotungstic acid $H_2W_2O_{11}$ as shown in Scheme 20.

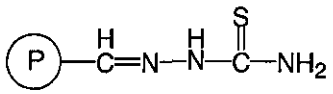


Scheme 20: Polymethacrylate grafted phosphotriamide.

The epoxide selectivity (77-91%) after 0.75 hour of reaction using **36** were far higher than that of the soluble model (57% after 3 hours). Nevertheless, although the leaching was less than 2 ppm of tungsten, further studies are necessary to improve the recyclability due to the high toxicity of tungsten.

1.2.5.2) Other polymer-supported metal complexes

Numerous transition metals have been studied for the epoxidation of olefins using aqueous hydrogen peroxide.[90,91] Polystyrene-supported thiosemicarbazone complexes **37** loaded with Fe(III), Co(II), Ni(II) and Cu(II) ions, were employed by Chettiar and Skreekumar.[90]

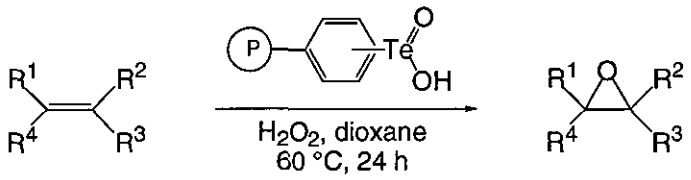


37

Cyclohexene and styrene were epoxidised by the supported Fe(III), Co(II), and Cu(II) complexes using 30% aqueous hydrogen peroxide, whereas Ni(II) was found to be inactive. It was found that the catalytic activity of the polymeric thiosemicarbazone metal complexes was influenced by the nature of the support, the nature of the metal coordinated and the geometry of the complexes. Unfortunately, these reactions gave only low to moderate yields of cyclohexene oxide (3-20%) and styrene oxide (12-67%).

1.2.5.3) Polymer-supported metal oxides

The search for methods for epoxidation of olefins has also led to the development of resin-bound metal oxides. Early work on epoxidation highlighted organoselenium or organoarsenic reagents as suitable catalysts.[91] However, arsenic and selenium based catalysts are environmentally detrimental, even at low concentrations; they also cause epoxide hydrolysis during product isolation. To circumvent these problems, arsenic and selenium were incorporated to insoluble supports. In 1979, Jacobson and Mares assessed arsenated polystyrenes as catalysts using a triphasic system.[92] This system consisted of a water-immiscible solvent (chloroform), aqueous hydrogen peroxide and the solid catalyst. The latter was easily separated by filtration, and recycled, but arsenated supported polystyrenes induced only moderate to low regio- and stereoselectivity compared to the soluble arsenated counterpart. Polystyrene-bound phenylseleninic acid was also prepared a few years later by Taylor and Flood.[93] Oxidation was again performed in a triphasic system, but unlike the arsenated example, the supported selenium catalyst only afforded diols. Nevertheless, tellurium, was also evaluated in the catalytic epoxidation system, because in the periodic table, this metal can be found under selenium. To test its utilisation as an oxidation catalyst, tellurium was incorporated to crosslinked polystyrene, and the resin was subsequently reacted with alkenes and hydrogen peroxide (Scheme 21).



Alkenes used: 1-methylcyclohexene, cyclohexene
3-methylcyclohexene, (*E*)-2-butene, styrene

Scheme 21: Epoxidations of various alkenes with an anchored tellurium catalyst

The reactions provided up to quantitative and stereospecific epoxidation, (*Z*):(*E*) geometry being retained in the epoxide product.[94] The catalytic activity was dependent on the degree of crosslinking in the co-polymer, whereas the alkyl substitution on the olefin increased the reaction rate, as observed in the case of the arsenated polymer.[92] It is noteworthy that soluble organotellurium compounds have no activity as oxidation catalysts. These metals remain very toxic, and metals safer for the environment have therefore attracted much more interest in the development of epoxidation catalysts.

More recently, the synthesis of polymer-supported vanadium(IV) catalysts for epoxidation with hydrogen peroxide was outlined by Singh.[95] Vanadyl acetylacetonate $VO(acac)_2$ complex was immobilised on non-porous Amberlite IR-120 beads and studied in the epoxidation of maleic, fumaric and crotonic acids (Fig. 6).

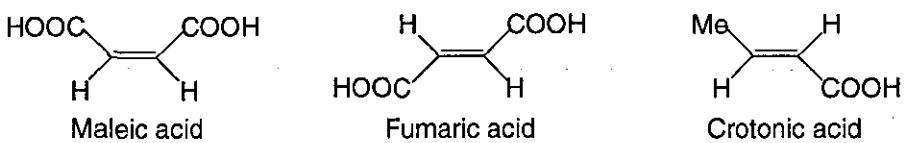
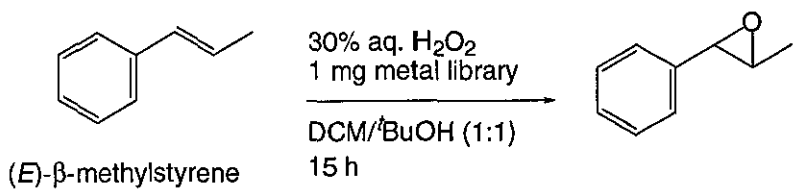


Figure 6: Substrates studied for epoxidation

The resin-bound catalyst provided faster reaction (by a factor of 2) than the unsupported vanadium catalyst. Unfortunately, the selectivity remained poor, due to the production of hydroxyl radicals which can initiate radical-chain competing decomposition.

In 1999, Jacobsen reported the use of metal-binding combinatorial libraries for the discovery of novel alkene epoxidation catalysts.[96] The strategy for the identification of catalysts involved a three step process. First, compatible reaction conditions for the epoxidation of the model substrate (*E*)-β-methylstyrene were assessed by screening of the

entire pooled catalyst library. Hydrogen peroxide was identified as the most viable and also most practical oxidant. No epoxidation activity was detected using molecular oxygen, sodium periodate, 4-methyl morpholine-*N*-oxide, or 4-phenyl pyridine-*N*-oxide. The optimal solvent system found was a 1:1 mixture of dichloromethane/*tert*-butanol, which was selected for its inertness towards redox reactions and its ability to dissolve appreciable amounts of hydrogen peroxide, while still swelling polystyrene beads. The second step of the process was the determination of active metal libraries for the epoxidation of (*E*)-β-methylstyrene with hydrogen peroxide. Thirty individual metal sources and 192 ligands were chosen to prepare the catalyst sub-libraries, and each sample of the library was exposed to the epoxidation conditions (Scheme 22).



Scheme 22: Screening of metal complexes for the epoxidation of (*E*)-β-methylstyrene

The third step of the screening process was the identification of the ligand structures necessary for catalytic activity. For this purpose the ligand library was prepared and screened under the epoxidation conditions, to be finally deconvoluted and analysed. In addition, a parallel library was subsequently screened to establish chiral ligands affording 20% enantioselectivity. This efficient screening of a library of 5760 ligand-metal complexes revealed three catalysts (Fig. 7) for the epoxidation of (*E*)-β-methylstyrene using aqueous hydrogen peroxide.

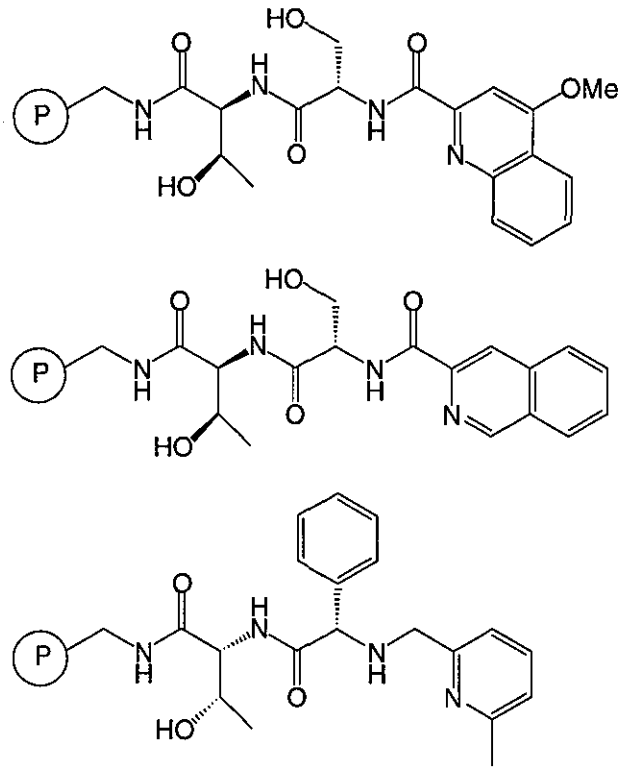


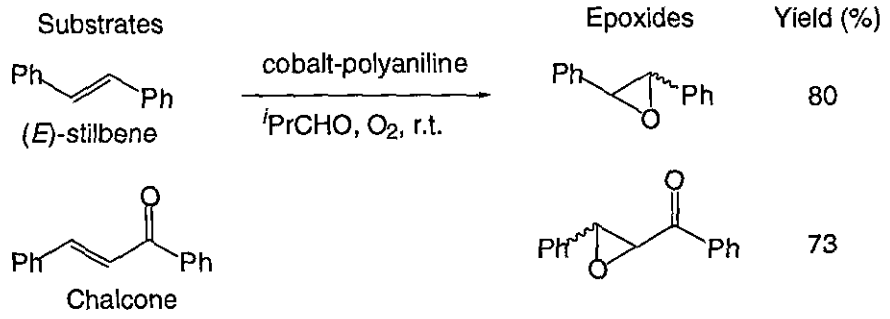
Figure 7: Ligands identified by library screening

The direct synthetic application of hydrogen peroxide remains limited to the epoxidation of electron-donating alkenes. Therefore, other strategies have been considered for the catalytic epoxidation of olefins, and one of the most environmentally important involves the utilisation of dioxygen.

1.2.6) Polymer-supported epoxidation using molecular oxygen

Molecular oxygen is the ideal oxidant in terms of environmental and economic assets. This cheap and readily available oxidising agent is easy to use and completely safe for the environment. Recent advances in polymer-supported catalysis as well as governmental restrictions on the environment prompted several groups to examine the oxidation of alkenes using molecular oxygen and metal catalysts.

In 1997, Iqbal demonstrated that polyaniline-supported cobalt(II) acetate can function as an efficient catalyst in the oxidation of various olefins in the presence of 2-methylpropanal and dioxygen.[97] For example (*E*)-stilbene and chalcone (Scheme 23) were epoxidised to yield between 50-80% of epoxides without stereospecificity.



Scheme 23: Examples of substrates epoxidised with Cobalt-polyaniline

The preparation of the polymeric metal complex was performed by mixing equal amounts of polyaniline and cobalt(II) acetate hexahydrate for 72 hours. The nitrogen atom of the polyaniline anchoring the cobalt through coordination, gave a stable cobalt catalyst which could be recycled.

More recently, Lei reported the catalytic oxidation of cyclohexene using polymer-bound bipyridine cobalt complexes and dioxygen at 70 °C without any solvent.[98] The reaction, however, afforded only a small amount of epoxide, the main products being cyclohexenol and cyclohexenone.

Nolte and Sherrington also published their work on the aerobic epoxidation of (*S*)-limonene (**38**) using several types of polymer-tethered metal catalysts.[99] Nickel, cobalt and molybdenum were evaluated, and four different polymer resins were tested: polybenzimidazole (PBI), Dowex A, Dowex B and a resin from the BP company (BP), which are illustrated in Figure 8:

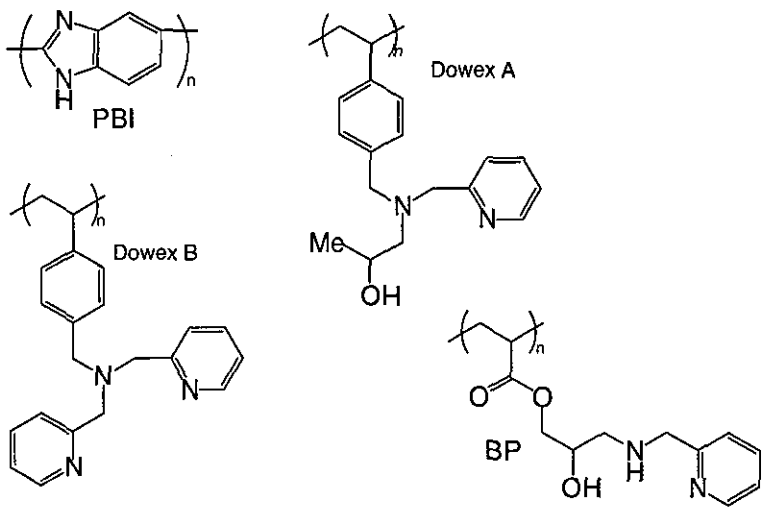
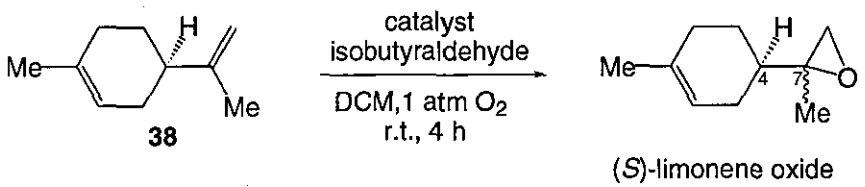


Figure 8: Structures of four resins examined by Nolte and Sherrington

The epoxidations provided the 1,2-epoxide, as a 60:40 mixture of (4S,7S) to (4S,7R) diastereoisomers (Scheme 24). The nickel polybenzimidazole complex (PBI.Ni) was identified as the most efficient catalyst, since the latter displayed better activity and selectivity than the soluble $Ni(acac)_2$ catalyst, and was more selective than PBI.Co complex (Table 2).



Scheme 24: Epoxidation of (*S*)-limonene under aerobic conditions

Catalyst	Conversion	Yield of 1,2-epoxide
PBI.Ni	93%	74%
PBI.Co	99%	61%
PBI.Mo	0%	0%
DowexA.Ni	61%	31%
DowexB.Ni	0%	0%
BP.Ni	0%	0%

Table 2: Epoxidation of (*S*)-limonene with various polymer-supported catalysts

The nickel supported Dowex A resin permitted a moderate conversion and selectivity, whereas neither the BP resin, and the molybdenum polybenzimidazole resin, nor the nickel coordinated Dowex B resin exhibited any activity. The PBI.Ni complex was also effective for the epoxidation of α-pinene (88% yield) and oct-1-ene (52% yield), in contrast with the low selectivity obtained with styrene (23%). However, 20% of metal leaching was detected in the course of the epoxidation, causing a loss of activity upon regeneration of the polymer complex.

In conclusion, many epoxidation reactions involve a polymer-supported catalyst containing a metal ion. Some of the systems described exhibit good enantioselectivity, but unfortunately, these strategies commonly encounter problems associated with metal leaching and/or catalyst stability. These inconveniences need to be addressed before a possible industrial application can be envisaged.

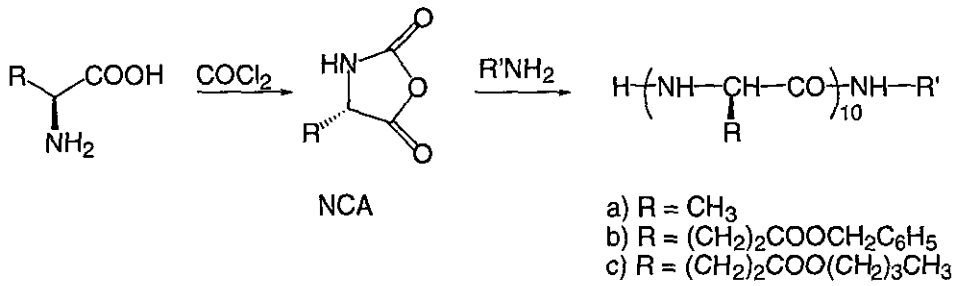
While much research has been directed toward the optimisation of metal complex-catalysed epoxidation, the strong interest in polymer-supported catalysis and the commercial importance of olefin epoxidation has also led to the development of various heterogeneous, but purely organic-based epoxidation methodologies.

1.3) Polymer-supported epoxidations without metals

The number of purely organic epoxidation systems that have been adapted to asymmetric solid phase synthesis is limited. Among these enantioselective oxidation methods, the most well-known is the Julià epoxidation.[100,101]

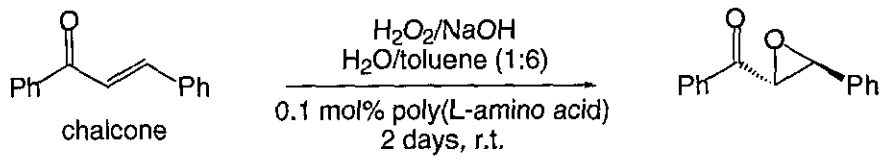
1.3.1) Polymer-supported Julià epoxidation

In 1980, the synthesis and utilisation of polyamino acids as valuable catalysts for the asymmetric epoxidation of α,β-unsaturated carbonyl compounds was reported for the first time by Julià.[102] The polypeptides derived from alanine or glutamic acid were prepared by the polymerisation of *N*-carboxy anhydrides (NCA) shown in Scheme 25.



Scheme 25: Synthesis of polyamino acids by Julià

The epoxidation of chalcone was achieved in a triphasic system composed of toluene, water and the insoluble polypeptide, with hydrogen peroxide/sodium hydroxide as the oxidant system (Scheme 26).

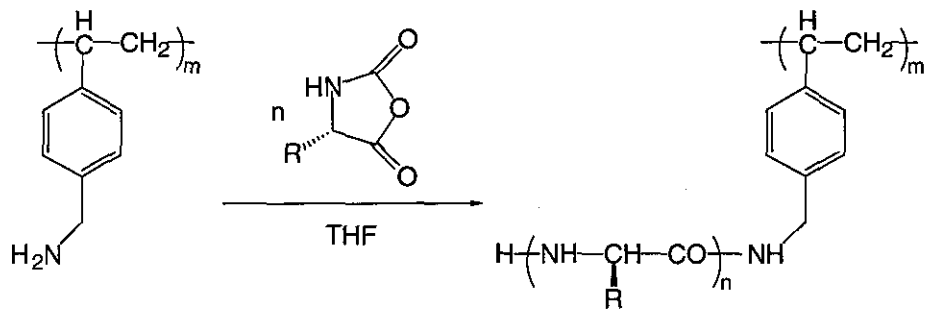


Scheme 26: Asymmetric epoxidation of chalcone mediated by polyamino acids

Poly(L-alanine) afforded the highest stereoselectivity and displayed better performance in terms of conversion and enantioselectivity, than did the polyglutamate species. Indeed, an enantiomeric excess of 97% was obtained with the poly(L-alanine) in the conditions described in Scheme 26, proving that poly-α-amino acids exhibit enzyme-like stereoselectivity leading to optically active epoxides with high enantiomeric excesses.[103] The epoxidation of chalcone was subjected to a detailed study,[103-105] which highlighted the important features of this triphasic system. Poly(L-alanine) catalyses the epoxidation of chalcone derivatives as well as some electron-poor olefins. It was also found that the reaction depends on the degree of polymerisation (n).[104] Indeed, the best enantiomeric excess was attained when n=30, but ees decreased with lower polymerisation levels. In fact, when the polymer chain contains less than ten amino acids, no optical activity is induced. The change in the degree of polymerisation presumably causes conformational modifications in the polymer. When the polymerisation degree is higher than ten, the α-helical conformation is favoured, probably due to hydrogen bonding.[105] It is presumed by

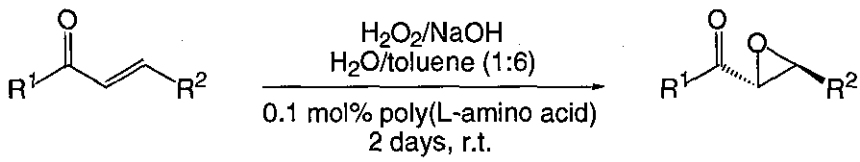
Julià that the high asymmetric induction stems from the hydrogen bonding between the peptide group of the catalyst and the carbonyl group of the substrate.[103,105] Nonetheless the poly(L-isoleucine), which is reported to exist as a β-sheet, also proved to be an excellent catalyst.[100] It also appeared that both organic solvent and water are necessary to achieve the asymmetric epoxidation. Furthermore, the relative proportions of liquid/solid/liquid phases have an important influence on the yields of epoxides and on the optical purity. For example, an increase in toluene proportion lowered the asymmetric induction, while an increase in polymer quantity induced a decrease in the chemical yield.[102] Toluene and carbon tetrachloride were found to be the solvents of choice for this reaction. Despite the difficulty of separation of the polyamino acids (n=10) from the reaction mixture, the poly(L-alanine) was recovered and recycled; however, both activity and enantioselectivity decreased dramatically. When the temperature of epoxidation was increased from 0 to 50 °C, the chemical yield diminished from 86 to 36%.[104] Other oxidants such as *m*CPBA or ^{t}BHP in basic media were tested in the chalcone epoxidation, but either the reaction did not take place or the resulting product was racemic.[104] Among other poly-α-amino acids synthesised, such as poly(L-leucine), poly(L-proline), or poly(L-isoleucine), a crosslinked polystyrene anchored poly(L-alanine) was evaluated and provided 82% yield of chalcone oxide with 84% ee.[105] The isolation and purification of the catalyst was facilitated by simple filtration, but a loss of stereoselectivity upon recycling was noticed.[105]

To overcome the difficulties of the catalyst recovery, Itsuno synthesised two polystyrene/DVB supported polyamino acids, poly(L-alanine) and poly(L-leucine) (Scheme 27).[106]



Scheme 27: Synthesis of immobilised poly(L-alanine) and poly(L-leucine)

These chiral catalysts efficiently epoxidised chalcone under the conditions described in Scheme 28 to yield the epoxy ketone in high enantiomeric purity. Poly(L-leucine) with a high degree of polymerisation (n=32), provided the best result with 92% yield and 99% ee of epoxy chalcone. The separation of the anchored catalysts was remarkably improved and the catalysts could be reused without significant loss of activity. After 12 recyclings of poly(L-leucine) (n=32), the chiral epoxide was obtained in 95% yield and 94% ee. The epoxidation of a range of α,β-unsaturated ketones was also examined (Table 3) using the poly(L-leucine), and again the corresponding epoxides showed excellent optical purity (76-99% ee).



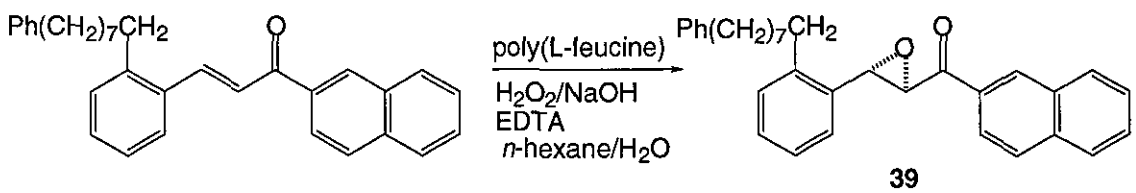
Scheme 28: Epoxidation conditions using immobilised catalysts

Substrates		Epoxides	
R¹	**R²**	**Yields (%)**	**ee (%)**
Ph	*p*-NO_2Ph	90	99
Ph	*o*-MeOPh	56	76
Ph	*o*-EtOPh	56	83
p-ClPh	Ph	98	99

Table 3: Examples of α,β-unsaturated ketones epoxidised using poly(L-leucine)

A similar approach to the immobilisation of poly(L-alanine) was achieved by Carrière for the asymmetric epoxidation of chalcone.[107] The stereoselective epoxidation was carried out by poly(L-alanine) grafted *N*-benzylacrylamide-co-*N*-aminopropyl methacrylamine co-polymer in the triphasic system water/carbon tetrachloride/polymer catalyst. The resulting epoxide was obtained in 60% yield and 80% ee. However, after recycling three times, a diminution in yield and enantiomeric excess was observed.

Attracted by the mild, efficient and simple Julià procedure, Ferreira applied the same conditions to produce polyoxygenated chalcone epoxides aimed at the enantioselective synthesis of flavanoids.[108] Also interested by the appealing strategy of the polypeptides, Lantos employed the Julià epoxidation to prepare the epoxide **39** (Scheme 29), one of the key intermediates in the enantioselective synthesis of a potent leukotriene antagonist.[109]



Scheme 29: Lantos variation of the asymmetric epoxidation

In order to determine the optimum conditions for this asymmetric epoxidation, Lantos established some variations to the Julià procedure. Stable, inert, and easy to handle poly(L-leucine) was prepared on larger scale (>200 g), and the epoxidation was performed in a mixture of *n*-hexane/water instead of toluene/water (the latter only allowing a sluggish reaction). The catalyst poly(L-leucine) was pre-activated by stirring for 24 hours in the solvent of choice containing an excess of sodium hydroxide at room temperature. During this period, the polymer swells and apparently adopts a more reactive physical state. The catalyst thus pre-activated permitted complete epoxidation within 20-24 hours, instead of 72 hours. The poly(L-leucine) was recycled six times without decrease of either yield or enantiomeric excess.

Nevertheless, the scope of substrates oxidised by the Julià methodology remained limited to substituted chalcones or closely related entities. Substrate specificity added to

the problem of long reaction times (associated with the decomposition of the oxidant), adding to the drawbacks of this system.

To investigate the full versatility of the Julia reaction, Roberts utilised the poly(L- or D-leucines) with hydrogen peroxide/sodium hydroxide in dichloromethane or hexane. Sometimes a milder oxidant like sodium perborate with sodium hydroxide in the presence of a phase-transfer catalyst (aliquat 336) was employed. A range of substrates were studied of which the corresponding epoxides were successfully isolated.[110-112] Among the numerous substrates assessed, a broader range of enones (for example **43**), dienones (**40**, **42**, **45**), tetraene (**41**), enynone (**44**), enediones (**47**, **49**), α-substituted-β-unsubstituted enone (**46**), and unsaturated ketone ester (**48**) gave epoxide products with high ees (Fig. 9).

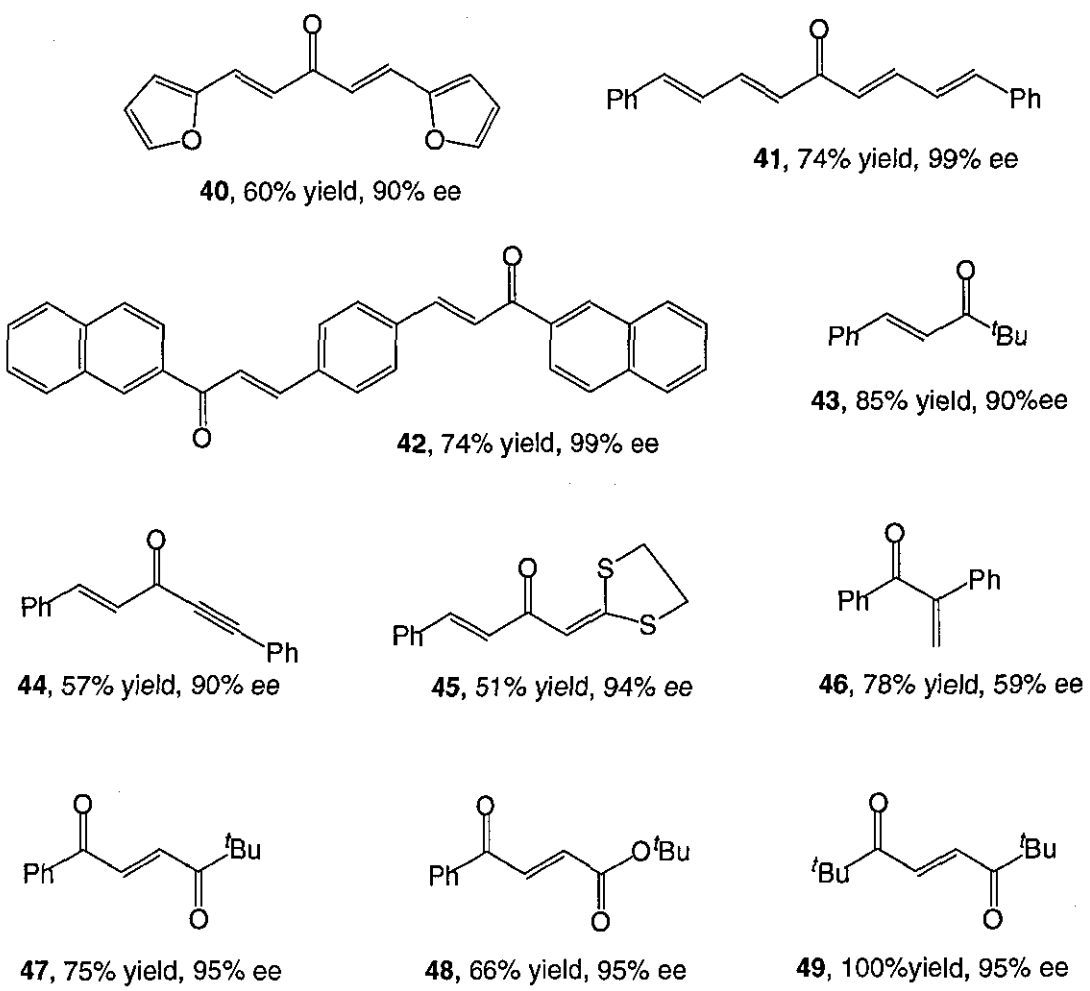
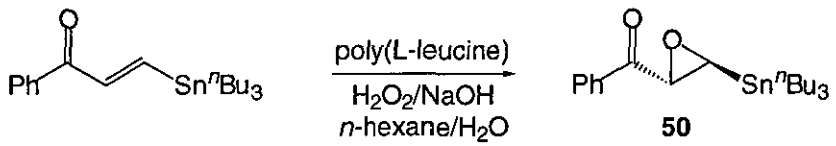


Figure 9: Some of the enones epoxidised by Roberts using poly(leucines)

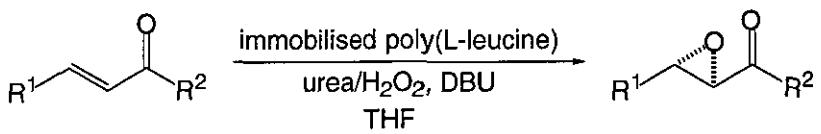
It is noteworthy that Falck also used the Julià procedure to prepare the epoxy stananne **50**, which was retrieved with 90% yield and 99% ee (Scheme 30).[113]



50

Scheme 30: Synthesis of epoxy stananne **50** by Falck

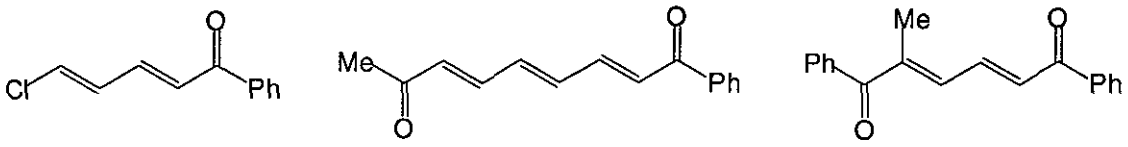
Following the work of Itsuno and interested in the utilisation of catalysts easy to recycle (without reduction of enantioselectivity), Roberts also achieved asymmetric epoxidations using an immobilised poly(L-leucine), prepared by attachment of the polyamino acid to a polystyrene/DVB co-polymer.[112] Under the Julià triphasic conditions, this supported catalyst afforded the best yields and ees (> 95%) for the epoxidation of the unsaturated keto ester **48** (Fig. 9) and a selection of enediones. In his efforts to contribute to Julià methodology, Roberts also demonstrated that a biphasic system, consisting of the polymer-anchored poly(L-leucine) and urea/hydrogen peroxide/DBU in tetrahydrofuran, can provide good asymmetric inductions in the epoxidation of chalcone derivatives.[114,115] Oxidations were effected very efficiently, with reduced reaction times, and no pre-treatment of the polypeptide with aqueous organic solvent was required. Some of the alkenes tested are shown in Table 4.



R^1	R^2	Time	Yield	ee
CH=CHPh	2-naphthyl	2 h	85%	98%
cyclohexyl	Ph	3 h	91%	89%
Ph	Me	6 h	70%	80%
Ph	^{t}Bu	12 h	76%	94%
p-MeOC$_6$H$_4$	^{t}Bu	28 h	90%	96%

Table 4: Robert's alkene epoxidation in the biphasic system

The catalyst was recycled six times without diminution of oxidation rate or optical purity. With these non-aqueous conditions, the range of substrates epoxidised was again expanded, and hence the chlorodiene (**51**), trienone (**52**), and alkylated dienone (**53**) produced the epoxides in good optical purity (Fig. 10).[100]



51, 57% yield, 86%ee **52**, 43% yield, 90%ee **53**, 70% yield, 92%ee

Figure 10: Further substrates of Roberts for the Julià epoxidation

However, the biphasic system using urea/hydrogen peroxide/DBU displayed a significant background epoxidation leading to racemic products. Therefore, due to the rate of the uncatalysed reaction which occurs concurrently with the catalysed oxidation, Roberts developed a protocol where the asymmetric epoxidation of chalcone can be effected with sodium carbonate Na_2CO_3 as the dual source of base and oxidant.[116] A 1:1 mixture of water/1,2-dimethoxyethane (DME) proved to be the solvent of choice to enhance the dissolution of the sodium carbonate and the release of hydrogen peroxide in the medium. Hence, the epoxidation of chalcone catalysed by poly(L-leucine) supported on a polyethyleneglycol grafted polystyrene co-polymer, with the Na_2CO_3/H_2O_2 system, gave a quantitative conversion to the epoxide with a 96% ee. Under these conditions, the background reaction was diminished and the enantioselectivity remained constant throughout the reaction. In addition, this method is environmentally more benign, cheaper and practically more convenient than the previously reported conditions. The ratio of substrate to catalyst can be increased without affecting the final product. Roberts, who thus solved some of the weaknesses of the Julià procedure, illustrated the usefulness of the epoxides generated by the Julià system in the synthesis of a number of optically active structures of biological interest, including Diltiazem,[115] the Taxol® side chain,[115] and (+)-clausenamide (Fig. 11).[117]

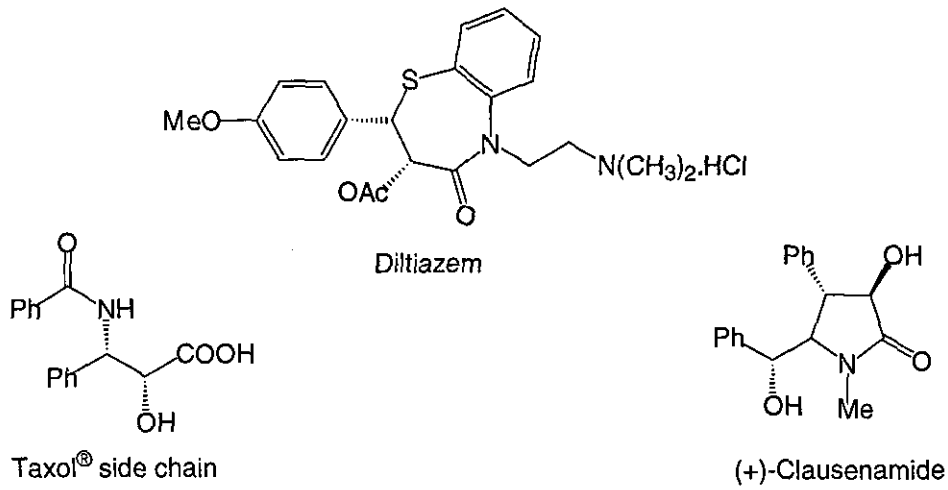
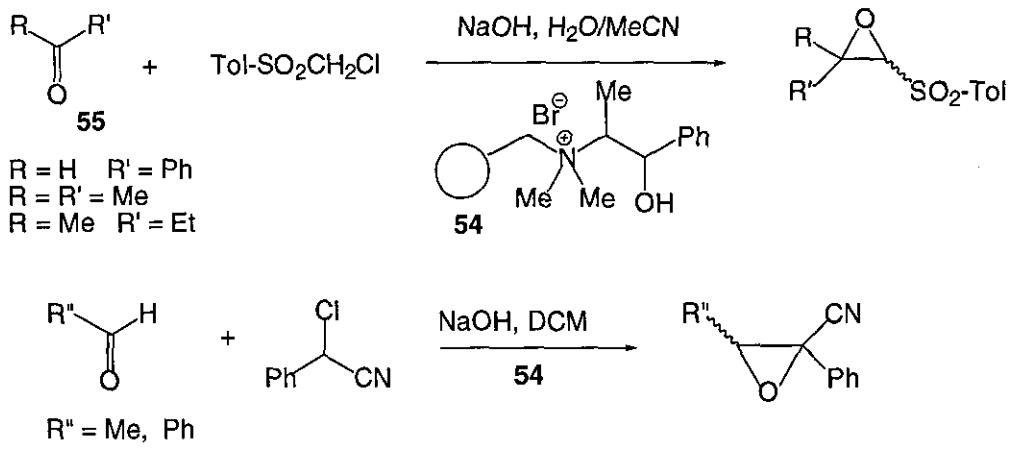


Figure 11: Bioactive compounds synthesised through the Julià asymmetric epoxidation

The Julià process offers many advantages and provides a powerful tool for the synthesis of epoxy ketones. Nevertheless, substrates such as vinyl chlorides and electron rich alkenes are totally unreactive; even α-methylchalcone is far less reactive than chalcone. This limitation of substrates suitable for the application of Julià method therefore remains a problem.

1.3.2) Polymer-supported Darzens epoxidation

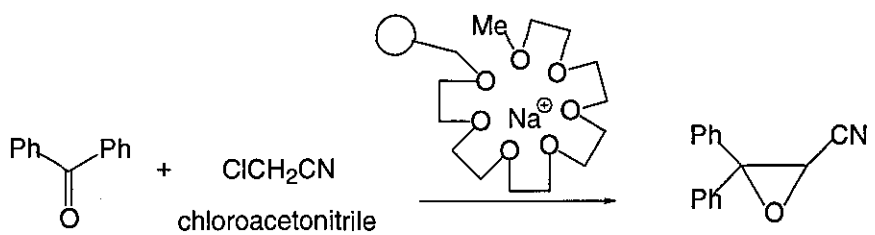
In 1978, Colonna achieved the Darzens reaction of carbonyl compounds with chloromethyl-*p*-tolyl sulfone or with chlorophenyl acetonitrile in a triphasic system of aqueous/organic solvents and polymer-bound catalyst **54** (Scheme 31).[118]



Scheme 31: Darzens reaction catalysed by a polymer-supported ammonium salt

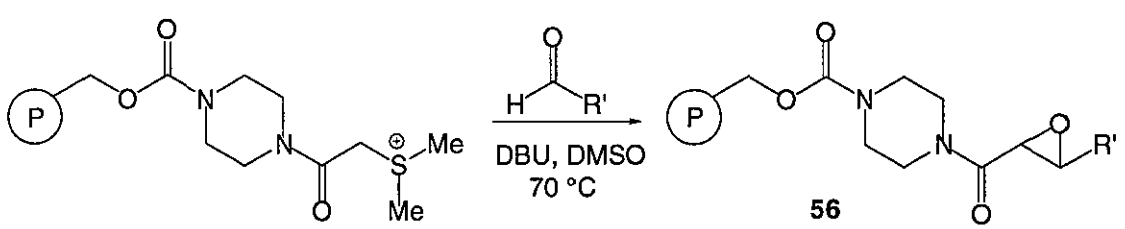
The (–)-*N*-methyl-*N*-methylephedrinium bromide salt **54*** acted as a chiral catalyst in the Darzens reaction and afforded in some cases optically active α,β-epoxy sulfones or nitriles. When the unsymmetrically substituted ketones **55** were submitted to the Darzens reaction conditions, a mixture of *cis* and *trans*-epoxides were obtained. The results indicated that the nature of the substrate influences the diastereoisomeric ratio of the products. Moreover, compared to the soluble ammonium salts, the heterogeneous catalyst afforded an increased optical purity of epoxysulfone, providing up to 23% optical yield versus 2.5% with the homogeneous catalysts. In contrast, the epoxynitrile products resulting from Darzens reaction using the same immobilised catalyst **54**, exhibited lower asymmetric induction than those of the soluble counterparts.

An example of an achiral Darzens reaction in a triphasic system was reported by Yanagida.[119] The technique developed involved the polystyrene-bound poly(oxyethylene) monomethyl ethers as a phase transfer catalyst for the reaction of benzophenone and chloroacetonitrile with powdered anhydrous sodium hydroxide (Scheme 32).



Scheme 32: Darzens reaction usind poly(oxyethylene) monomethyl ethers

Recently, Peschke designed a methodology for the synthesis of a library of amino alcohols.[120] This synthesis involved the preparation of some epoxides on solid support using an immobilised sulfonium ion-mediated Darzens reaction (Scheme 33).



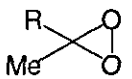
* Absolute stereochemistry not defined

Scheme 33: Polymer-supported epoxidation using a sulfonium ion

The reaction with aromatic aldehydes in the presence of DBU furnished the epoxides **56**, which were then ring-opened with amines to provide the supported amino alcohols. This example illustrates the polymer-supported epoxidation as a synthetic step in the synthesis of a library of compounds. However, the Darzens reaction remains limited, compared to epoxidations of alkenes.

1.3.3) Epoxidation using polymer-supported dioxiranes

Dioxiranes are versatile reagents and environmentally safe oxidants which can be generated *in situ* from ketones and Oxone® (potassium peroxymonosulfate). Alternatively they can be isolated in solution, notably dimethyldioxirane **57** and methyl(trifluoromethyl) dioxirane **58**, which are the most commonly used dioxiranes.

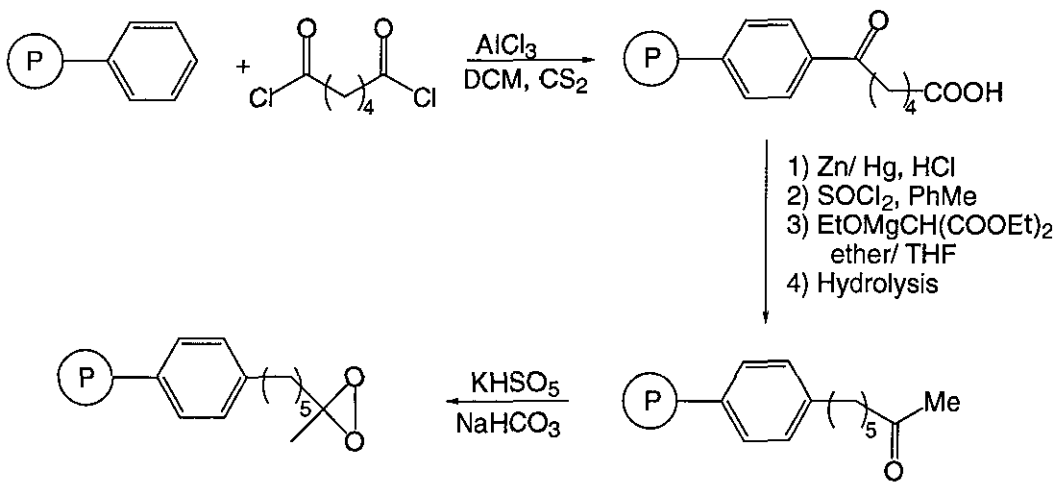


57: R = Me
58: R = CF_3

Dimethyl dioxirane can be prepared at very low temperatures, but is generally unstable at room temperature and towards light. As a consequence, storage at low temperature and in the dark is necessary. Using dioxirane as the stochiometric oxidant in the presence of chiral ketones offers a powerful system for the catalytic asymmetric epoxidation of alkenes.[121] However, the ketone catalyst proved to be unstable under the reaction conditions. Indeed, the catalyst may get involved in competing reactions, including the Baeyer-Villiger oxidation.[122] To minimise the instability of dioxiranes and prevent the decomposition of the ketone catalysts in these epoxidations, the heterogenisation of this oxidant was attempted.

In 1996, Sreekumar synthesised a polymeric dioxirane reagent in six steps, starting from a 2% crosslinked polystyrene-anchored dioxirane resin (Scheme 34).[123] The dioxirane functionality was linked to the polymer through an alkyl chain spacing group. This spacer places the active function away from the resin backbone to facilitate access of the substrate to the active centre.[49] In the case, when the spacer was short (n=0-4) (the

active site being too near to the polymer matrix), the immobilised dioxirane was ineffective, whereas, when the spacing group was long (n=5) the substrate was able to reach the active dioxirane function, thus allowing reaction.



Scheme 34: Synthesis of polystyrene-anchored dioxirane by Sreekumar

Epoxidations of styrene and cyclohexene were achieved using this first resin-bound dioxirane in chloroform at 30 °C, with a substrate/resin ratio of 1:2. No products of over-oxidation were found in the reaction mixture, and easy filtration as well as isolation of the polymer was possible. The dioxirane active species was regenerated on the spent resin by treatment with Oxone® in tetrahydrofuran/water medium, and was reused without any loss of activity for five subsequent reactions.

Interested by dioxirane oxidations, Marples preferred the use of methyl(trifluoromethyl)dioxirane,[124] since it is a more powerful oxidant, available in more concentrated solutions than dimethyl dioxirane.[125] Hence, the solid-supported trifluoro ester **59** was prepared by attachment of the 4-(trifluoroacetyl)benzoic acid to a hydroxymethyl polystyrene/DVB resin, while the catalyst **60** was prepared using the brominated TentaGel® resin and the same benzoic acid derivative. The resin-bound fluoromethyl aryl ketones **59** and **60** were tested as catalysts in the epoxidation of (*E*)-stilbene, (*Z*)-stilbene, cholesterol and (*E*)-chalcone under the conditions shown in Scheme 35.

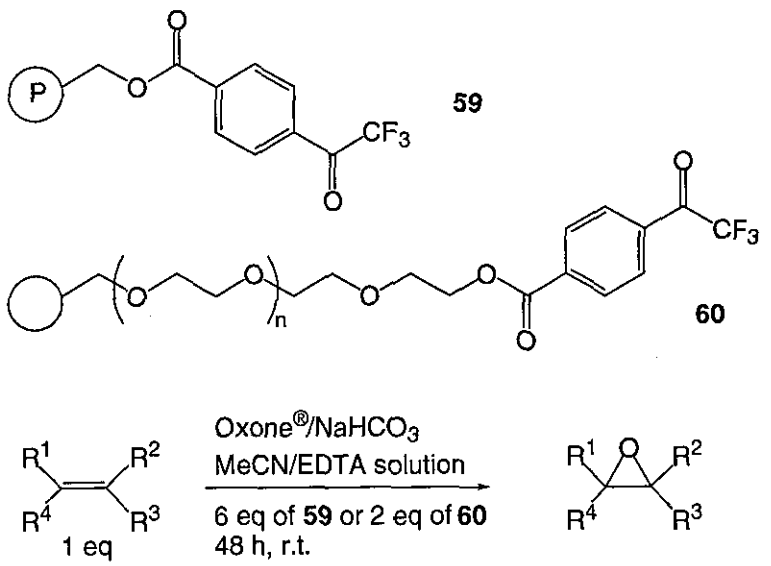


Figure 35: Epoxidation mediated by polymer-supported dioxiranes

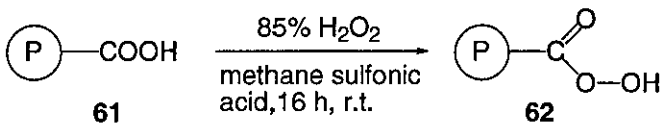
The polystyrene and Tentagel® resins gave epoxides in yields of 9-64% and 13-97% respectively, while in both cases the lowest yields were obtained with (*E*)-chalcone. After epoxidation, the polymeric esters were reported to be reusable many times as *in situ* catalysts in the same reactions.

In addition to the immobilised dioxiranes described above, it is noteworthy that Song outlined the covalent attachment of a trifluoromethyl ketone to a solid support such as silica gel.[126] Inorganic supports are however not detailed in this review.

To conclude, there are very few published examples of immobilised dioxiranes, probably due to the relatively recent emergence of these oxidants. Nevertheless, the immobilisation of ketones can provide better catalyst stability for dioxirane-mediated epoxidations. Therefore, supported dioxiranes require further research to determine the efficiency of this strategy, which is still relatively new.

1.3.4) Stoichiometric epoxidation using polymer-supported peroxy-acids

In 1974, Hodge described the preparation of 1 or 2% DVB crosslinked polystyrene peroxy-acid resins **62** (Scheme 36) and their utilisation as oxidants with various mono-, di-, tri-substituted olefins.[127,128]



61 62

Scheme 36: Formation of polymer-supported peroxy-acid

The polymeric reagent **61** (2 or 3 eq) was suspended in a solution of the olefin in tetrahydrofuran at 40 °C for 4 hours and provided the epoxides in moderate to good yields, except for the monosubstituted olefins, which are known to be rather unreactive towards organic peroxy-acids. The resin-bound peroxy-acid **62** was stable over several months and did not lose any activity when stored at -20 °C. Nevertheless, two main disavantages were noticed. Primarily, the amount of resin used was much higher than the amount of substrate, and secondly some side reactions also occurred. For example, 1-methylcyclohexene was converted to its epoxide which then rearranged to 2-methylcyclohexanone. In addition, a few products contained small amounts of γ-butyrolactone produced by the oxidation of tetrahydrofuran. Moreover, significant quantities of unreacted olefins were retrieved from the reaction mixture.

At the same time, Fréchet was also investigating solid phase oxidations. Frechet's approach to polymeric peroxy-acids was in one way similar to Hodge's method.[129] The insoluble peroxy-acid **62** was prepared by the reaction of a resin bearing a benzoic acid functionality **61** with 70% hydrogen peroxide in *p*-toluene sulfonic acid. Additionally, Frechet described two other routes to these peroxy-acids. In the first pathway, a co-polymer containing benzoyl chloride units underwent peroxidation with a mixture of sodium peroxide and 70% hydrogen peroxide. The second pathway involved a resin containing aldehyde species and ozone, which upon reaction also produced the desired resin **62**. Among the three types of polymer-supported peroxy-acid formation, the carboxylic acid resin **61** was identified as the most useful precursor of peracid **62**. All the heterogeneous peroxy-acids were found to be stable and could be stored at 4 °C for long periods, without loss of activity. While both macroporous and gel-type resins were utilised in the peroxidations, the macroporous polymer afforded quantitative yields and provided more consistent results in repeated reactions. Nonetheless, the gel-type resins were more

active than the macroporous resin in the epoxidation of cyclohexene using a resin/substrate ratio of 1.5:1, in dioxane, dichloromethane or acetone.

Takagi also synthesised several crosslinked poly(acrylic)-bound peroxy-acid resins by oxidation of carboxylic acid-based ion exchange resins with hydrogen peroxide in sulfonic and sulfuric acid media.[130] Each polymeric peroxy-acid was characterised, and it was found that an increase in the crosslinking of the resin caused a diminution of the rate formation of the peracid. The epoxidation of olefins such as cyclohexene, styrene, 2-pentene, cyclododecene and cholesterol were performed in polar solvents such as *tert*-butyl alcohol or dioxane, using the polymer-supported peroxy-acid, and they proved to be faster than with the low molecular weight peracids (*m*CPBA or perbenzoic acid). Takagi's procedure for the epoxidation of cyclohexene was later utilised in undergraduate experiments at Cambridge to illustrate the common avantages of polymer-supported reagents.[131]

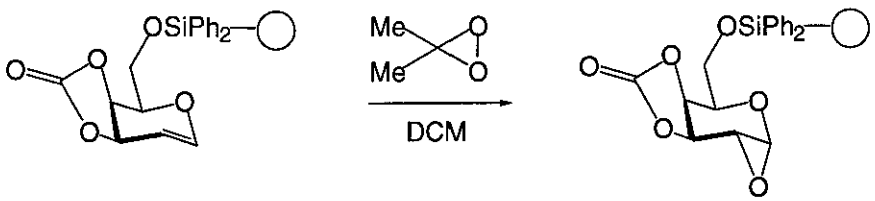
Following the work of Takagi, Hodge, and Fréchet, Pande converted a resin-anchored sulfonic acid into its peroxy-acid by reaction with hydrogen peroxide, in order to check whether this type of resin could successfully act as an oxidising agent in selected organic reactions.[132] Thus, using commercially available cation exchange resins, polymer-supported sulfonic acids were either stirred with potassium persulfate in an aqueous solvent or reacted with hydrogen peroxide to provide the desired persulfonic acids. Both preparations gave identical resins which upon reaction with olefins, namely cyclohexene, styrene, (*E*)-stilbene, vinyl acetate and chalcone produced the corresponding epoxides.

However, the excessive amount of peroxy-acid resin necessary for the reaction to proceed, renders this method impractical. Nevertheless, the importance of epoxide compounds in organic synthesis is undeniable. Several epoxides immobilised on polymeric supports have been used in a number of stereoselective and complex multi-step syntheses of biologically active structures.

1.3.5) Polymer-supported epoxides involved in target syntheses

Efficient sequences for the synthesis of chiral and highly functionalised molecules on solid phase have now emerged due to the new possibilities offered by the field of combinatorial chemistry for the discovery of bioactive substances.

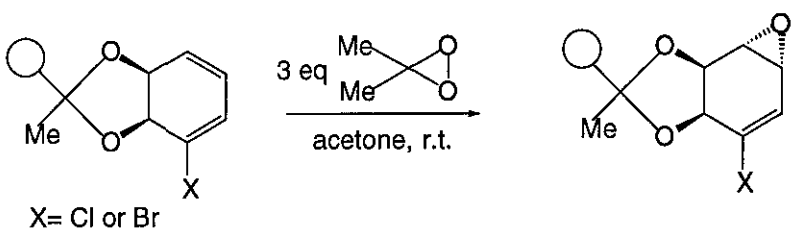
Danishefsky designed a strategy for the solid phase synthesis of oligosaccharides, where glycals were attached to a polystyrene co-polymer and activated with dimethyldioxirane to function as glycosyl donor (Scheme 37).[133]



Scheme 37: Dimethyldioxirane epoxidation of an immobilised glycal

According to Danishefsky, the epoxidation was nearly quantitative and highly stereoselective. As a consequence, this key epoxidation step was included in an iterative strategy leading to a simplified synthesis of oligosaccharides. Two years later, Danishefsky repeated the utilisation of this methodology for the synthesis of polymer-supported glycopeptides.[134]

Recently, Wendeborn successfully transformed resin-bound cyclohexadiene diols into their optically pure epoxides using dimethyldioxirane in acetone (Scheme 38).[135]



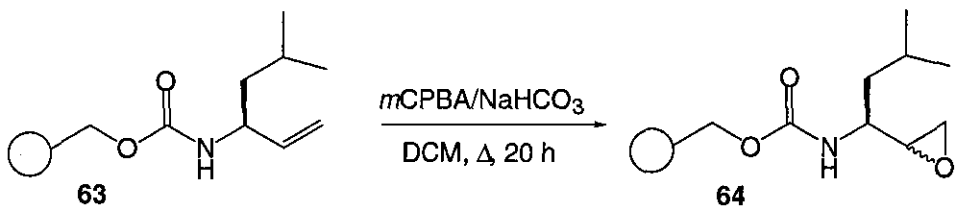
Scheme 38: Dimethyl dioxirane epoxidation of an immobilised cyclohexadiene

The epoxidation took place with complete facial selectivity and was achieved with 92% yield and 95% ee, as deduced by further reaction of the epoxide with dimethylamine

followed by the cleavage of the resin. This epoxidation step contributed to the construction of several highly elaborated structures synthesised for small molecule libraries.

In contrast to the dimethyl dioxirane as the oxidising agent for the polymer-supported epoxide preparation, the widely available *m*CPBA was more commonly considered for achiral epoxidations.

In an approach to peptidomimetics in solid phase, Rotella outlined the epoxidation of the resin-bound allylic amine **63** with *m*CPBA in buffered dichloromethane, which gave the epoxide **64**. The stereoselectivity was not defined, but described as only modest (*anti* > *syn*), probably due to the elevated temperatures employed (Scheme 39).[136]

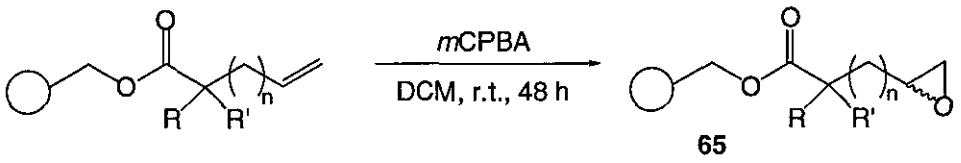


63 **64**

Scheme 39: Epoxidation of an immobilised allylic amine

The epoxidation step permitted the solid phase synthesis of peptides which could be further expanded to the preparation of various libraries useful for enzyme inhibitor studies.

Carreaux and David were interested in the synthesis of functionalised γ- and δ-lactones, due to their importance in insect pheromones, antifungal substances and flavour components.[137] They synthesised polymer-anchored epoxides as convenient precursors of γ- and δ-lactones. The alkenoic acids used as starting materials were bound to 1% crosslinked polystyrene/DVB co-polymer and the resulting resin was submitted to epoxidation with *m*CPBA to furnish the oxirane **65** (Scheme 40).

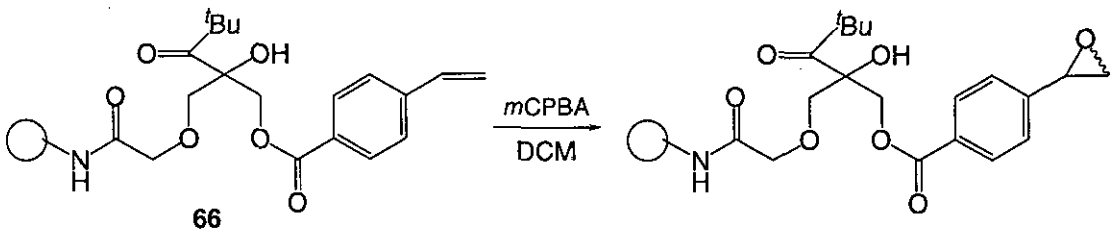


a) n = 1, R = H, R' = H
b) n = 1, R = H, R' = Me
c) n = 1, R = R' = Me
d) n = 2, R = H, R' = H

Scheme 40: Epoxidation of immobilised olefins

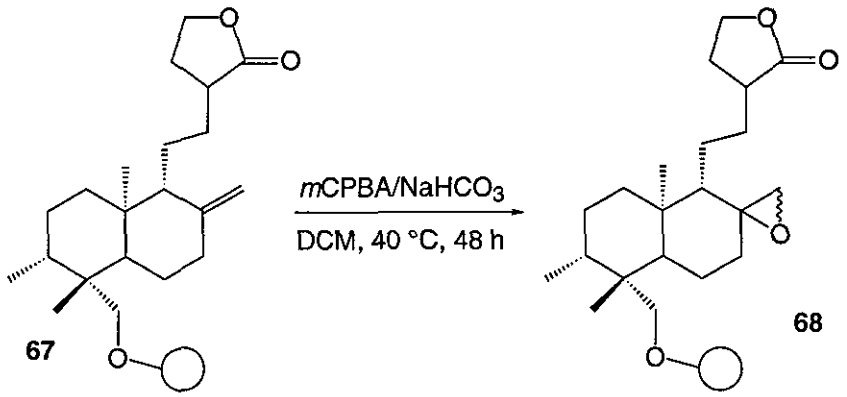
The conversion of the alkene to the epoxide was complete since the FT-IR monitoring showed the disappearance of the carbon-carbon double bond absorption.

In order to demonstrate the wide applicability of a newly synthesised photolabile anchored linker in solid phase synthesis, Giese performed the epoxidation of the resin bound vinylbenzoic acid **66** with *m*CPBA in dichloromethane to yield 65% of resin tethered epoxide (Scheme 41).[138]



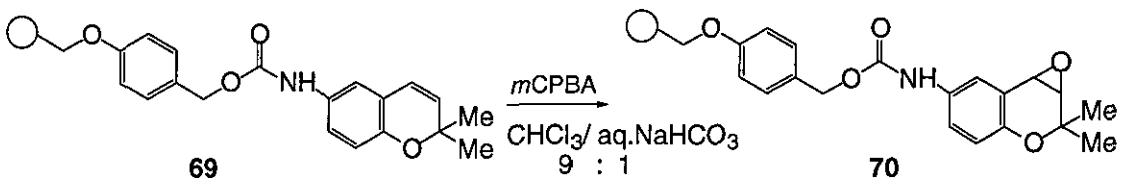
Scheme 41: Epoxidation of an immobilised vinylbenzoic acid derivative

Very recently, Kundu and Biabani aimed to generate a combinatorial library based on diterpenoid lactone derivatives,[139] since these moieties possess many biological activities.[140] Several classical reactions were carried out on solid phase to provide a variety of novel compounds which could then serve as good precursors for the generation of structurally diverse derivatives. Hence the selective epoxidation of the exocyclic carbon-carbon double bond of **67** with *m*CPBA/$NaHCO_3$ afforded the epoxide product **68** (Scheme 42).



Scheme 42: Epoxidation of an immobilised terminal olefin in a diterpenoid lactone

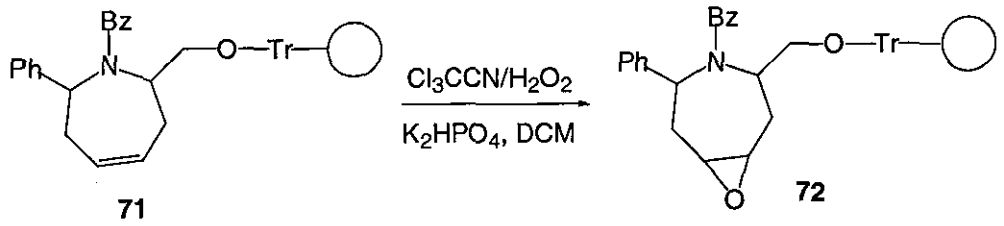
In Korea, Yoo investigated the epoxidation conditions of polystyrene-supported chromene derivatives for the synthesis of a library of benzopyrans.[141] Under normal oxidation conditions with *m*CPBA in dichloromethane, the substrate **69** furnished a product resulting from the preferential ring-opening of the epoxide intermediate, probably due to the presence of excess *m*CPBA. Although various oxidants such as Oxone®, dimethyldioxirane, H_2O_2, ^tBHP and sodium perchlorate were examined in dichloromethane, acetone or water media, the epoxidation failed to give the desired product. It was finally found after assessing several solvent systems, that a biphasic solvent system consisting of chloroform and saturated aqueous sodium carbonate was an effective medium to effect the epoxidation of **69** to **70** in satisfactory yield (Scheme 43).



Scheme 43: Epoxidation of an immobilised chromene derivative

The reason for this success may be the ability of the basic aqueous solution to remove the excess of *m*CPBA.

The final example of polymer-supported epoxide synthesis was applied to the resin-bound functionalised azacycles.[142] Epoxidation of compound **71** with the Cl_3CCN/H_2O_2 system[143] provided the epoxide **72** in good yield (Scheme 44).



71 72

Scheme 44: Epoxidation of an immobilised azacycle

To conclude, the commercial importance of epoxidation reactions has led to numerous investigations of polymer-supported catalysts. The majority of these studies involves a metal complex as chiral catalyst and, although their effectiveness is undoubtedly demonstrated, most systems still suffer from metal leaching. Therefore, due to environmental and economical requirements, this problem must be solved before industrially viable processes can be developed. Regarding the metal-free epoxidations, the peroxy-acid method was found impractical, while the Julià and Darzens reactions only succeed with specific substrates, and the supported dioxirane-mediated epoxidation needs to be further evaluated. The asymmetric epoxidation of unfunctionalised alkenes thus remains a vast domain of intensive research and new strategies towards chiral epoxides continue to be created. However, the development of a solid phase methodology usually stems from preliminary studies in solution phase. More often, it is only after exhaustive examinations of the homogeneous systems that the solid phase adaptation is implemented.

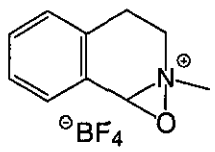
Recently, a homogeneous iminium salt catalysed asymmetric epoxidation method for unfunctionalised alkenes has been developed.[144]

1.4) Solution phase epoxidations using iminium salt catalysts

1.4.1) Introduction

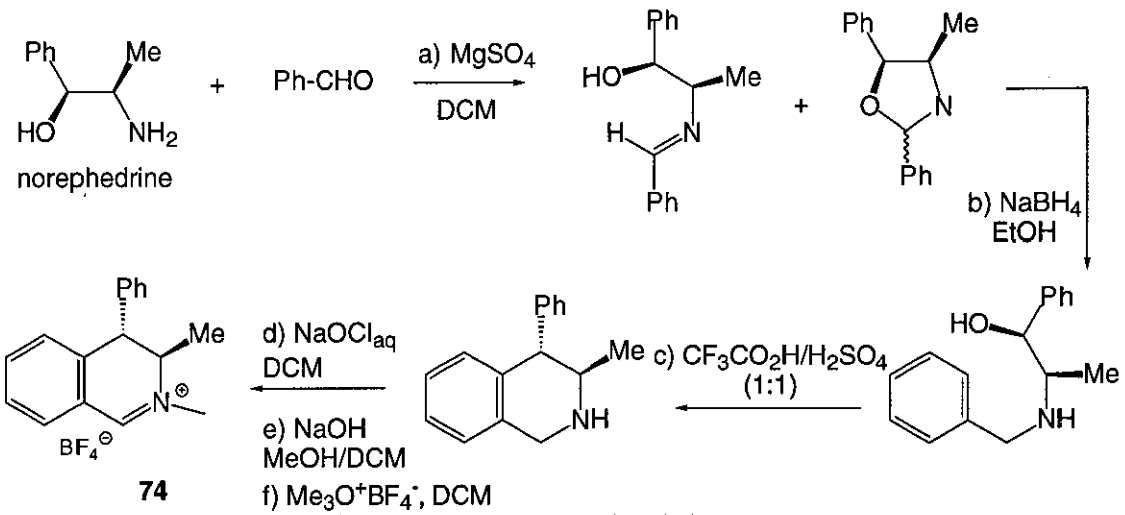
The development of iminium salts as epoxidation catalysts stem from the identification of oxaziridinium salts as reactive intermediates by Hanquet and Lusinchi.[145] The electrophilic character of oxaziridinium salts was evaluated for the epoxidation of alkenes[146,147] and oxidation of sulfides.[148] The oxaziridinium fluoroborate salt **73** was

found to react faster and more stereoselectively with stilbenes than did peracids such as *m*CPBA or *p*-nitroperbenzoic acid.



73

Oxaziridinium salts can be prepared *in situ* from iminium salts and an oxidant. Hence, in 1991, the iminium salt **74** was reported to catalyse alkene epoxidations under basic conditions using Oxone® as the stoichiometric oxidant.[149] The tetrahydroisoquinoline precursor of this chiral iminim salt was prepared in three steps from norephedrine by an intramolecular Friedel-Crafts alkylation (Scheme 45).[150-152]

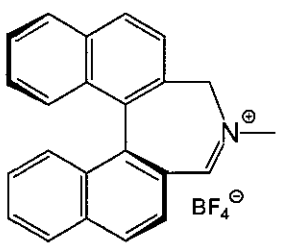


Scheme 45: Synthesis of the iminium salt **74**

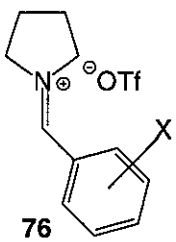
The stereoselective cyclisation was primarily facilitated by the ease of the benzylic cation formation. Secondly, the steric hindrance between the phenyl and methyl groups forced the two substituents to adopt *trans*-diequatorial position across the heterocyclic ring in compound **74**. The stereoselectivity of the epoxidation process and the influence of the functionalities neighbouring the double bond were evaluated.[153]

Attracted by the pioneering work of this French group, Aggarwal synthesised an enantiopure iminium salt **75** based on the binaphthyl moiety, and derived from an intramolecular condensation of a carbonyl group and an amine.[154] Thus, 72% and 33% ee

were obtained for the epoxidation of 1-phenylcyclohexene and (*E*)-stilbene respectively. While Aggarwal used an expensive BINAP derivative as starting material, thus rendering the synthesis of a wide range of iminium salts prohibitively expensive, Amstrong evaluated several exocyclic iminium triflate salts (**76**) derived from pyrrolidine and activated aromatic aldehydes.[155]



75



76

X = H, *p*-MeO, *p*-Cl, *o*-Cl, *o*-CF_3, 2,6-dichloro

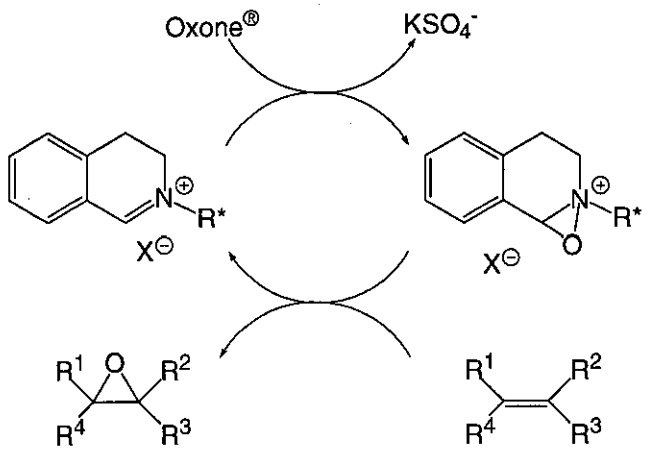
The catalytic activity of these salts was tested for the epoxidation of unfunctionalised alkenes with Oxone® in acetonitrile/water. In spite of the good conversion of the olefins to the corresponding epoxides, attempts to prepare chiral variants of **76** remained unsuccessful, presumably due to their ready hydrolysis.[156]

In the Page group, the approach to iminium salts was based on the incorporation of the asymmetric centre on an exocyclic carbon atom in the nitrogen substituent of a dihydroisoquinolinium salt, derived from a chiral amine (Scheme 46). The idea was thus to insert an asymmetric centre closer to the site of the oxygen transfer than in Lusinchi's system.

Scheme 46: Introduction of a chiral centre on the nitrogen atom

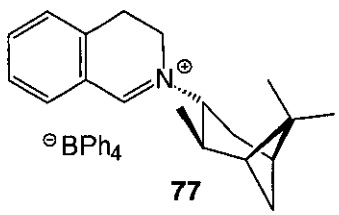
The iminium salts, prepared by condensation between 2-(2-bromoethyl)benzaldehyde and a wide range of chiral amines, were found to be effective as asymmetric epoxidation catalysts.[157] Typical oxidation conditions, using Oxone® (2 eq) as oxidant, acetonitrile/water (1:1) as solvent, sodium carbonate (4 eq) as base, and 0.5-10 mol% of

dihydroisoquinolinium salt as catalyst, were used to investigate the epoxidation of 1-phenylcyclohexene. The mechanism of epoxidation that is thought to be in operation is illustrated in Scheme 47.



Scheme 47: Mechanism of the epoxidation with Oxone® and the iminium salts

One of the more selective catalysts, the *N*-isopinocampheylamine derivative **77**, afforded 73% ee for (*E*)-stilbene as substrate.



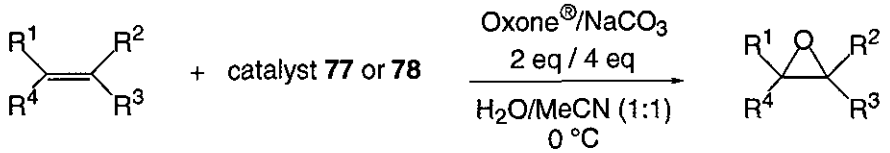
77

A complete retention of double bond stereochemistry was observed. In additon, this catalyst was readily available in both enantiomeric forms, as both enantiomers of the parent amine are commercially available.

The effectiveness and selectivity of the process is governed by a number of factors, including the structure of the substrate, the concentration, the catalyst loading, the solvent system, the temperature, the counter-ion involved, and particularly the catalyst structure.[158] Therefore a diverse range of iminium salts were synthesised and tested for the catalytic asymmetric epoxidation of 1-phenylcyclohexene. Among the various iminium structures assessed, catalysts derived from amino ethers were examined and are discussed below.

1.4.1.1) Dihydroisoquinolinium salts derived from amino ethers

Among the catalysts prepared from aminoethers, that derived from 5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (**78**) furnished moderate yields of epoxides with reasonable degrees of enantioenrichment. This catalyst was evaluated in the catalytic epoxidation of several simple alkenes under the conditions depicted in Scheme 48.

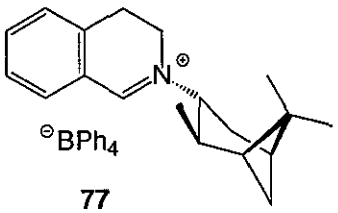


Scheme 48: Epoxidations conditions using soluble iminium salt catalysts

The results obtained with catalyst **78** can be compared to the performance of **77** in Table 5. These data show that the dioxane mediator **78** is less substrate specific than the terpenoid **77** or any other derivative tested. These two catalysts afforded the best enantioselectivity for the epoxidation of several unfunctionalised alkenes. Nonetheless, other catalysts were also evaluated.

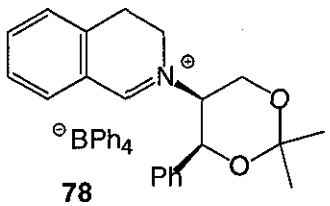
Table 5: Epoxidations conducted with 5 mol% of catalysts under standard conditions

Isopinocampheylamine-derived catalyst

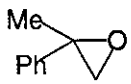
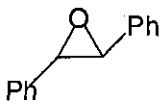
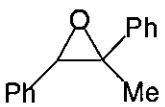
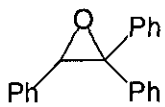
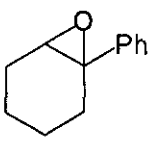
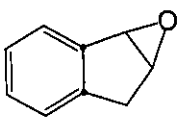
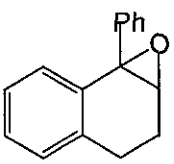


77

Dioxane-derived catalyst



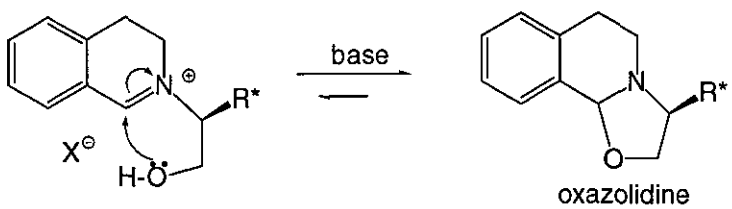
78

Epoxide	Isolated yield % / **ee** %		Isolated yield % / **ee** %	
	68	**8**	64	**20**
	73 75	**68** **73** *	48	**43**
	72	**15**	52	**47**
	43	**5**	54	**58**
	68	**40** *	55	**40**
	34	**3**	52	**17**
	73	**63**	64	**50**

* 10 mol% of catalyst was used

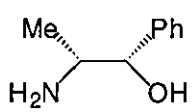
1.4.1.2) Dihydroisoquinolinium salts derived from amino alcohols

Catalysts derived from chiral amino alcohols with a primary hydroxyl group were investigated for the epoxidation, but disappointingly these iminium salts produced almost racemic epoxides. It was noticed that the rate of the catalytic process was slow compared to that exhibited by the mediators without the pendant hydroxyl group. This observation was rationalised as being a result of the equilibrium between the iminium salt and the corresponding oxazolidine, which is not expected to be catalytically active. Moreover, the oxazolidine is thought to be the predominant component under the alkaline conditions employed in the reaction (Scheme 49).[159]



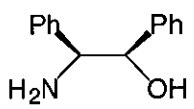
Scheme 49: Oxazolidine formation in basic conditions

However, the dihydroisoquinolinium salts derived from amino alcohols bearing a secondary hydroxyl group proved to be more enantioselective in epoxidation reactions. For example, the norephedrine derived iminium salt **79** catalysed the epoxidation of 1-phenylcyclohexene with enantioselectivity of 30% ee, while the 1,2 diphenyl derivative **80** furnished the same epoxide with 24% ee. The yields of epoxides were *ca.* 60%.



(1S,2R)-norephedrine

79



(1R,2S)-1,2-diphenyl-2-amino ethanol

80

Catalyst improvments are still necessary and therefore, further investigations are underway in order to attain higher asymmetric induction. For this purpose, two strategies can be considered: i) further variations of the structure of the homogeneous iminium

catalyst,[160] and ii) the immobilisation of iminium salts on polymer supports to permit the evaluation of numerous catalysts through combinatorial or parallel libraries. Tempted by the attractive features of solid phase chemistry and the challenging task of developing solid phase techniques in our laboratory, we decided to undertake the heterogenisation of the catalysts involved in the asymmetric epoxidation of functionalised and unfunctionalised alkenes.

1.5) Research project purpose

The aim of this work is to develop heterogeneous catalysts which will enable the catalytic enantioselective epoxidation of a variety of olefins under simple conditions. Toward this goal, the simple homogeneous methodology previously outlined for the iminium salt catalysed asymmetric epoxidation, could be combined with polymer-supported synthesis, and hence permit the identification of active polymer-bound catalysts. In addition, attaching the isoquinoline derivatives to a solid support would make the preparation and utilisation of these catalysts much simpler. Thus, to determine optimum reaction conditions which would allow effective stereoselective epoxidation, we initially investigated the adaptation of the solution phase method for the solid phase synthesis. This first step then led to the preparation and evaluation of a range of immobilised catalysts, thus identifying the suitable combinations of catalyst and support for the heterogeneous oxidation reaction. We also examined the influence of the substrate nature in the process. Finally, the synthesis of a catalyst precursor which would allow the efficient catalyst screening power of solid phase chemistry was attempted.

Chapter 2: RESULTS and DISCUSSION

2.1) Resins, some general aspects

To carry out polymer-supported reactions, great care must be taken in designing, preparing and using heterogeneous systems. Indeed, it is fundamental to identify the suitable polymeric matrices required for optimal performances. In order to achieve this identification, the most important factor to consider when dealing with solid phase resins is the swelling factor.[161] The swelling characteristics are affected by factors such as the degree of crosslinking, the hydrophobicity of the substrate and the nature of the core matrix itself. The swelling property is important in that reaction kinetics in solid phase organic synthesis are often diffusion-controlled. Therefore, a resin that swells more will have a higher diffusion rate of substrate into the core of the matrix, resulting in shorter reaction times and more complete chemical conversions. Another factor to consider is the shaking mode, which can be kinetically important, as the most efficient reaction mixing method will maximize encounters between the solid-bound reactant and the soluble reagent,[162] thus also shortening the reaction time.

2.1.1) Resin structures

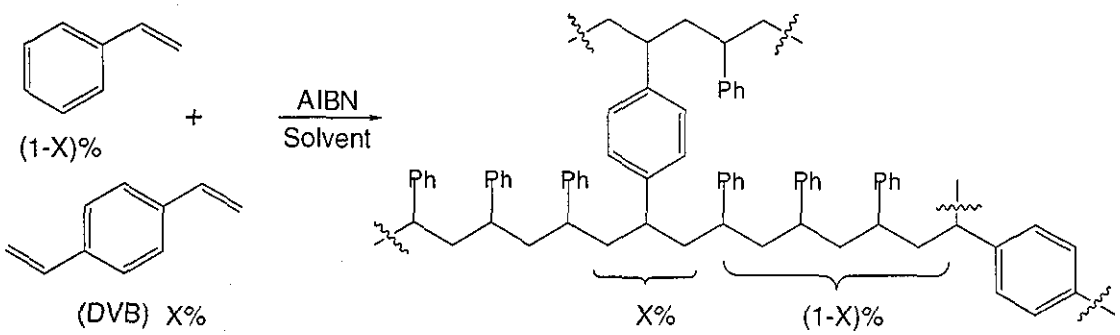
Currently, two main types of resin matrices are routinely used for solid phase organic synthesis:

- Polystyrene crosslinked with 1 or 2% DVB.

- TentaGel® resin, which is a polystyrene-polyethylene glycol graft co-polymer.

2.1.1.1) Polystyrene resin

Polystyrene crosslinked with divinylbenzene is the polymeric support most commonly used in solid phase organic synthesis. Polystyrene/DVB resins, also known as Merrifield resins, are obtained by radical polymerisation (Scheme 1).

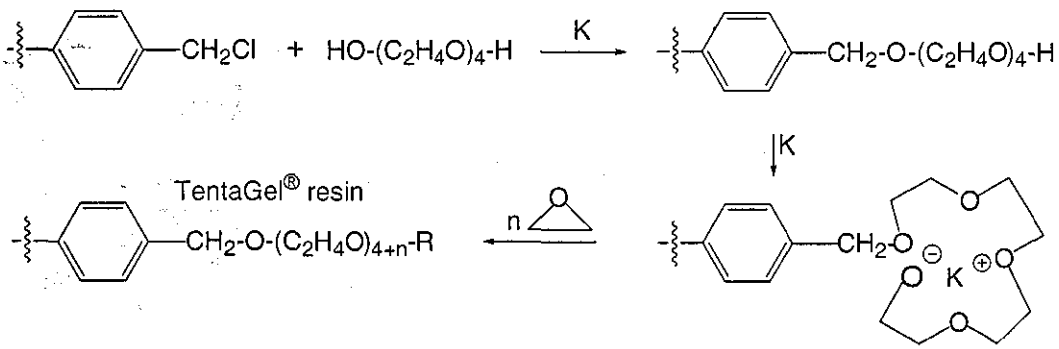


Scheme 1: Synthesis of polystyrene resin

This system was first used by Merrifield in 1963 and consists of polystyrene with a chloromethyl functionalisation.[10] The polystyrene matrix is a hydrophobic resin which swells in apolar solvents such as toluene and dichloromethane, but does not swell in polar solvents such as water and methanol. The percentage of crosslinking is responsible for the general physico-chemical behaviour and mechanical stability of the polymer. Those which have 1 or 2% DVB crosslinkage are normally employed; but the latter is favoured for reactions at elevated temperatures or for those involving organometallic reagents.[14] Polystyrene beads are available in diameter sizes ranging from less than a micron to 750 microns. Bead size is commonly reported in Tyler Mesh size which is inversely proportional to the nominal diameter. The two most commonly used resin sizes are 100-200 and 200-400 mesh (75-150 micron and 35-75 micron respectively). In addition, the polystyrene backbone has a loading capacity varying between 0.6-4.3 mmol/g, this being significantly higher than that of TentaGel® resin.

2.1.1.2) TentaGel® resin

TentaGel® resins[163] are graft co-polymers with polystyrene backbones and polyethylene glycol (PEG) chains. These co-polymers usually contain about 70% of linear PEG and only about 30% of crosslinked polystyrene matrix. The properties of these supports are therefore largely determined by the PEG portion of the molecules. The synthesis of polyethylene glycol-polystyrene (PEG-PS) graft co-polymer is carried out by anionic polymerisation of ethylene oxide (Scheme 2).



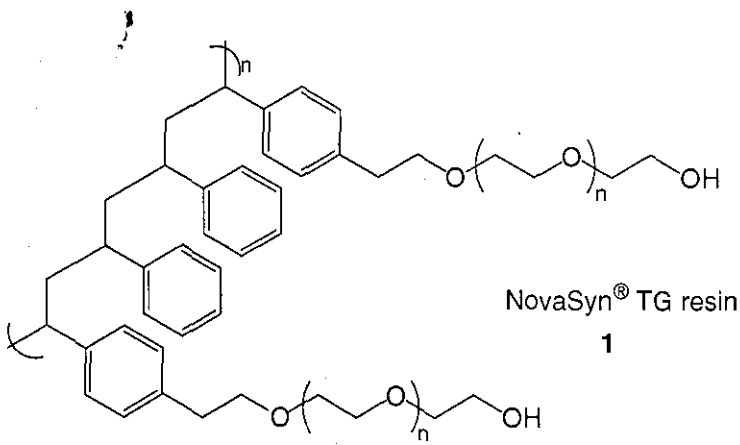
Scheme 2: Synthesis of TentaGel® resin

Each polymer bead made from a bulk sample has uniform bead size. The total reaction space, located in the polymer support, is divided into small and equal spaces. The effect upon the reaction is that identical conditions are encountered at each bead at any time. A correlation of particle size and capacity per single bead shows that beads between 90 μm and 130 μm have a much higher capacity than those ranging from 10 μm to 750 μm. The 90 μm bead size resin is generally preferred for peptide libraries, whereas the higher capacity of the large beads make the 130 μm resin ideal for the production of non-peptidic libraries.[22] These resin beads have a narrow size distribution and a loading *ca.* 0.4 mmol/g of resin. They swell in water and in almost all organic solvents with the exception of aliphatic hydrocarbons and diethyl ether.

More recently, other resin types have been employed in various reactions and due to their interesting properties and the rapid development in the solid phase area, several resins have become readily available commercially. Four of these resins, that were tested during this research work, are highlighted below.

2.1.1.3) NovaSyn® TG resin

These resins are based on a composite of low crosslinked hydroxyethylpolystyrene and polyethylene glycol, which has been terminally functionalised.[22] The resin swells in a wide range of solvents from toluene to water. The environment provided by the PEG is thought to resemble closely that found in tetrahydrofuran. In NovaSyn® TG resin (**1**), the PEG chain is not anchored to the polystyrene backbone through an acid-sensitive benzylic ether but rather through a more acid-stable ethyl ether. The loading is essentially the same as for the TentaGel® resin.



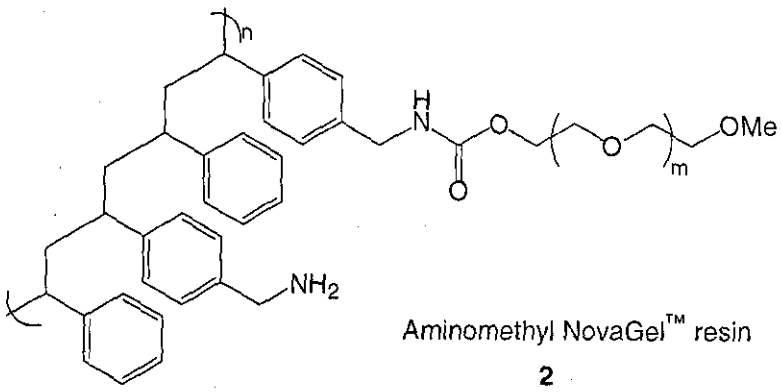
NovaSyn® TG resin

1

Sometimes, the use of these resins has been associated to the leaching of PEG. This phenomenon arises through formation of PEG peroxides by the action of oxygen and light during long-term storage. This degradation is an intrinsic property of all PEG resins.

2.1.1.4) NovaGel™ resin

NovaGel™ is a new type of PEG-PS resin that has been designed to provide resins of high substitution with broad solvent compatibility.[22] NovaGel™ resins are prepared from a special high-swell version of aminomethyl polystyrene resin by partial derivatisation with methyl PEG-*p*-nitrophenylcarbonate.



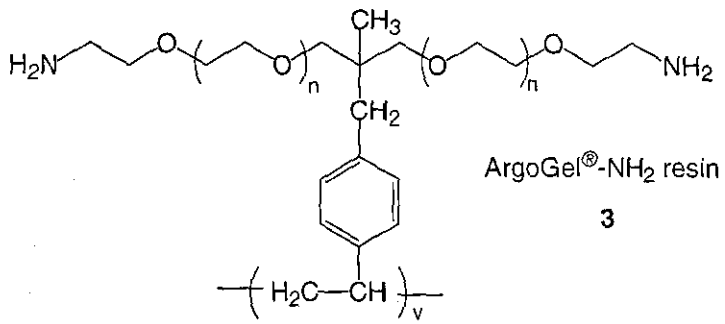
Aminomethyl NovaGel™ resin

2

The resin contains approximately 48% PEG, with a loading of 0.7 mmol/g (almost twice that of conventional PEG-PS supports), which swells in solvents of widely different polarities. The urethane linkage between the PEG and the base resin is stable to strongly acidic, basic and reducing conditions, ensuring minimal loss of PEG chains during synthesis. However, if leaching of PEG does occur, this does not result in loss of amine substitution as can be the case with other PEG-PS-based resins, because the free amino group is not attached to the end of the PEG chains, but on the polystyrene.

2.1.1.5) ArgoGel® resin

The graft component of ArgoGel® is a bifunctional PEG chain attached to the polystyrene backbone.[164] This effect results in ArgoGel resins (**3**) having approximately twice the loading of TentaGel® resins, with values typically ranging from 0.4-0.55 mmol/g for functionalised resin. ArgoGel® resin exhibits excellent swelling properties in a range of solvents from strongly polar protic to moderately polar aprotic.

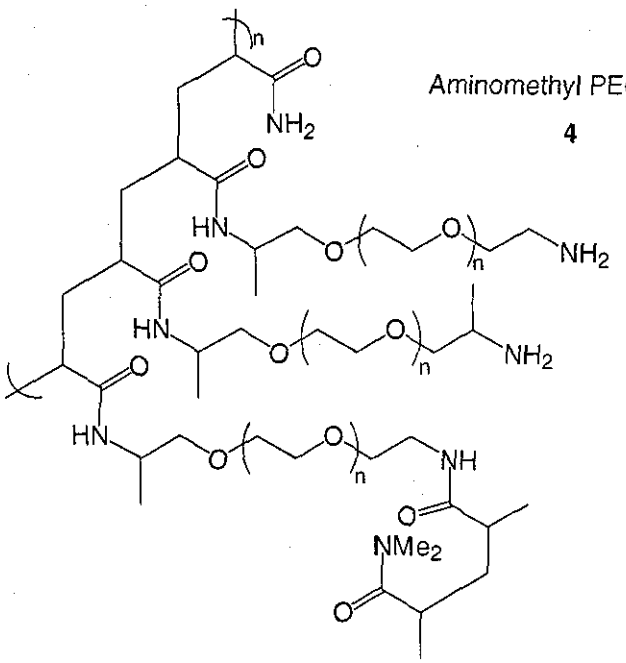


ArgoGel®-NH_2 resin

3

2.1.1.6) PEGA resin

Acryloylated bis-aminopropyl polyethylene glycol resins, also called PEGA resins are a new range of hydrophilic resins that consist of 2-acrylamidoprop-1-yl-(2-aminoprop-1-yl) polyethylene glycol and dimethylacylamide crosslinked with bis 2-acrylamidoprop-1-yl polyethylene glycol.[22] In simple terms, PEGA resin (**4**) is a polyacrylamide polymer possessing long polyethylene glycol spacers, and a loading of 0.4 mmol/g.



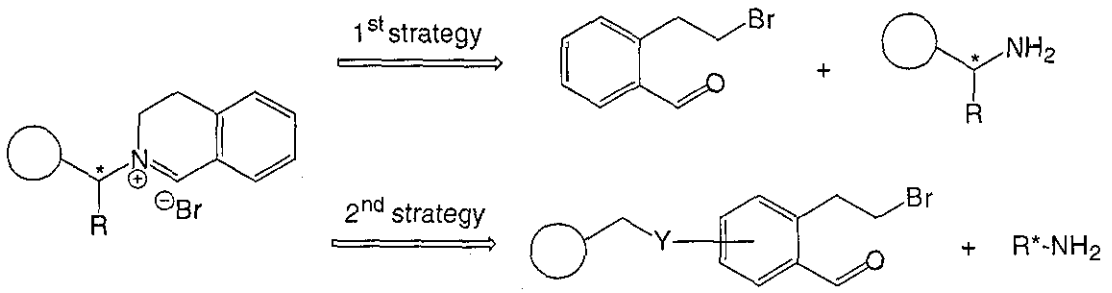
These supports swell extensively in a wide range of solvents and are freely permeable to macromolecules.

Due to the different properties of all these resin structures, it was envisaged that the evaluation of these supports for the reactions developed in our laboratory would be beneficial.

2.2) Strategies for the immobilisation of iminium salts

The initial aim of this work was to adapt the solution phase catalysed reaction conditions to suitable polymer-supported systems. To synthesise polymer-supported iminium salt catalysts, two routes have been envisaged (Scheme 3). The first strategy involves the attachment of the soluble 2-(2-bromoethyl)benzaldehyde to resin-bound

chiral amines. In the second route, the (bromoethyl)benzaldehyde was immobilised onto a polymer-support, and subsequently linked to soluble chiral amines.



Scheme 3: Two strategies for the synthesis of polymer-supported iminium salt catalysts

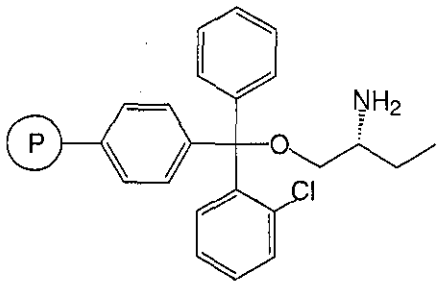
The second method offers the advantage of screening a large variety of chiral amines for iminium salt library synthesis. Hence, a wide range of iminium salts could be tested as potential epoxidation catalyst. This method has been discussed in section 2.8. However, at the beginning of this research, it appeared to be more convenient to start this work with the first strategy, as the techniques of solid phase chemistry had to be introduced for the first time in our group. Additionnally, since large quantities of (bromoethyl)benzaldehyde could easily be prepared in our laboratory, and since resin-supported chiral amines are commercially available, the first method would allow more rapid access to heterogeneous salts than does the second pathway.

2.3) First strategy for the immobilisation of the catalyst

The immobilisation of iminium salt catalysts onto commercially available resins was investigated by attaching the (bromoethyl)benzaldehyde to polymer-supported amines. To synthesise the first chiral polymer-bound iminium salt, the chiral amino ether (*R*)-(–)-2-aminobutan-1-ol 2-chlorotrityl resin (**5**), was selected from a resin catalogue as a suitable polymeric precursor of the catalyst. This chiral resin based on 2-chlorotrityl polystyrene/1% DVB matrix was identified as the only polymer support containing a chiral amino alcohol. Since iminium salts derived from amino alcohols (secondary hydroxyl group) proved to afford promising enantioselectivity (section 1.4.1.2), it seemed intersting to choose a polymer-supported derivatised amino alcohol. However, because of

the high cost of this chiral resin (£ 75.00/g), we initially decided to utilise an achiral resin, in order to set and optimise the solid phase reaction conditions. Hence, the non-chiral glycinol 2-chlorotrityl resin (**6**) which was chosen from the same supplier, was identified as the nearest analogue of the chiral resin **5**.

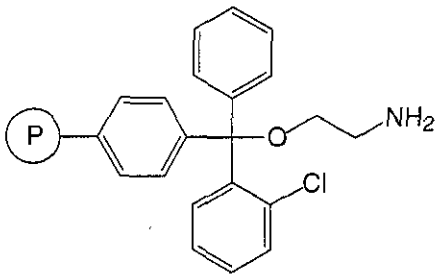
Chiral



(R)-(–)-2-Aminobutan-1-ol 2-chlorotrityl resin

5

Non-chiral



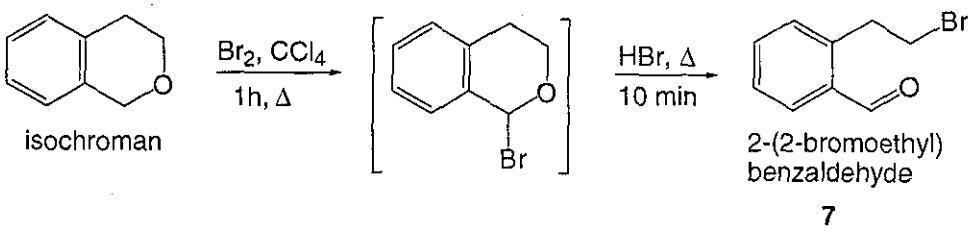
Glycinol 2-chlorotrityl resin

6

This achiral resin was thus selected to serve as the polymeric support for the immobilisation of the iminium salt catalyst. Nevertheless, in order to compare the reactivity of the polymer-supported iminium salts with the related unsupported analogues, preliminary work with the corresponding chiral and achiral catalysts in solution was necessary.

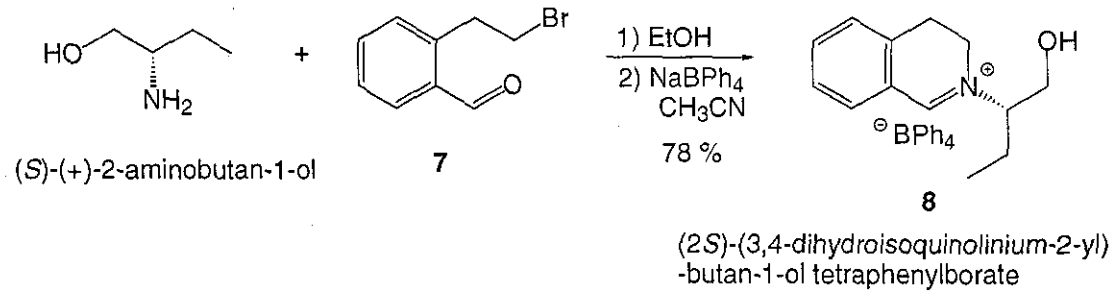
2.3.1) Preliminary reactions with soluble catalysts

Solution phase reactions were completed in order to obtain analytical data on the soluble iminium salts **8** and **9** corresponding to the supported iminium salts derived from **5** and **6**. The synthesis of these homogeneous dihydroisoquinolinium salts starts from the key intermediate 2-(2-bromoethyl)benzaldehyde (**7**), which was prepared from isochroman according to the procedure described by Rieche and Schmitz (Scheme 4).[165] Bromination of isochroman gave 1-bromoisochroman, which was reacted *in situ* in acidic conditions to furnish the compound **7** in 90% crude yield from 60.0 g of isochroman.



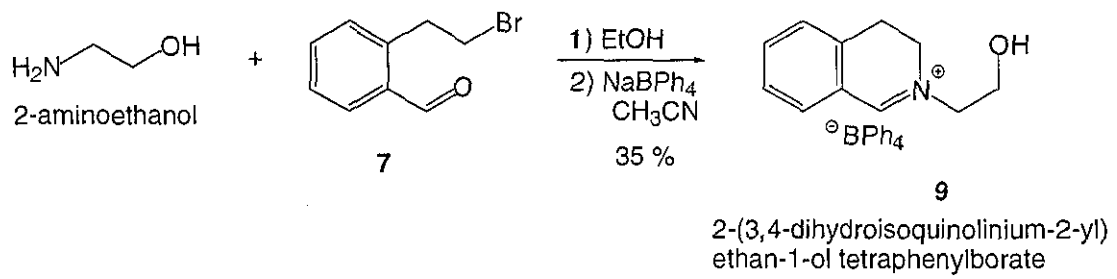
Scheme 4: Synthesis of the 2-(2-bromoethyl)benzaldehyde

After distillation, this benzaldehyde **7** was reacted with (*S*)-(+)-2-amino-butan-1-ol in ethanol, and the resulting iminium bromide was subjected to anion exchange by treatment with sodium tetraphenylborate to give the corresponding tetraphenylborate salt **8**, as a crystalline product (Scheme 5).



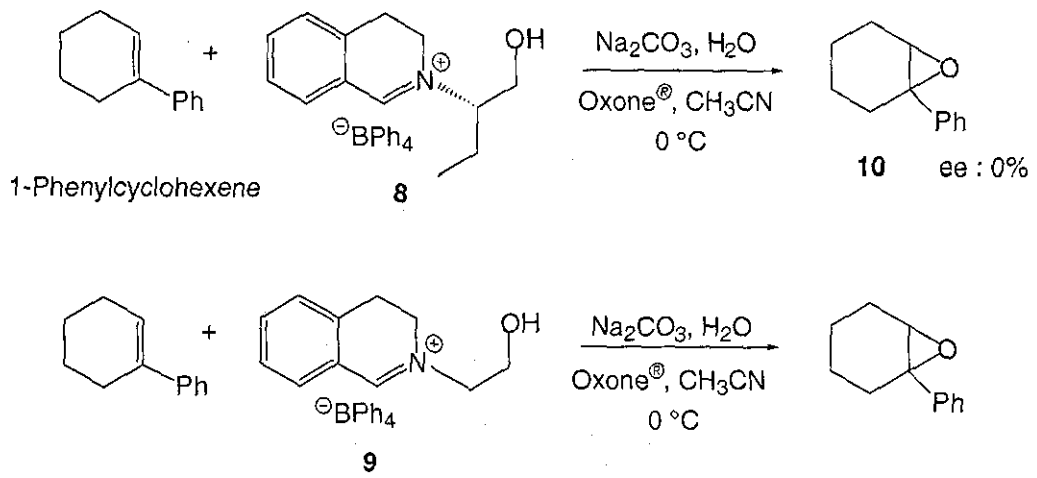
Scheme 5: Synthesis of the chiral iminium salt **8** from the (bromoethyl)benzaldehyde

The same reaction was performed using 2-aminoethanol, and furnished 35% yield of the salt **9** (Scheme 6). The low yield of the reaction can be explained by the slow reaction rate of the condensation between the amino alcohol and the benzaldehyde derivative, presumably caused by the equilibrium between the iminium salt and the oxazolidine discussed in section 1.4.1.2.



Scheme 6: Synthesis of the achiral iminium salt.

The efficiency of each of the catalysts **8** and **9** was tested for the epoxidation of 1-phenylcyclohexene using 2 equivalents of Oxone® and 4 equivalents of sodium carbonate in acetonitrile/water (2:1) (Scheme 7).



Scheme 7: Epoxidation of 1-phenylcyclohexene mediated by iminium salts

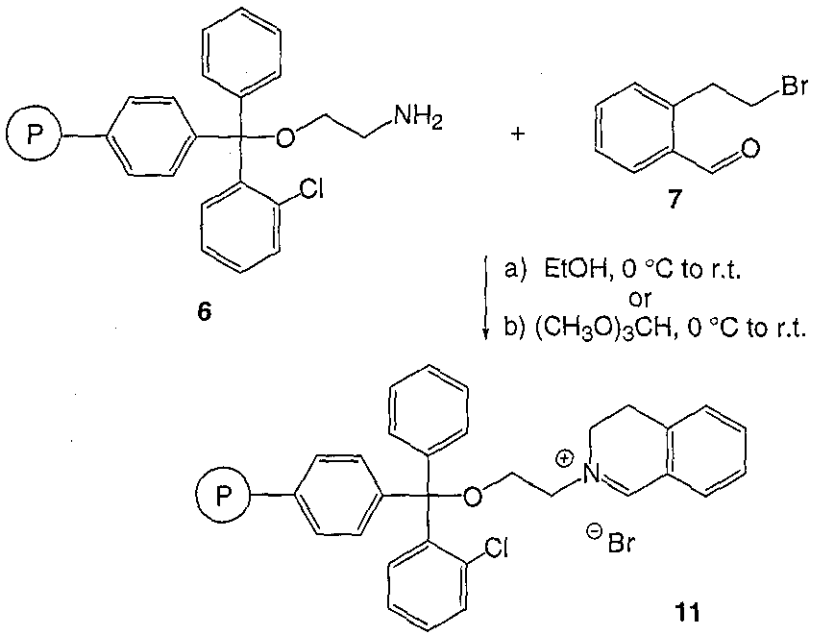
Both catalysts **8** and **9** gave complete conversion of the alkene to the epoxide in less than 3 hours. However, as expected from earlier work with such amino alcohol derivatives,[144] the chiral iminium salt **8** did not induce any enantioselectivity in the formation of the epoxide.

Having prepared the catalysts **8** and **9** in solution phase and achieved the epoxidation, the synthesis of the related dihydroisoquinolinium salts on solid phase was initiated.

2.3.2) Solid phase reactions using the 2-chlorotrityl polystyrene resin

Glycinol 2-chlorotrityl resin was condensed with the benzaldehyde **7** to give our first polymer-supported iminium salt **11** (Scheme 8). Prior to reaction, the resin beads were swollen in dichloromethane, since this solvent is known to diffuse well into the polystyrene beads. The synthesis of the iminium salt **11** was performed with two equivalents of 2-(2-bromoethyl)benzaldehyde, from 0 °C to room temperature (r.t.), either in ethanol as in the solution phase procedure, or in trimethylorthoformate, since the latter is a good dehydrating agent, reported by Gallop for the formation of imines.[166]

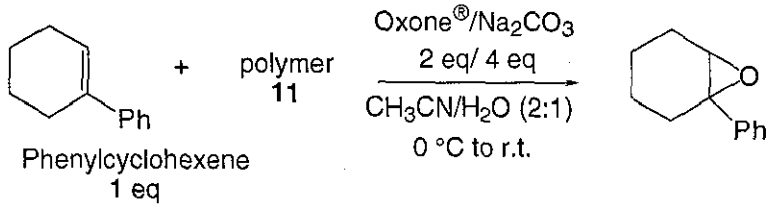
Furthermore, the reaction mixture was agitated overnight with an orbital shaker, to avoid the magnetic stirring which could damage the beads, rendering inadequate their reuse.[24]



Scheme 8: Synthesis of the immobilised catalyst **11**

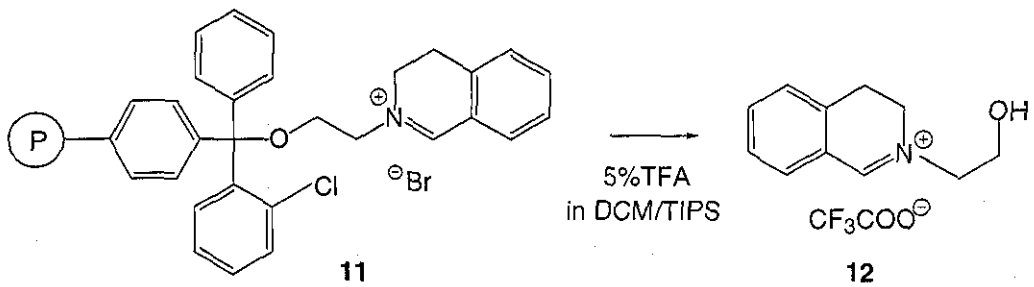
In order to check whether the iminium salt was effectively formed or not, each reaction was analysed by FT-IR spectroscopy, using KBr disks of powdered beads. Indeed, FT-IR measurements, achieved under defined conditions can sometimes furnish quantitative as well as qualitative data, since the difference in measurements on the free and loaded support under identical conditions permit the detection of absorption bands.[24] However, in our case, the absorption band of the C-N double bond, which is usually detected around 1700-1600 cm^{-1}, could not be identified in the FT-IR spectrum of **11**, because several peaks in this region were identical to those already present in the resin **6**. Additionally, the spectrum of each reacted sample showed the presence of the same characteristic band at 3420 cm^{-1}, as in the starting material resin. This band was primarily assumed to correspond to the presence of unreacted amine functionality, thus indicating that the reaction did not proceed to completion. Nevertheless, after several experiments, we realised that this absorption could also be due to a hydroxyl group belonging to the starting material resin (. Therefore, FT-IR analyses were not useful for this reaction.

Hence, the iminium salt **11** was tested as epoxidation catalyst using 50 to 100 mg of resin in acetonitrile/water, with Oxone® as the oxidant as shown in Scheme 9. Unfortunately, only moderate conversions of 1-phenylcyclohexene to epoxide were displayed (*ca.* 50% according to the ^{1}H NMR spectrum of the crude product).



Scheme 9: Epoxidation of 1-phenylcyclohexene with immobilised catalyst **11**

Because of the lack of information regarding the presence of the iminium salt on the resin, we decided to check whether the formation of the iminium salt had taken place. Hence, the cleavage of the iminium salt was achieved by treatment of the resin **11** with a 5% solution of trifluoroacetic acid in dichloromethane/ triisopropylsilane (95:5), which gave the trifluoroacetate salt **12** (Scheme 10).[22]



Scheme 10: Cleavage of the catalyst

The ^{1}H NMR spectrum of the crude compound **12** proved effectively that the desired iminium salt had been synthesised. Thus assured of the presence of the catalyst on the beads, various conditions were then applied to the synthesis of the iminium salt, in order to evaluate the effect of certain parameters. Hence, reaction times were prolonged from few hours to one week, but the conversion in the subsequent epoxidation did not improve. In other experiments, the condensations of **7** and the chlorotrityl support were repeated once

or twice to ensure better conversion to the dihydroisoquinolinium salt; nonetheless, the epoxidation remained unpredictable. An exchange of bromide counter-ion to tetraphenyl borate was also performed to obtain the same catalyst as in solution phase; unfortunately, the yield of epoxide did not exceed 42%. In another attempt, the iminium salt formation was carried out at room temperature, but again the epoxidation was unchanged. Despite these disappointing results, we were encouraged to pursue our efforts, since the epoxidations had provided a significant amount of epoxide, thus proving the activity of the immobilised iminium salt catalysts.

The parameters of the epoxidation reaction were therefore next examined. Hence, the reaction time was prolonged from 3 hours to overnight, but the epoxidations did not provide better results. The resin was swollen prior to epoxidation in acetonitrile instead of dichloromethane, but mainly the alkene was recovered. When the solvent medium was replaced by a mixture of dichloromethane/water instead of acetonitrile/water, again the alkene was recovered.

The difficulties encountered in analysis of the iminium salt synthesis and the epoxidation stemmed from the absence of analyses allowing the qualitative and quantitative characterisation of the resin-bound product or possible by-products. Indeed, FT-IR spectroscopy was inefficient in our case and nuclear magnetic resonance spectroscopy for solid phase (MAS-NMR) was not available at this time. Therefore, an investigation of the polymer-supported iminium salt formation was envisaged using the Kaiser test.

2.3.2.1) Influence of the solvent on the iminium salt formation

The Kaiser test, also known as the ninhydrin color test, is principally employed for the detection of primary amines.[167] The test consists of reacting the resin beads with few drops of three solutions, namely ninhydrin dissolved in ethanol, phenol in ethanol, and an aqueous solution of potassium cyanide in pyridine. The sample is then heated to 110 °C for 4 minutes and if the beads turn to a blue colour this indicates the presence of amino groups, whereas if the beads remain yellow, amino groups are absent. To identify the best

solvent for the iminium salt reaction, the solvents outlined below were assessed using the 2-chlorotrityl polystyrene resin, and the reactions were monitored by the Kaiser test in order to check for the presence of free amine in the reaction mixture.

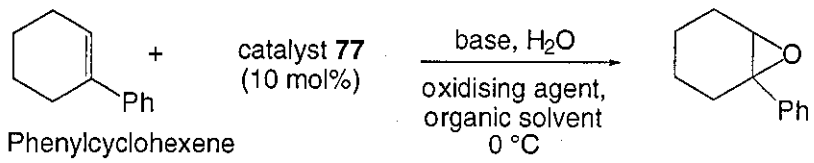
- 1) Methanol
- 2) Ethanol
- 3) Trimethylorthoformate/Dichloromethane (1:1)
- 4) Dimethylformamide
- 5) Tetrahydrofuran
- 6) 1% acetic acid in dimethylformamide
- 7) Trimethylorthoformate/Dichloromethane (9:1), with 6% acetic acid in methanol

The reactions performed in methanol or ethanol both provided deep blue bead coloration, although the polymer-supported species was allowed to react with the benzaldehyde **7** for 5 days. With the four other solvents or solvent mixtures, the colour of the beads turned to a colour varying between green and light purple. Unfortunately, none of resin beads ever became yellow. Nonetheless, a similiar case was reported by Sarin who underlined the high sensitivity of this test and the difficulty in its interpretation.[168] Furthermore in 2001, Ley reported that caution should be exercised when thermally labile protecting group such as trityl group is employed in the substrate molecule, because the heating at 110 °C can give rise to misleading results.[169] Nevertheless, although the effect of the different solvents could not be analysed, the epoxidation reactions were attempted in acetonitrile/water with the iminium resins prepared in the solvents above. Unfortunately these attempts gave either the alkene or only a small amount of the epoxide. It was therefore decided to study the epoxidation reaction in detail.

2.3.2.2) Influence of a biphasic system on the epoxidation reaction

As the epoxidation reaction mixture in our system consists of three different layers (organic phase, resin, aqueous phase), attempts were made to reduce the number of phases from three to two, the aim being to allow better interactions between the catalyst, the

substrate and the oxidant. Hence, instead of using the inorganic salt Oxone®, the related tetra-*n*-butylammonium oxone, an oxidant soluble in organic solvents, was prepared according to Trost's procedure.[170] Since the efficiency of this oxidising agent had to be tested in solution phase before further possible applications in heterogeneous conditions could be considered, the oxygen source was first evaluated for epoxidations with the homogeneous isopinocampheylamine catalyst (see section 1.4.1, compound **77**). This chiral catalyst, readily available in the laboratory and known to afford good yields in epoxidations under solution phase conditions, was chosen for the epoxidation of 1-phenylcyclohexene (Scheme 11).



When oxidant = NBu_4Oxone	Epoxide yields
in H_2O/DCM	4%
in H_2O/MeCN	5%

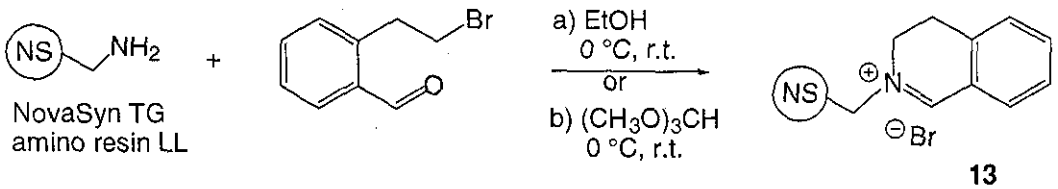
Scheme 11: Epoxidations in a biphasic system

Unfortunately, the epoxidation attempts carried out using tetra-*n*-butylammonium oxone and sodium carbonate, either in acetonitrile or in dichloromethane, did not give significant amounts of epoxide. The monoperoxyphthalic acid magnesium hexahydrate was also tried as the oxidising agent, in acetonitrile/water, but no formation of epoxide was observed. The replacement of the base by tetramethylammonium hydroxide pentahydrate in acetonitrile or in dichloromethane, or using a methanolic solution of tetramethylammonium hydroxide in the same solvents, did not afford any improvement.

As a consequence of these results, this route was abandoned and investigations turned toward the utilisation of more hydrophilic resins, which seemed to be more appropriate for our epoxidation system. Therefore an investigation using NovaSyn® TG resin was initiated.

2.3.3) Solid phase reactions using aminomethyl NovaSyn® TG resin

NovaSyn® TG amino resin, which has good swelling properties in water, was reacted with the (bromoethyl)benzaldehyde (Scheme 12).



Scheme 12: Iminium salt synthesis using NovaSyn® TG amino resin

Unfortunately, it was not possible to observe differences between the FT-IR spectra of the aminomethyl NovaSyn® TG resin and **13**, due to their low loading (only 0.29 mmol/g of resin). This low loading does not allow for a good FT-IR spectrum, even though an FT-IR microspectroscopy analysis on a single bead was carried out in the Perkin Elmer main office.

Similarly to the reactions achieved with the trityl polystyrene resin **11**, many conditions for both the formation of the iminium salt and the epoxidation have been employed. The synthesis of the catalyst **13** was performed either in ethanol or trimethylorthoformate, at 0 °C or at room temperature, with 2, 3, 5, even 10 equivalents of benzaldehyde, and for 16 hours to one week. Nevertheless the variation of such parameters did not seem to influence the epoxidation conversions. The epoxidations were realised using 50 mol% of **13** under the conditions described in scheme 9, with Oxone®/Na_2CO_3 in acetonitrile/water, and the resin was preferably swollen in water. The reaction time was varied from 4 hours to overnight shaking, the temperature was changed to room temperature, and the swelling solvent was replace by acetonitrile or a mixture of acetonitrile/water. But these variations did not significantly affect the rate of epoxidation. However, the catalyst **13** afforded an improvment of activity compared to the utilisation of polystyrene resin **11**. The best conversion of 1-phenylcyclohexene to 1-phenylcyclohexene oxide reached 80% yield, when **13** was prepared from

trimethylorthoformate at room temperature, and the epoxidation carried out at room temperature, with prior swelling of the resin in water.

2.3.3.1) Influence of the agitation mode

Among the parameters examined, the effect of the agitation method was studied. A batch of the polymer-supported iminium salt on NovaSyn® TG resin was prepared in trimethylorthoformate, which had become our preferred solvent for the catalyst formation. Further epoxidations were then attempted. Initially reactions were performed in round-bottomed flasks using an orbital shaker. However we also ran the reactions in fritted and stoppered disposable syringes, which were rotated through 360°* as a method of agitation. Unfortunately, epoxidations using this method were longer than by shaking. As shown in Table 1, magnetic stirring as well as sonication were also tested for the epoxidations.

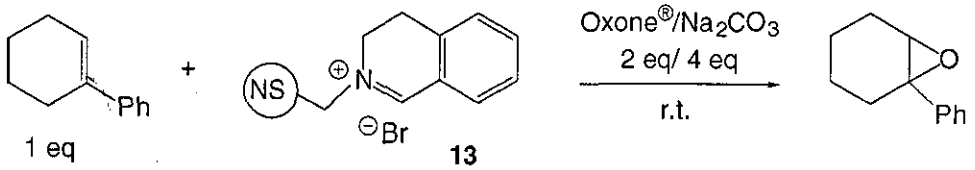


Table 1: Epoxidations using different solvent mixtures or agitation methods

Solvent	Agitation	Conversion
MeCN/H_2O 2:1	Magnetic stirrer Orbital shaker Sonication	Starting material
Dioxane/H_2O 2:1	Orbital shaker Sonication	Starting material
MeCN/H_2O 1: 2	Orbital shaker Sonication	66% in 7.5 h 71% in 7.5 h
MeCN/H_2O 1:1.5	**Orbital shaker**	**80% in 6 h**
Dioxane/H_2O 1:1.5	Orbital shaker	28% in 6 h

Although sonication afforded slightly improved conversion to epoxide, the orbital shaking was preferred, because this agitation mode was more practical and only a 5% increase was

* The syringes were mounted perpendicular to the axis of rotation

displayed under sonication. Table 1 also proves that acetonitrile/water medium is more favourable than dioxane/water. A 80% conversion of alkene to epoxide was attained in acetonitrile with 50 mol% of the polymer-supported iminium salt, versus 28% conversion in dioxane/water.

2.3.3.2) Analyses by gel phase ^{13}C NMR spectroscopy

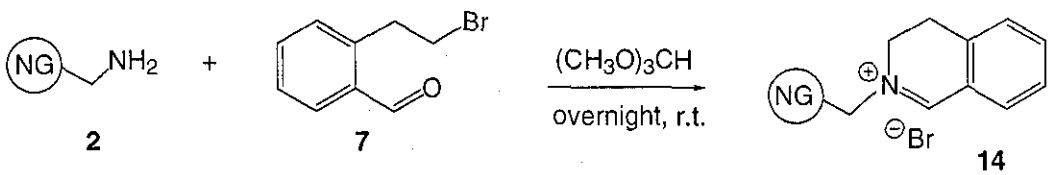
The absence of quantitative data about the presence of the iminium on the solid support prompted a few attempts of gel phase NMR analyses with the NovaSyn® TG resin. Gel phase NMR spectroscopy is a mixture of standard solution phase and solid state NMR spectroscopy. To achieve this analysis, a solid sample of resin is transferred to an ordinary NMR tube and allowed to swell in a suitable solvent. The NMR spectra can then be recorded under the conditions typically used for dissolved samples. Some samples of ^{13}C NMR gel phase spectra were run in Loughborough on a Bruker spectrometer, operating at 100 MHz. However, the spectra obtained either from deuteriated chloroform or benzene,were not satisfactory, despite long acquisition times. The ^{13}C NMR spectra were dominated by the strong resonance signals of the polymeric support, while the weak signals of the polymer-bound substrate could not be seen.

Samples of the derivatised NovaSyn® TG resin **13** were sent to the EPSRC Solid State NMR service at Durham for magic angle spinning (MAS) experiments. A ^{13}C direct polarisation MAS experiment gave a spectrum (appendix 1), which matched exactly with the ^{13}C NMR spectrum of the corresponding soluble iminium salt (appendix 1'). In the spectrum of the polymer-supported iminium salt **13**, the peak at 42.3 ppm characterising the amino alkyl group of the starting material resin had disappeared. It was concluded that there was very little trace of free amine left on the reacted resin, thus indicating that the iminium salt reaction was complete.

This information prompted us to focus our efforts on the epoxidation reaction. However, despite numerous attempts, complete conversion to the epoxide could not be achieved. We therefore examined another type of resin.

2.3.4) Solid phase reactions using aminomethyl NovaGel™ resin

Aminomethyl NovaGel™ resin was chosen for its high loading (0.74 mmol/g) and its good swelling characteristics in a large range of solvents. This resin provided the polymer-supported iminium salt **14** by condensation with the 2-(2-bromoethyl)benzaldehyde, after prior swelling of resin **2** in a 1:1 mixture of *trimethylorthoformate/dichloromethane* (Scheme 13).



2 **7** **14**

Scheme 13: Iminium salt synthesis using aminomethyl NovaGel™ resin

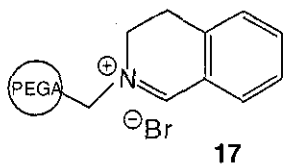
An FT-IR analysis was performed on the derivatised resin **14**: it was noticed that the carbamate band at 1710 cm^{-1} had disappeared and that two other bands (1650 cm^{-1} and 1600 cm^{-1}) corresponding to the iminium unit, had appeared (appendix 2). The ^{13}C MAS-NMR experiment operated without solvent, failed to detect the iminium salt. Therefore, the sample was swollen in deuteriated chloroform. However, it was difficult to observe the signals of the iminium salt on the spectrum due to the iminium unit being direcly linked to the polystyrene backbone. As a consequence, there was not enough molecular mobility to enable the detection of all the peaks of the iminium catalyst, partly because of the relatively low concentration and also because there was too much interference from the signals from the polystyrene. Nevertheless, a few characteristic peaks are visible, thus confirming, as did the FT-IR spectrum, the presence of the iminim salt.

The epoxidation reactions using the derivatised resin **14**, 2 equivalents of Oxone®, 4 equivalents of sodium carbonate and the solvent systems outlined below, provided only a small percentage of epoxide.

- THF/H_2O
- $Dioxane/H_2O$
- DMF/H_2O

2.3.6.3) Reactions with PEGA resin

The iminium salt formation was performed in trimethylorthoformate to furnish PEGA iminium (**17**). The ^{13}C MAS-NMR spectrum of **17** indicated the presence of the iminium salt on the resin. Although this spectrum was difficult to assign, some of the peaks characterising the iminium salt were identified.



17

The unfunctionalised and functionalised resins (50 mol%) were employed in the epoxidation of 1-phenylcyclohexene under the conditions shown in Scheme 15. While the unfunctionalised PEGA-NH_2 resin also gave large amount of epoxide (33%) in 1.5 hours, the immobilised catalyst **17** provided complete conversion of the alkene in the same period of time. PEGA iminium salt thus proved to have the best catalytic activity based on reaction time. Although the conversion using the unfunctionalised resin was high, PEGA resins offered promising results.

2.3.6.4) Conclusion

Hence, the epoxidations of 1-phenylcyclohexene can be performed with several types of polymer matrices, namely NovaSyn® TG, ArgoGel®, NovaGel™, and PEGA resins. Nevertheless, the reactions of section 2.2.6 could not be compared, because the Oxone® concentrations of each reaction mixture were not identical. Indeed, in these reactions, the amount of 1-phenylcyclohexene was calculated according to the loading of 100 mg of polymer. As the loading of each resin type was different, the amounts of substrate and oxidant involved in epoxidation changed for each type of polymer. We decided, therefore, to perform some experiments using the same quantities of reagents to compare the different resins under identical reaction conditions.

2.4) Resin comparison for epoxidation reaction

A new series of reactions was performed using new standard conditions. For each experiment, identical amount of 1-phenylcyclohexene, sodium carbonate, and Oxone® were used in the same amount of acetonitrile/water (1:2). The resin was employed in a catalytic amount (25 mol% or 35 mol%) and reacted with 1 equivalent of 1-phenylcyclohexene, 4 equivalents of Oxone® and 8 equivalents of sodium carbonate in acetonitrile/water at room temperature (Table 3). Between 50 and 98 mg of resin were used for the epoxidations, which were carried out using an orbital shaker. The times for the experiments were governed by the time taken for complete reaction catalysed by the polymer-supported iminium salt species, as determined by TLC.

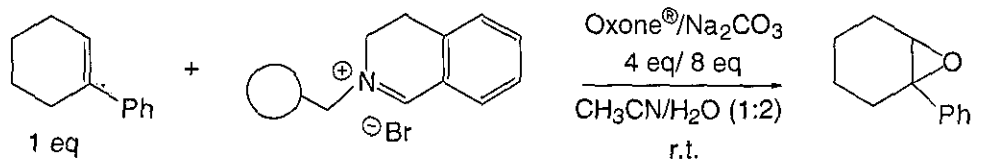


Table 3: Epoxidations comparing derivatised and non-derivatised resins

Resin	Equivalents	Time	Conversion
NovaSyn® iminium	25 mol%	4.75 h	100%
NovaSyn®-NH_2	25 mol%	4.75 h	24%
none		4.75 h	50%
NovaGel™ iminium	35 mol%	1 h	100%
NovaGel™-NH_2	35 mol%	1 h	4%
none		1 h	11%
ArgoGel® iminium	25 mol%	1 h	100%
ArgoGel®-NH_2	25 mol%	1 h	15%
PEGA iminium	25 mol%	25 min	100%
PEGA-NH_2	25 mol%	25 min	4%
none		25 min	1%

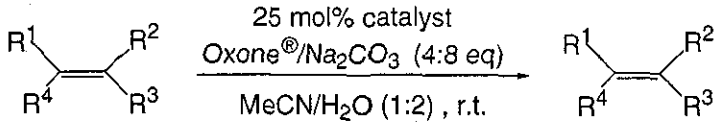
NovaGel™, ArgoGel® and PEGA iminium resins furnished complete conversion of the alkene to the epoxide in a reasonable period of time. While the PEGA catalyst afforded the fastest reaction, NovaSyn® iminium resin was almost 6 times slower. Indeed, 4.75

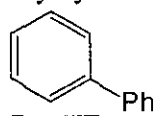
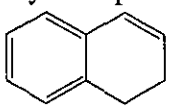
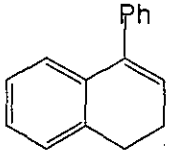
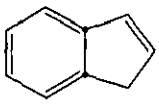
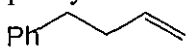
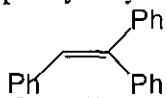
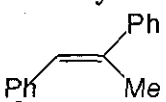
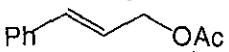
hours were necessary to complete the epoxidation of 1-phenylcyclohexene with the NovaSyn® iminium bromide resin, while it took only 25 minutes with the PEGA analogue. Due to this long reaction time and the high conversion obtained in the background reaction (without any catalyst), the NovaSyn® resin was less interesting than the other polymers. Nevertheless, the conversion with the unfunctionalised NovaSyn®-NH_2 resin was surprisingly lower than in the absence of resin, at 24 and 50% respectively. The same effect was observed with NovaGel™ resin, which gave 4% epoxide with the unfunctionalised NovaGel™-NH_2 resin and 11% in the absence of resin. Hence, the unfunctionalised polymers suppress the background reaction to some extent. The origin of this effect, however, has not been yet determined, although there is no doubt that the nature of the resin matrix is the major factor of influence. The NovaGel™ iminium resin displayed a complete epoxidation in 1 hour using 35 mol% of the iminium. Nonetheless, with 25 mol% of the same catalyst, the reaction took 2.5 hours to go to completion. This NovaGel™ resin was not as efficient as the PEGA matrix, which affords the best results of this study, with a good catalytic activity and minimal background reaction. Nevertheless, a practical inconvenience render the use of this resin unfavourable: the PEGA resin is initially supplied swollen in methanol, and the utilisation of the polymer requires the prior drying of the beads under vacuum. Once the beads are dried, they become sticky and difficult to handle, rendering their manipulation tedious. Therefore, in practice, the use of the PEGA resin is inconvenient. ArgoGel® beads are much easier to handle and they provided good catalytic activity. When the epoxidation was performed with 25 mol% of the ArgoGel® iminium, 1-phenylcyclohexene was transformed to its oxide in 1 hour, while the unfunctionalised ArgoGel®-NH_2 and the background reaction without resin did not exceed 15% conversion. As the ArgoGel® resin afforded good epoxide conversion in reasonable time and was more practical to use than PEGA, this resin structure was chosen for the catalytic epoxidation of various substituted alkenes.

2.5) Epoxidation of various alkenes

The epoxidation of several olefinic substrates was performed in acetonitrile/water (1:2) at room temperature, using 4 equivalents of Oxone®, 8 equivalents of sodium carbonate and 25 mol% catalyst. Between 70-80 mg of resin were used for each reaction. Reactions were carried out using an orbital shaker, and the results are displayed in Table 4. Each reaction was compared to the epoxidation of 1-phenylcyclohexene as a reference. The epoxidation of 1,2-dihydronaphthalene was rather fast (40 min); unfortunately, the activity was not influenced by the iminium catalyst, since the three reactions, namely with the polymer-supported iminium species, the unfunctionalised resine or without resin furnished a complete conversion of the alkene. However, after 20 minutes, the TLC showed that the reactions were not complete. The epoxidation of 1,2-dihydro-4-phenylnaphthalene with the ArgoGel® iminium catalyst yielded 33% epoxide after 2 hours, while only the starting material was detected with either the ArgoGel®-NH_2 or without resin. This reaction is much slower than the epoxidation of 1-phenylcyclohexene. With indene as substrate, the background oxidation produced 50% conversion after 1 hour, whereas 37% was obtained with the iminium resin catalyst. Additionally, some by-products were detected by TLC, but could not be characterised by NMR spectroscopy. For the epoxidation of the terminal olefin 4-phenylbut-1-ene, only the starting material was retrieved after 1 hour reaction. However, several spots appeared on TLC and the amount of alkene retrieved was less than half of the amount of substrate employed initially. It is possible that the epoxide might be hydrolysed to water-soluble side-products, which would be eliminated in the aqueous work-up; nevertheless, this hypothesis has not been demonstrated. In the case of triphenylethylene, no reaction took place after 1 or 2 hours. Even after overnight shaking, the starting material was quantitatively recovered after work-up. This absence of reactivity may stem from the low solubility of the substrate in acetonitrile/water. Similarly, (*E*)-α-methylstilbene and (*E*)-cinnamyl acetate did not react, although a longer reaction time was permitted.

Table 4: Various alkenes epoxidations



Alkenes	Resin catalyst	Reaction time	Conversion
1-phenylcyclohexene 	AG-Iminium AG-NH_2 none	1 h	100% 15% 11%
1,2-dihydronaphthalene 	AG-Iminium AG-NH_2 none	40 min	100%
1,2-dihydro-4-phenylnaphthalene 	AG-Iminium AG-NH_2 none	2 h	33% 0% 0%
Indene 	AG-Iminium AG-NH_2 none	1 h	37% 28% 50%
4-phenylbut-1-ene 	AG-Iminium AG-NH_2 none	1 h	0%
triphenylethylene 	AG-Iminium AG-NH_2 *none*	overnight	0%
(*E*)-α-methylstilbene 	AG-Iminium AG-NH_2 none	3 days	0%
(*E*)-cinnamyl acetate 	AG-Iminium AG-NH_2 none	overnight	0%
triphenylethylene	PEGA Iminium PEGA-NH_2 none	4 h	0%
4-phenylbut-1-ene	PEGA Iminium PEGA-NH_2 none	1 h	100% 100% 0%

For the (*E*)-α-methylstilbene, again the low solubility of the alkene could explain the lack of reactivity in this supported system. (*E*)-Cinnamyl acetate did not react, presumably because the double bond is electron-deficient as a result of the conjugated carbonyl group.

These epoxidations of alkenes have not been fruitful compared to the values exhibited with the 1-phenylcyclohexene. Since these epoxidations were unsuccessful using ArgoGel® resin, the PEGA resin was tested with two of the unreactive alkenes. Hence, triphenylethylene was submitted to epoxidation mediated by the PEGA iminium catalyst, the unfunctionalised amino resin, and in the absence of resin. In all these three cases, no reactions occurred and the starting material was recovered. However, the 4-phenylbut-1-ene produced complete conversion to the corresponding epoxide in 1 hour using both the PEGA iminium resin and the unfunctionalised amino PEGA resin. No epoxide was generated in the absence of resin, but some uncharacterised spots were seen by TLC.

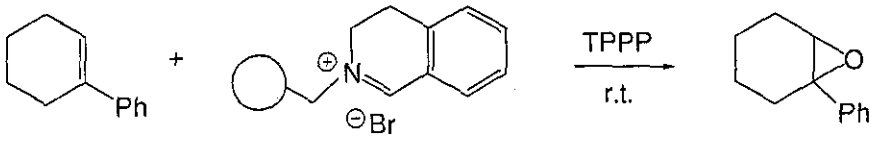
Each the olefinic substrates presumably requires specific studies for optimised epoxidation conditions. In an alternative strategy, a new oxidising agent was next examined.

2.6) Epoxidations of 1-phenylcyclohexene using TPPP

Tetraphenylphosphonium monoperoxysulfate Ph_4PHSO_5 (TPPP) has recently been developed as an oxygen source for the epoxidation of unfunctionalised alkenes by our group. In these oxidations mediated by homogeneous iminium salts, TPPP proved to have advantages over Oxone®. The advantages of TPPP stem from its solubility in organic solvents such as dichloromethane or acetonitrile. In solution phase, the epoxidations can, therefore, be performed in either of these solvents, using 10 mol% of the iminium catalyst, 2 equivalents of the oxidant, without base, at -40 °C. The reactions are very fast, and the asymmetric epoxidations exhibit excellent ees. For these reasons, attempts were made to adapt the homogeneous system to solid phase synthesis. Instead of the triphasic system using Oxone®, the reactions were carried out with the soluble TPPP in organic solvents,

and immobilised iminium salts (biphasic system). The oxidations of 1-phenylcyclohexene were first accomplished in dichloromethane, using 50 mol% of resin, at room temperature (Table 5).

Table 5: *epoxidations of 1-phenylcyclohexene in dichloromethane*



Resin catalyst	Reaction time	Equivalents of TPPP	Conversion
AG-Iminium AG-NH_2 none	24 h	2	0%
PS-Iminium PS-NH_2 none	24 h	2	0%
AG-Iminium AG-NH_2 none	24 h	4	0%
PS-Iminium PS-NH_2 none	24 h	4	0%

While the ArgoGel® resins were preferred for test reactions, we also assayed the polystyrene resin, because this polymer is known to swell very well in dichloromethane. Unfortunately, the epoxidations either with ArgoGel® or polystyrene resins, with 2 or 4 equivalents of TPPP did not afford any epoxide after 24 hours reaction. Only the starting material was detected by TLC analysis. This absence of reactivity (or very slow) with the supported catalyst might be due to the limited diffusion of the oxidant inside the polymer beads, and thus access the active sites of the iminium salt. Therefore, the epoxidations were also performed in acetonitrile which affords an improved solubility of TPPP, although this solvent is not favourable for swelling of the beads.

Table 6: Epoxidations of 1-phenylcyclohexene in acetonitrile

Resin catalysts	Reaction time	Equivalents of TPPP	Conversion
AG-Iminium AG-NH_2 none	overnight	4	traces of epoxide
PS-Iminium PS-NH_2 none	24 h	4	traces of epoxide

Four equivalents of the oxidant were used in the same epoxidations, but only traces of epoxide were detected after overnight shaking with the ArgoGel® iminium species and the unfunctionalised amine resin, as well as in the background reaction with no resin present. These traces are imparted to the uncatalysed oxidation, since all three examples gave identical data. Traces of 1-phenylcyclohexene oxide were also obtained when the polystyrene resins were treated in acetonitrile. As the polystyrene beads do not swell in acetonitrile, this result is not surprising. Therefore, to improve both solubility of TPPP and the swelling factor, the reactions were assayed in a mixture of acetonitrile/dichloromethane. After 48 hours reaction, the polystyrene-supported iminium salt gave 79% conversion to epoxide, while the unfunctionalised polystyrene amine furnished 9%, and the background experiment showed only the starting material.

Table 7: Epoxidation of 1-phenylcyclohexene in acetonitrile/dichloromethane

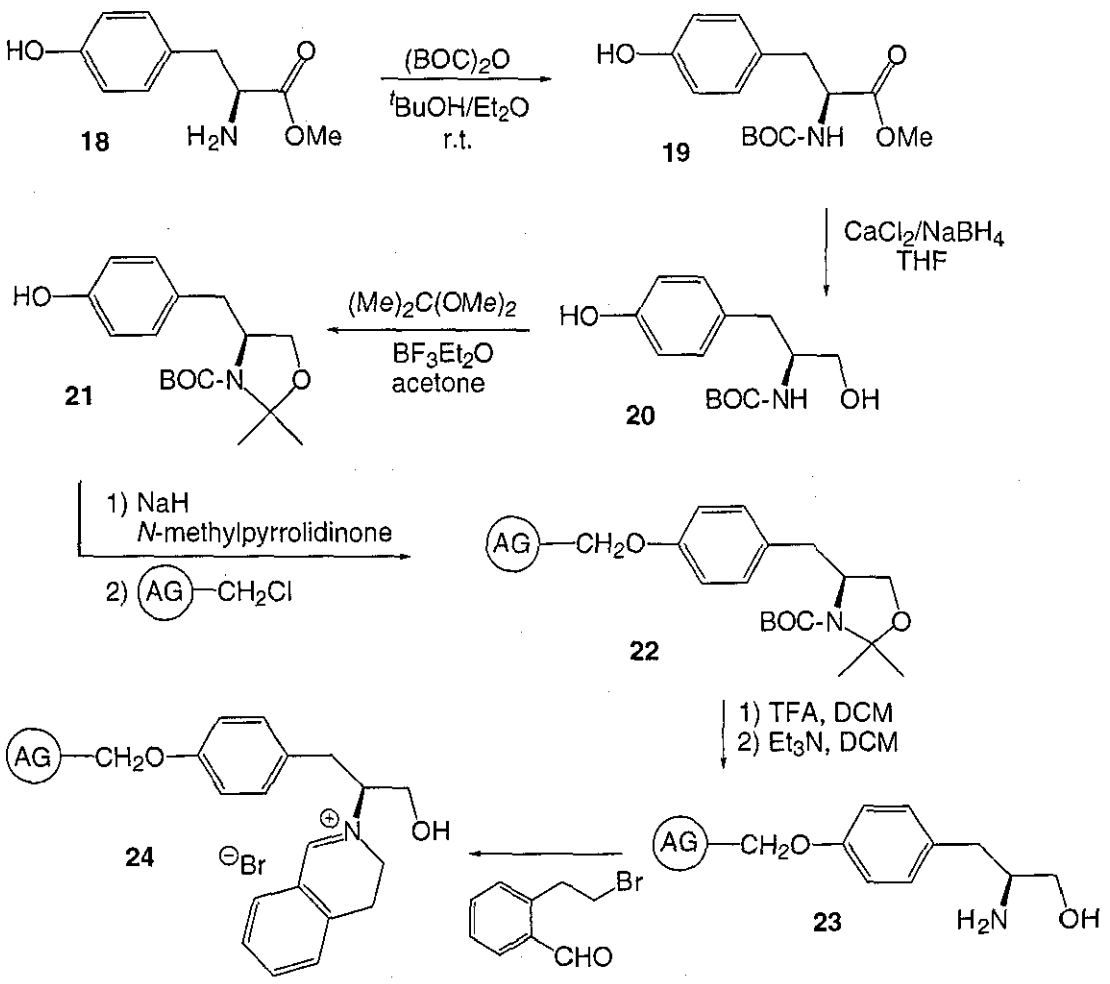
Resin catalysts	Reaction time	Equivalents of TPPP	Conversion
PS-Iminium PS-NH_2 none	48 h	4	79% 9% 0%

The epoxidation with TPPP catalysed by supported iminium salt does occur. The reaction time is much longer than in the previous examples, however, it seems that the epoxidation

does not progress after 24 hours. As a consequence, we believe that these conditions of reaction have to be further studied and optimised for a better understanding of the parameters influencing this reaction.

2.7) Approach to a polymer-bound chiral iminium salt

We next envisaged a new approach to linking a chiral iminium salt onto ArgoGel® resin. This route is described in Scheme 16. *N*-BOC-Tyrosine methyl ester (**19**) was obtained from (L)-tyrosine methyl ester (**18**) by BOC-protection using di-*tert*-butyl dicarbonate.[171] This reaction was followed by reduction with $NaBH_4$ in tetrahydrofuran,[172] and subsequent protection with dimethoxypropane to furnish the hemiaminal **21**.



Scheme 16: Synthesis of a polymer-supported chiral iminium salt

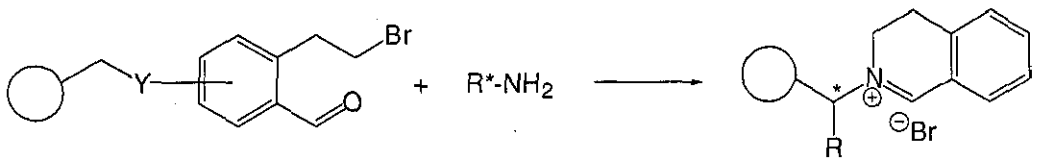
The ^{1}H and ^{13}C NMR spectra of compound **21** performed at room temperature, showed a doubling of the peaks for the isopropylidene group. This effect was also reported by Garner regarding the isopropylidene group of oxazolidine derivatives.[173] Oxazolidine species such as **21**, exist as slowly interconverting rotamers on the NMR time scale and samples require heating to obtain average spectra. Therefore, to avoid the doubling of the peaks, the ^{1}H and ^{13}C NMR experiments were carried out in DMSO at 100 °C. The protected derivative **21** was reacted with the chloromethyl ArgoGel® resin in the presence of sodium hydride in *N*-methyl pyrrolidinone for 58 hours to give the product **22** attached to the support.[174] After filtration and drying under vacuum, analysis of this resin by ^{13}C MAS-NMR spectroscopy, confirmed that the attachment was achieved (appendix 4). The doubling of the isopropylidene peaks was again observed in the ^{13}C MAS-NMR spectra of **22** performed at 25 °C. While the loading of the starting chloromethyl ArgoGel® resin was 0.4 mmol/g, the loading of resin **22** was very low, with only 0.1 mmol/g, according to the nitrogen percentage of **22** obtained by microanalysis. Nevertheless, the synthesis was pursued, and the amino alcohol functionality was regenerated by treatment of **22** with trifluoroacetic acid, followed by neutralisation with triethylamine. The formation of the desired iminium salt was then carried out using the resin-bound **23** with (bromoethyl)benzaldehyde in trimethylorthoformate/dichloromethane (1:1). The ^{13}C MAS-NMR spectrum of product **24** confirmed the presence of the dihydroisoquinolinium salt (appendix 5). However, the loading of resin **24** was still fairly low at only 0.1 mmol/g. The epoxidation of 1-phenylcyclohexene using 25 mol% (based on 0.1 mmol/g) of the polymer catalyst was assayed under the standard conditions: 4 equivalents of Oxone®, 8 equivalents of sodium carbonate, in acetonitrile/water (1:2). Although the epoxidation reaction was repeated, the reaction did not go to completion in both cases. Indeed, the mixture was characterised as a 1:1 ratio of alkene/epoxide according to the ^{1}H NMR spectrum. Furthermore, the epoxide obtained was shown to be racemic using the chiral shift reagent $Eu(hfc)_3$. The low conversion and absence of asymmetric induction can be explained, since iminium catalysts derived from amino alcohol are known to be prone to oxazolidine cyclisation under the basic condition of epoxidation.[144] Indeed, we believe that

the solid phase reaction is slowed down, primarily due to the undesired oxazolidine cyclisation and secondly by the solid support, because adaptation of homogeneous to heterogeneous systems is reported often to induce slower reactions.[6] Alternatively, this slow reaction rate may be caused by the very low loading of the resin **24**.

This method, which was aimed to produce a chiral iminium catalyst for epoxidation had therefore no future. As a consequence, our efforts focused on the immobilisation of (bromoethyl)benzaldehyde on a solid support.

2.8) Second strategy for the synthesis of the immobilised catalyst

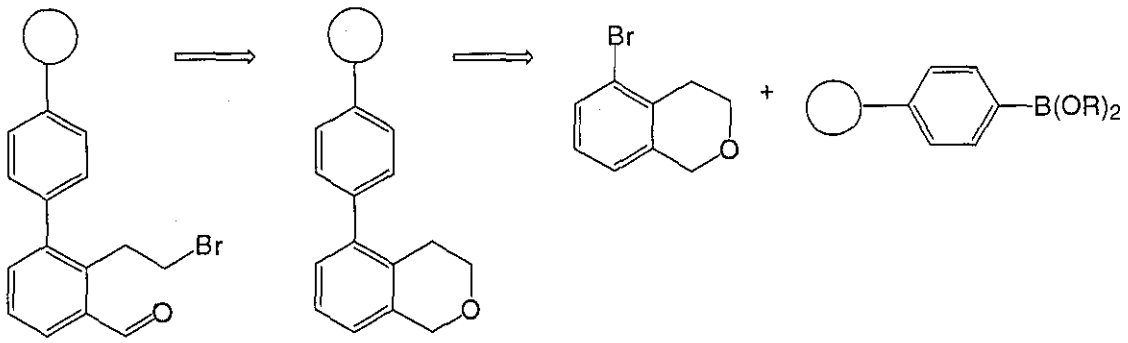
Our second synthesis plan involved a reversal of reacting centres, *ie.* instead of having a polymer-supported amine reacting with a soluble (bromoethyl)benzaldehyde, we would synthesise a polymer-bound (bromoethyl)benzaldehyde and react with a soluble chiral amine (Scheme 17).



Scheme 17: Synthesis of iminium salts from supported (bromoethyl)benzaldehyde

We envisaged this route would provide a larger range of catalysts because of the single common polymer-supported moiety, and the large number of chiral amines commercially available. Previously, our range of iminium salt catalysts was limited due to the scarcity of polymer-supported chiral amines.

The first approach for this synthetic route involved the synthesis of a bromoisochroman and attachment to a polymer support using Suzuki chemistry (Scheme 18). The bromine substituent was sited on position 5 of the isochroman in order to place the attachment point of the resin opposite to the ether functionality. In this case, the reactivity of the related iminum salt (derived from the 5-bromoisochroman) would not be affected by the polymer.



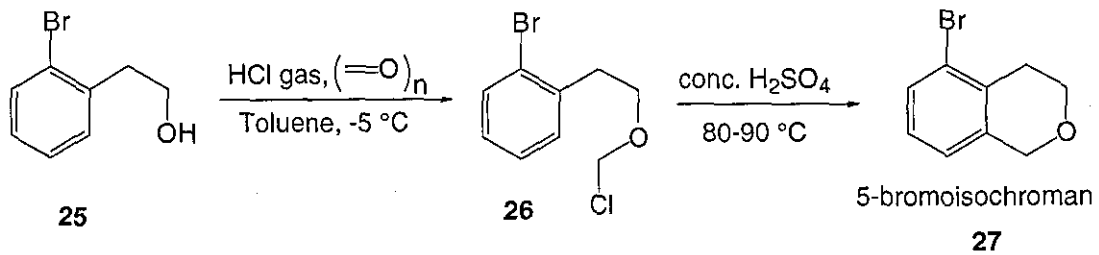
Scheme 18: Retrosynthesis of the polymer-supported (bromoethyl)benzaldehyde

The preparation of 5-bromoisochroman and various bromoisochromans is discussed below.

2.8.1) Synthesis of bromo-substituted isochromans

2.8.1.1) Reaction with HCl gas

The synthesis of several bromo-substituted isochromans was reported in 1996 by Unterhalt.[1] A range of aromatic-ring-substituted isochromans were synthesised *via* the cyclisation of the appropriate chloromethyl-2-phenylethylethers.[175] In order to obtain a polymer-bound (bromoethyl)benzaldehyde, the synthesis of 5-bromoisochroman was performed in the conditions shown in Scheme 19.



Scheme 19: Synthesis of 5-bromoisochroman using HCl gas

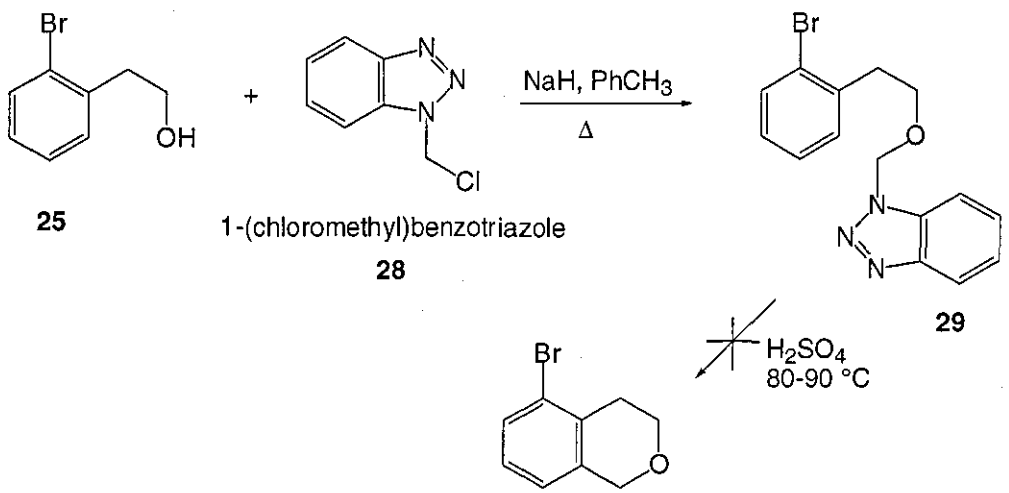
The starting material 2-bromophenylethanol (**25**) underwent the first reaction step, using paraformaldehyde in dry toluene and bubbling HCl gas through the reaction mixture for 4 hours. Subsequently, the resulting (chloromethyl)bromophenylethyl ether (**26**) was heated

at 80-90 °C with concentrated sulfuric acid for 5 hours and afforded 55% yield of **27** as a white solid, after purification by chromatography and recrystallisation. An attempt was made to scale-up the same reactions to 9 g of starting material, however these reactions did not give the results expected, affording only 100 mg of the bromoisochroman **27**. During the reaction the outlet tube of the HCl gas cylinder became corroded and broke, exposing the anhydrous system to air. Therefore, the expected ether **26** was not detected in the ^1H NMR spectrum of the crude reaction product. Nevertheless, the mixture retrieved after the first step was allowed to undergo the cyclisation step and 100 mg of pure 5-bromoisochroman was isolated.

Due to the difficulty and the lack of safety on large scale for the chloromethylation step, a variation of the route was envisaged. To overcome the use of the problematic HCl gas, the (benzotriazolylmethyl)phenylethyl ether was alternatively synthesised.

2.8.1.2) The benzotriazole intermediate

The synthesis of (benzotriazolylmethyl)phenylethyl ether (**29**) was performed by stirring 1-(chloromethyl)benzotriazole (**28**) and **25** with sodium hydroxide for 6 hours (Scheme 20). The isolation of the crude product **29** furnished 54% yield after work-up.[176]



Scheme 20: Synthesis of the derivatised benzotriazole intermediate

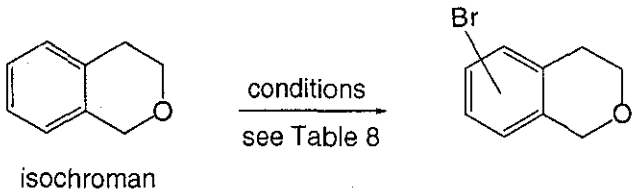
Subsequently, the crude derivative **29** was submited to treatment with concentrated sulfuric acid in toluene at 90 °C, but the cyclisation did not occur, giving only the starting material.

The cyclisation was attempted using zinc dichloride in ether or tetrahydrofuran, from 0 °C to room temperature, but again mainly the starting material was recovered.

This vain attempt led us to another strategy, which consisted of the direct bromination of any the aromatic ring of the isochroman.

2.8.1.3) Direct bromination reactions

Several methods were attempted to monobrominate the benzene ring of the isochroman on any of the four position available. The conditions assayed are summarised in Table 8.



isochroman

Table 8: Attempts to brominate the aromatic ring of the isochroman

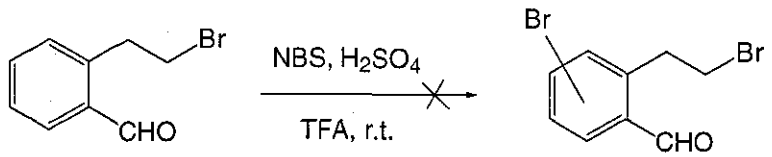
Entry	Reagents	Temperature	Time
1	HBr (48%), H_2O_2, TBAB	65 °C	26 h
2	NBS, TFA, H_2SO_4	r.t.	48 h
3	$KBrO_3$, H_2SO_4, H_2O	25 °C	24 h
4	Pyridinium tribromide	0 °C - r.t.	72 h
5	(Br_2-dioxane) in dioxane	5 °C - r.t.	48 h
6	Br_2 adsorbed on Al_2O_3	r.t.	15 min and 1.5 h

In entry 1, hydrogen peroxide was slowly added to a mixture of isochroman, 48% hydrobromic acid and tetra-*n*-butyl ammonium bromide (TBAB) at 65 °C.[177] Purification by column chromatography gave a mixture of products. As the different samples were

analysed by ^{1}H NMR spectroscopy and GC/MS, one of the fractions was identified as the (bromoethyl)benzaldehyde and another one contained two dibrominated species. However, some samples remained undefined. Bromination using *N*-bromosuccinimide in the presence of concentrated sulfuric acid in trifluoroacetic acid H_2SO_4/TFA (v/v) = 0.1 (entry 2) also gave a complex mixture of products, which was purified by chromatography.[178] Three samples were also analysed by GC/MS. The first one contained two dibromo species, and the second and third had different mixture of mono and dibromo moieties. In 1981, Harrison reported that potassium bromate ($KBrO_3$) in sulfuric acid/water permitted the bromination of benzene to bromobenzene.[179] Therefore, to a solution of concentrated H_2SO_4 and water was added isochroman, followed by potassium bromate (entry 3). After work-up and chromatography, the products were analysed by GC/MS as complex mixtures of mono- and dibromo species. When pyridinium bromide perbromide (entry 4) was reacted with isochroman in dichloromethane from 0 °C to room temperature,[180] the mixture afforded traces of aldehyde and mainly the starting material. The reaction was very slow and this brominating agent may have been too mild to break the aromaticity of the phenyl ring. Kosolapoff reported that complex between dioxane and bromine provide an interesting reagent for mild and direct bromination of sensitive aromatic compounds.[181] The reaction was carried out by the dropwise addition of a solution of bromine in dioxane to a solution of isochroman in dioxane at 5 °C (entry 5). Since there was no reaction, the mixture was then stirred at room temperature. The crude ^{1}H NMR spectrum of the resulting residue seemed to suggest the presence of a mixture of starting material and a monobrominated product; however, after chromatography and GC/MS analysis, this hypothesis could not be confirmed. The samples could not be identified. In 1992, a simple and improved procedure for selective ring bromination of alkyl-substituted aromatic hydrocarbons on the surface of alumina was reported.[182] In this procedure, bromine adsorbed on the surface of alumina was added to the aromatic substrates which were also adsorbed on alumina; the solids were magnetically stirred and the reactions were complete within one minute as indicated by the disappearance of bromine colour. The product was isolated by simple filtration chromatography through a short plug of silica gel. This

method was initially tested with toluene as substrate, and the reported yields of *ortho* and *para*-brominated derivatives were successfully reproduced. Unfortunately, the same procedure did not give satisfactory results with isochroman as substrate (entry 6). A mixture of compounds, containing the starting material, a monobrominated compound, an aldehyde and undefined species was obtained.

Since this scheme had failed, the direct bromination of the 2-(2-bromo-ethyl) benzaldehyde was attempted with the *N*-bromosuccinimide (Scheme 21).

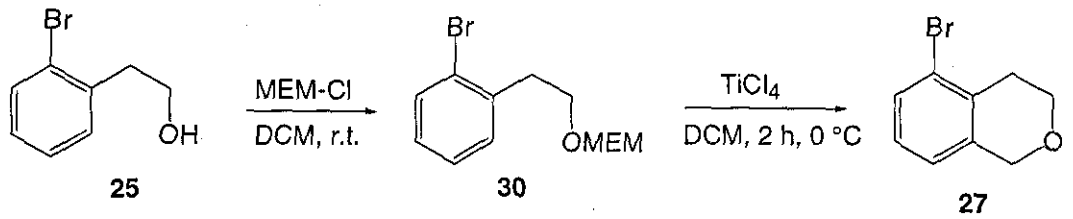


Scheme 21: Bromination using *N*-bromosuccinimide

The resulting mixture was purified by chromatography on silica gel and afforded several products, which after analysis by ^{1}H NMR spectroscopy and GC/MS, appeared to be a mixture of mono- and dibromo species as well as undefined compounds. As these bromination attempts were fruitless, the preparation of the 5-bromoisochroman was reconsidered.

2.8.1.4) Cyclisation using $TiCl_4$

A procedure describing the synthesis of several benzopyran derivatives through the cyclisation of MEM ethers was found in the literature.[183] Isochroman rings were prepared in two steps; the first one involved the protection of a phenyl alcohol by the methoxyethoxymethyl (MEM) group, and secondly, the resulting MEM ether was submitted to cyclisation using $TiCl_4$. As this procedure appeared to be more practical than the reaction with HCl gas (section 2.7.1.1), the synthesis of 5-bromoisochroman (**27**) was performed using alcohol **25** as the starting material (Scheme 22).



25 30 27

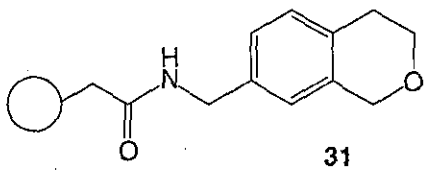
Scheme 22: Synthesis of 5-bromoisochroman *via* compound **30**

Compound **25** was converted to **30** in 80% yield and subsequently, **30** gave the product **27** in 68% yield.

However, before attempting linking **27** onto resins by Suzuki coupling, it was considered that an alternative approach would be more likely to succeed.[184] Instead of the bromoisochroman, a new strategy was designed to obtain the immobilised (bromoethyl)benzaldehyde.

2.8.2) Synthesis of the polymer-supported isochroman derivative

In our strategy leading to the immobilised 2-(2-bromoethyl)benzaldehyde, the resin-bound isochroman **31** was devised to act as a more convenient precursor.

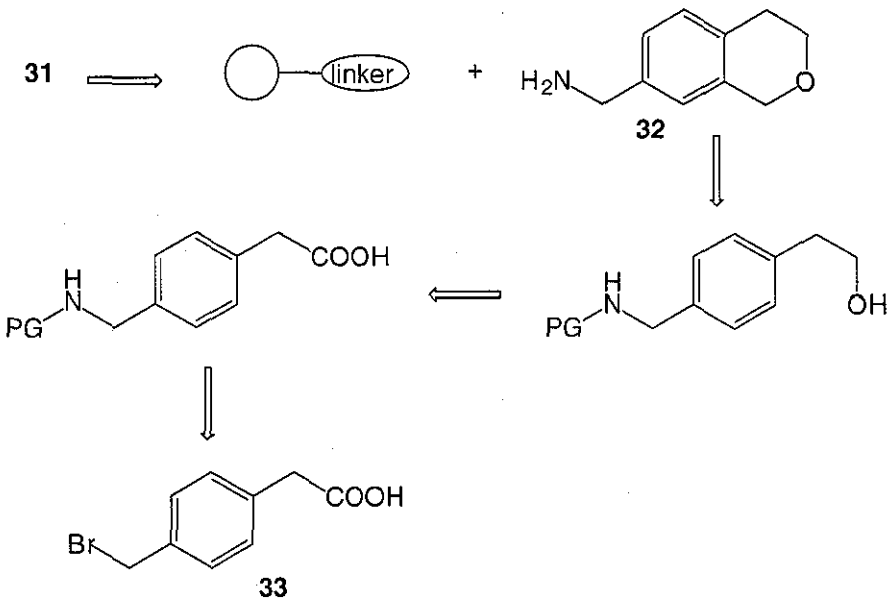


31

The amide linkage was chosen as a suitable stable linker to survive the various reaction conditions, acidic for the bromobenzaldehyde formation as well as alkaline for the epoxidation. Furthermore, the substituent was sited on position 7 of the isochroman in order to hinder this side of the isochroman and thus hinder the same side of the corresponding iminium salt. This hindrance might be beneficial to the stereoselectivity of the oxygen transfer during the epoxidation reaction.

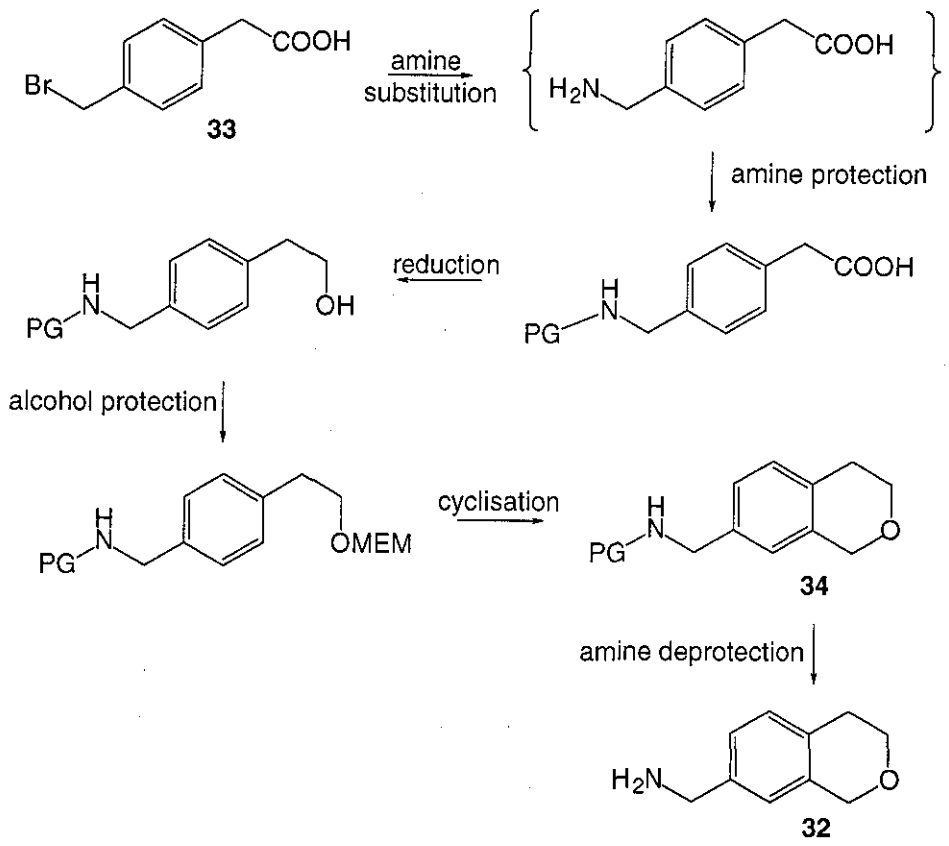
To realise this amide bond, the aminomethyl functionality was identified as the most suitable phenyl ring substitution, since it seemed a good compromise between the

requirements of the reaction conditions and the needs of the catalyst. The retrosynthetic strategy of compound **31** is illustrated in Scheme 23.



Scheme 23: Retrosynthesis of compound **31**

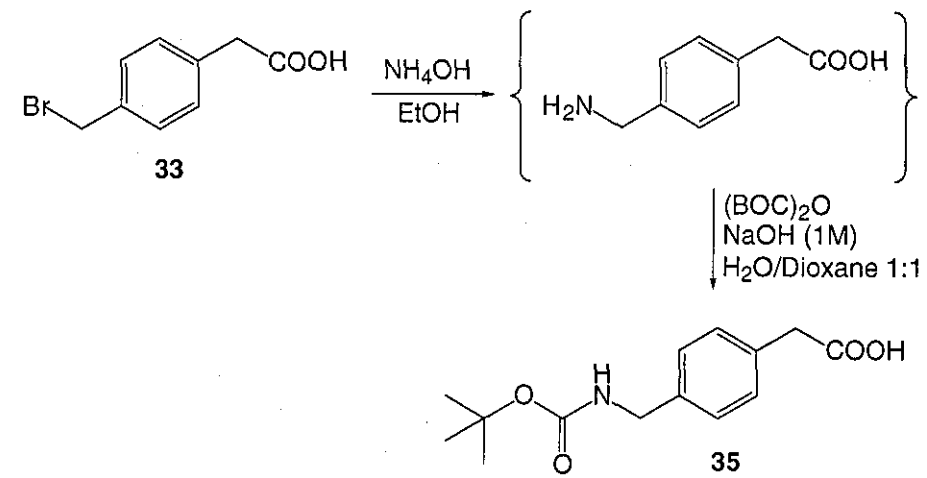
The 7-aminomethyl isochroman (**32**) appeared as the convenient isochroman species to attach to the solid support through a linker. Further disconnections involving alcohol and acid functionalities, led us to identify the commercially available 4-bromomethylphenylacetic acid (**33**) as the starting material. The six step synthesis leading to **32** includes successive protection, reduction and cyclisation steps, as outlined in Scheme 24. In the first step, the bromo acid undergoes an amine substitution, which is followed by the protection of the primary amine. The carboxylic acid functionality is reduced to the alcohol, which is then protected with a MEM group, before cyclisation leading to the substituted isochroman (**34**). The amine protecting group is then cleaved to provide the 7-aminomethyl isochroman (**32**), ready to be attached to a polymeric support. This synthesis was first performed using BOC (*tert*-butyloxycarbonyl) as the amine protecting group.



Scheme 24: Synthesis of 7-aminomethyl isochroman

2.8.2.1) BOC as the amine protecting group

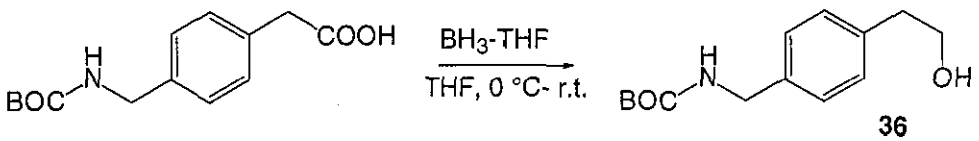
In the first step of the synthesis, the bromo acid **33** was stirred in a mixture of ethanol and concentrated ammonium hydroxide.[185] (Scheme 25).



Scheme 25: Synthesis of *N*-BOC-aminomethylphenylacetic acid

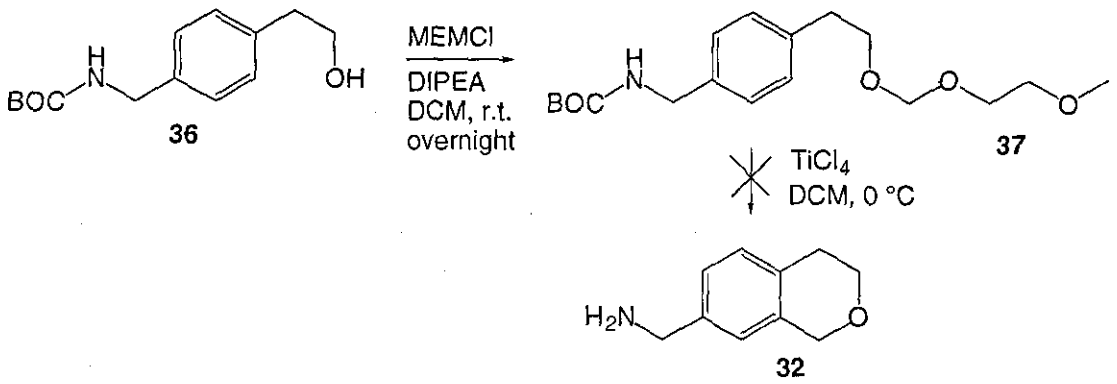
In this reaction requiring high dilution, the bromine was displaced by ammonia and the resulting intermediate was protected *in situ* using di-*tert*-butyl dicarbonate $(BOC)_2O$ in basic medium. The BOC protected aminomethylphenylacetic acid **35** was obtained in 57% yield after recrystallisation, and the analytical data were identical to those reported.[185]

The reduction of the acid to the alcohol was first attempted by reaction with ethyl chloroformate in tetrahydrofuran, followed by the addition of sodium borohydride in water.[186] Unfortunately, this reaction gave the ethyl ester of the corresponding acid. Another attempt was made using isobutyl chloroformate instead, but the isobutyl ester was isolated. Another method using BH_3-THF has been reported to achieve the reduction of the acid in the presence of the BOC group for various amino acids.[187] In our case, the reaction was performed in tetrahydrofuran over two hours, and provided the alcohol **36** in 75% yield after purification (Scheme 26).



Scheme 26: Synthesis of *N*-BOC-aminomethylphenylethanol

The cyclisation to the isochroman **32** was attempted by two differents methods. First, according to Iglesias, the alcohol **36**, paraformaldehyde and concentrated HCl were heated at reflux;[188] however these attempts did not provide the expected ring formation. In the second method, the cyclisation is constituted of two steps. First, the alcohol was protected with a MEM group, by treatment of the *N*-protected amino alcohol **36** with *N,N*-diisopropylethylamine (DIPEA) and MEM-Cl in dichloromethane.[183] The extraction and purification afforded compound **37** in 90% yield, as a colourless oil (Scheme 27).

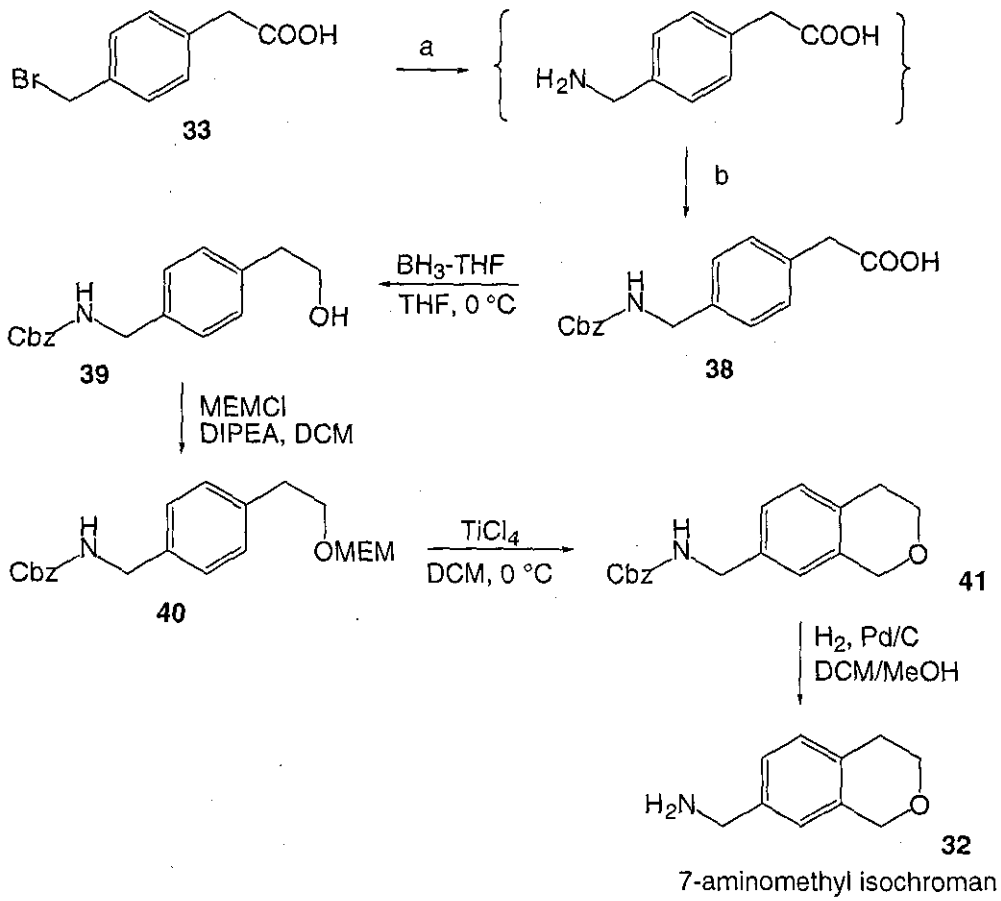


Scheme 27: Attempt to cyclise the MEM compound **37**

Secondly, the MEM protected compound **37** was subjected to cyclisation using $TiCl_4$ in dichloromethane at 0 °C. Although this procedure had proved to be effective for the preparation of 5-bromoisochroman (**27**) as substrate, in this case, compound **37** did not provide the cyclised product. The BOC group may have been cleaved in the presence of the strong Lewis acid, and thus may prevent the cyclisation. Therefore, the BOC group was replaced by the Cbz group in our synthesis.

2.8.2.2) Cbz as the amine protecting group

The same reactions, including amine substitution, amine protection, acid reduction, MEM protection, and cyclisation were repeated using the Cbz protection of the amine (Scheme 28). The first step involved the introduction of the amino group followed by the benzyloxycarbonyl protection of the primary amine, in a manner similar to the previous BOC protection.

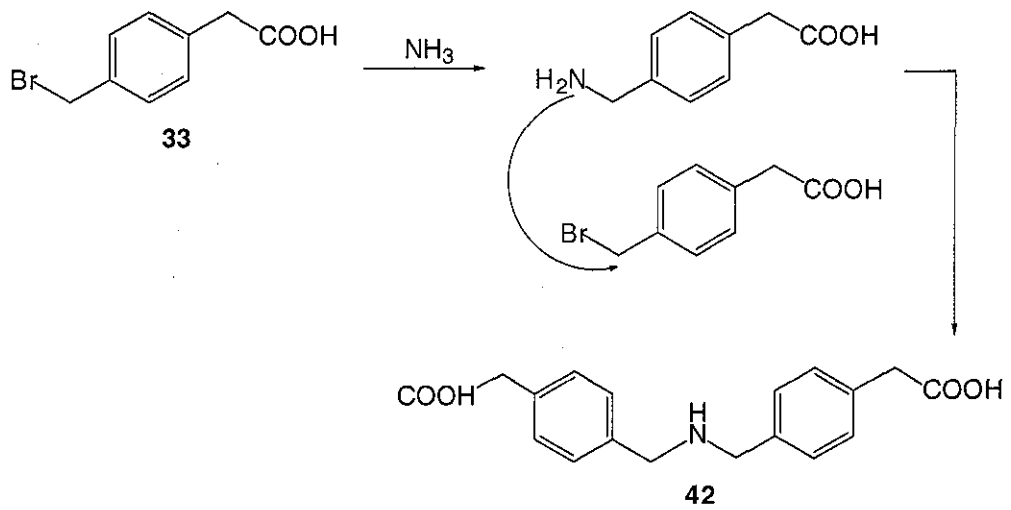


Method A: a) NH_4OH (*conc*), EtOH b) BnOCOCl, NaOH (1M), H_2O/Dioxane 1:1
Method B: a) NH_4OH (*conc*) b) BnOCOCl, NaOH (2M), Dioxane

Scheme 28: Synthesis of 7-aminomethyl isochroman using Cbz protection

The bromo acid **33** was initially treated in ethanol with concentrated ammonium hydroxide, and the resulting amine intermediate was protected by addition of benzylchloroformate in a 1:1 mixture of water/dioxane basified with a 1 M solution of sodium hydroxide (method A, Scheme 28). The first attempt, starting with 500 mg of the bromo acid **33**, afforded the Cbz protected amino acid **38** in 80% yield after recrystallisation. However, on a 2 g scale, the yield dropped to 58% and subsequently, only 29% yield was retrieved from a 4 g scale reaction. As we were not sure which step (amine substitution or protection) was affected, the procedure for the bromine displacement was first altered. Indeed, the synthesis of **38** can induce the formation of the side-product **42** resulting from the attack of the amine intermediate on the

bromomethylphenylacetic acid (Scheme 29). Although the amine preparation requires high dilution of the bromo acid **33**, we believe this side-reaction commonly occurs if the concentration of ammonia in the medium is too low.



Scheme 29: Diacid formation

The reaction was, therefore, performed using ammonia gas to saturate the ethanol solution. The ammonia gas was first liquefied at -78 °C in ethanol and the bromo acid was then added in small portions. Nonetheless, this reaction remained experimentally difficult to achieve on 4 g scale, since we were not sure when the ethanol had reached saturation in ammonia. Despite these problems, the Cbz protection step was repeated in a manner identical to the BOC protection protocol; however, the yield did not improve. In order to avoid the use of ammonia gas, the bromo acid was dissolved in concentrated ammonium hydroxide only, thus allowing the concentration of ammonia to be at a maximum. The procedure employed for the Cbz protection was in fact a method used for the previous BOC protection, therefore, we decided to follow a standard Cbz protection procedure. Hence, a 2 M solution of sodium hydroxide was utilised instead of water (method B, Scheme 28), to make sure the reaction medium remained basic, thus preventing any esterification of the acid.[2] These modifications proved to be fruitful and a reaction using 4 g of the starting material afforded the desired product **38** in 69% yield.

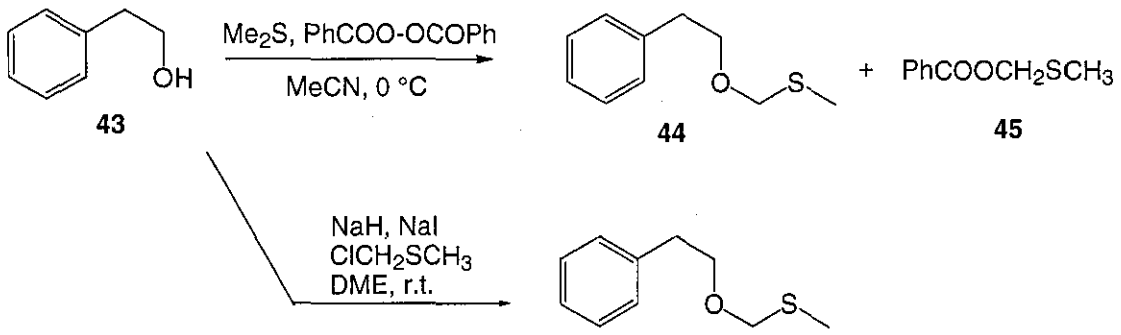
The reduction of the acid in the presence of the Cbz group was also carried out with the BH_3-THF complex, at 0 °C to room temperature. On a small scale (500 mg), the reaction gave 65% yield, but with 2 g of the Cbz amino acid, the yield decreased to 30%. After a few attempts, it was found that the reaction has to take place at 0 °C or below, and the addition of BH_3-THF complex must be very slow. If these two conditions are not fulfilled, the Cbz group is cleaved, and the resulting molecule is lost in the aqueous layer during the work-up procedure. Once this point was solved, the reduction of 5.28 g of the **38** furnished the corresponding alcohol **39** in 88% yield.

For the next step, the protection of the alcohol was achieved with the MEM group. As described for the *N*-BOC-*O*-MEM compound **37**, the MEM ether **40** was produced by stirring the alcohol **39** with DIPEA and MEM-Cl in anhydrous dichloromethane under nitrogen for 8 hours. The reaction took place at room temperature and allowed isolation of 82% yield of the product **40**. The MEM ether derivative has to be stored in the refrigerator, otherwise slow decomposition occurs. Cyclisation using $TiCl_4$ in dichloromethane at 0 °C provided the Cbz aminomethyl isochroman **41** in 69% yield on one occasion. However, several other attempts to cyclisation displayed variable yields (5-58%). This reaction is very sensitive to moisture and air and therefore had to be carefully carried out. Although numerous attempts at various temperatures (from -78 °C to 0 °C) were performed, the cyclisations were capricious. The effectiveness of other Lewis acids, such as tin tetrachloride ($SnCl_4$) and scandium triflate (ScOTf) was also tested, but the cyclisation did not take place. However, we noticed that the cyclisation reactions were not reproducible when more than 500 mg of the MEM product was used. The cause of this problem remained undetermined. Therefore, an alternative route to the isochroman cyclisation was devised.

2.8.2.2.1) MTM ether

Instead of using the MEM group, the methylthiomethyl (MTM) group was suggested as an alcohol protection which could permit the heterocyclic cyclisation by action of a soft metal ion. Hence, as a test compound, phenylethanol (**43**) was reacted with

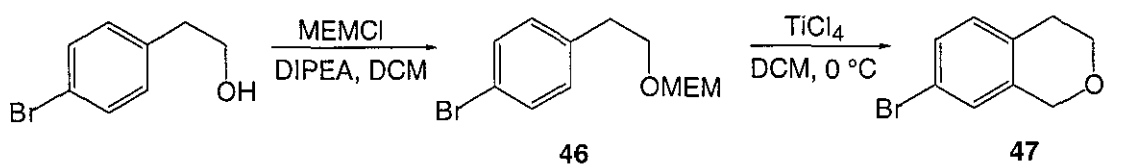
dimethylsulfide in anhydrous acetonitrile with benzoyl peroxide (Scheme 28).[189] This procedure yielded a mixture of the MTM ether **44** and ester **45**, which could not be separated by chromatography. For this reason, a second attempt was carried out in conditions developed by Corey.[190] This method, reported to be favourable for aryl alcohols,[191] involves a suspension of sodium hydride, sodium iodide and chloromethyl methyl sulfide in dimethoxyethane (Scheme 30). Unfortunately, only 18% of the desired MTM ether **44** was isolated after column chromatography.



Scheme 30: Syntheses of the methylthiomethyl ether **44**

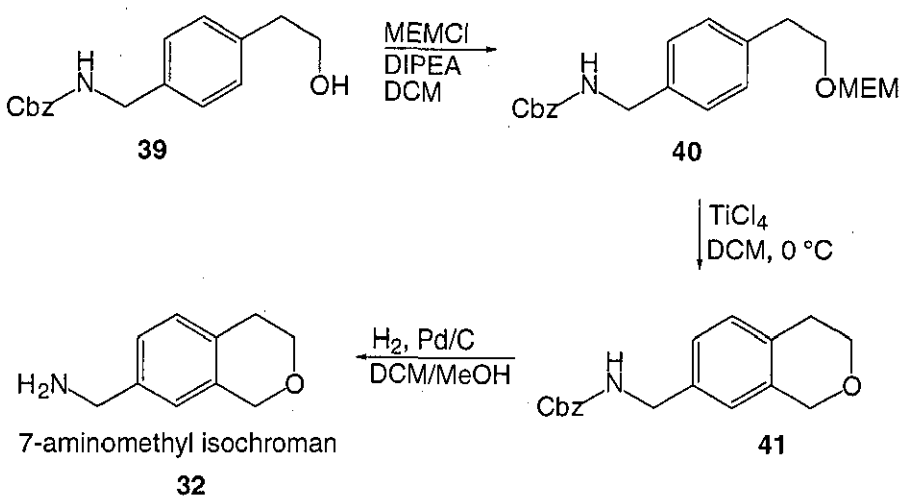
The small amount of MTM ether was submitted to a range of cyclisation conditions using Lewis acids: $HgCl_2$ in acetonitrile, $AgNO_3$ in tetrahydrofuran, and $AgBF_4$, $ZnCl_2$ and $TiCl_4$ all in dichloromethane; but none of these reactions provided the expected isochroman. As these reactions proved unsuccessful, cyclisation with the MEM group was reconsidered.

We found that an American patent described the synthesis of 7-bromoisochroman (**47**), *via* the *O*-MEM-*p*-bromophenylethyl ether intermediate **46** (Scheme 31).[192]



Scheme 31: Synthesis of the 7-bromoisochroman

In our case, the bromo alcohol was exposed to the MEM-Cl for 2 hours and the resulting product **46** was used in the next step without purification. The cyclisation was performed by adding a solution of the MEM ether **46** in dichloromethane to a solution of $TiCl_4$ in dichloromethane at 0 °C, whereas the previous method involved the addition of the $TiCl_4$ solution to **46** in dichloromethane. After 2 hours, the reaction yielded 70% of the 7-bromoisochroman (**47**) overall. Thus, the *N*-Cbz-aminomethyl phenylethanol (**39**) was submitted to the same reaction conditions to produce **40** (Scheme 32). Owing to this procedure, the cyclisation could be performed on larger scale, and thus 3.66 g of the MEM compound **40** furnished the *N*-Cbz aminomethyl isochroman (**41**) in 68% yield .



Scheme 32: Cyclisation of the MEM product followed by deprotection of the Cbz group

The Cbz deprotection of **41** was accomplished in methanol/dichloromethane by hydrogenolysis with a catalytic amount of palladium on charcoal.[193] The expected aminomethyl isochroman **32** was isolated in quantitative yield (Scheme 32).

Finally, the successful synthesis of 7-aminomethyl isochroman has been thus achieved. Each step exhibits good chemical yields and can be reproduced to afford large amount of the products.

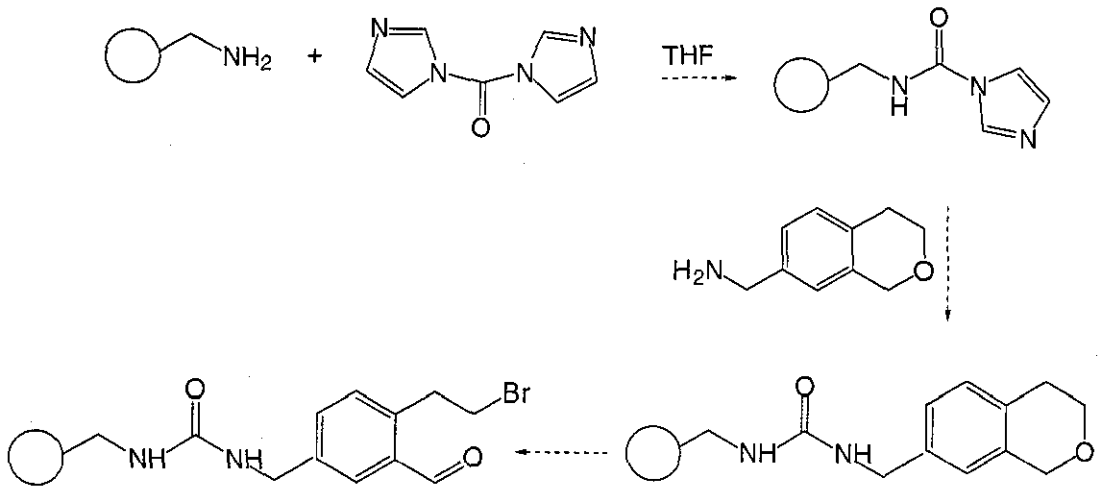
2.9) Conclusions and Future work

The epoxidation of alkenes mediated by iminium salts and Oxone® in acetonitrile/water has been successfully adapted to solid phase conditions. After numerous experiments, we have found that the ratio substrate/oxidant is the major parameter influencing the epoxidation reaction. Indeed, with a 1:4 alkene/Oxone® ratio, the epoxidations reach completion within 1 hour using the supported catalysts, whereas the reaction only gives 80% conversion with a 1:2 alkene/Oxone® ratio.

The iminium salts have been immobilised on six different resins, namely, the glycinol 2-chlorotrityl polystyrene, as well as the aminomethylated NovaSyn® TG, NovaGel™, ArgoGel®, PEGA and polystyrene matrices. The presence of the iminium salt on the solid support has been proved by ^{13}C magic angle spinning NMR analysis for some of theses resins. Additionally, it is the ArgoGel® and PEGA iminium resins which afford the best catalytic activity for the epoxidation of 1-phenylcyclohexene.

In an attempt to synthesise chiral iminium salts, we demonstrated that chiral polymer-supported catalysts derived from a primary amino alcohol are inactive for the enantioselective epoxidation.

As an alternative strategy to obtain a diverse range of supported chiral iminium catalysts, the immobilisation of 2-(2-bromoethyl)benzaldehyde was devised. The condensation of this anchored aldehyde with a large variety of chiral amines would provide many potential catalysts. For this purpose, we implemented the synthesis of a promising substituted isochroman which can serve as a precursor for the (bromoethyl)benzaldehyde preparation. This six-step synthesis, which led to the formation of 7-aminomethyl isochroman, involves the utilisation of readily available starting materials and reagents, and displays good chemical yields. The next step leading to the polymer-supported (bromoethyl)benzaldehyde can be envisaged as illustrated in Scheme 33. The aminomethyl resin could be activated by imidazole prior to the immobilisation of the aminomethyl isochroman onto the polymer support. Nevertheless, as we could not proceed further for lack of time, this synthesis remains for further investigations.



Scheme 33: Attachment of the the aminomethyl isochroman to a resin

Further studies are also necessary to improve the epoxidation conditions for variously substitued alkenes, since our initial reactions have been inefficient in the triphasic system. With the organic oxidising agent TPPP, further investigations have to be pursued in order to develop a biphasic methodology using supported iminium catalysts.

To conclude, this process involving polymer-supported catalysts merits a particular attention, because this system could mediate more general oxidation reactions.

Chapter 3: EXPERIMENTAL SECTION

3.1 Purification of reagents, compounds and solvents

Commercially available resins were purchased from the following companies:

-Novabiochem: glycinol chlorotrityl resins, NovaSyn® TG, aminomethyl polystyrene, aminomethyl NovaGel™

-Argonaut Technology: aminomethyl ArgoGel®, and chloromethyl ArgoGel®

-Polymer Laboratories: aminomethyl PEGA

Commercially available reagents were purchased from Aldrich, Lancaster or Avocado and were used as supplied, without further purification, unless otherwise stated. Air and moisture sensitive compounds were stored in a desiccator over self-indicating silica pellets.

Light petroleum ether (b.p. 40-60 °C) was distilled from calcium chloride prior to use. Ethyl acetate was distilled from calcium chloride. Dichloromethane was distilled from phosphorus pentoxide or calcium hydride. Tetrahydrofuran was distilled under nitrogen atmosphere from the sodium/benzophenone ketyl radical. Triethylamine was stored over potassium hydroxide pellets.

Flash chromatography was carried out using Merck 9385 Kieselgel 60-45 (230-400 mesh) and a hand bellows to apply pressure to the column. Thin layer chromatography (TLC) was carried out on glass or aluminium plates coated with a silica gel layer of 0.25 mm thickness, containing fluorescer. Compounds on this material were

visualised by UV radiation at wavelength of 254 nm, or stained by exposure to an ethanolic solution of phosphomolybdic acid (acidified with concentrated sulfuric acid) followed by charring where appropriate.

3.2 Preparation of glassware

Highly air and moisture sensitive reactions were carried out using glassware that had been dried overnight in an oven at 210 °C. These were allowed to cool in a desiccator over self-indicating silica pellets. The reactions were carried out under a slight positive static pressure of nitrogen.

3.3 Elemental analyses, optical rotation measurements and melting points

Microanalyses were carried out at Loughborough University and were performed on a Perkin Elmer Elemental Analyser 2400 CHN.

Optical rotation values were measured with an Optical Activity-polAAr 2001 instrument, operating at λ=589 nm, corresponding to the sodium line (D), at the temperatures indicated. The values are given in 10^{-1} deg cm^2 g^{-1}. The solvents used for these measurements were of spectrophotometric grade. The solutions for these measurements were prepared in volumetric flasks for maximum accuracy of the volume of the solvent used.

Melting points were determined either on an Electrothermal-IA 9100 or a Stuart Scientific SMP 3 melting point apparatus and are uncorrected.

3.4 Infrared and mass spectra (IR, MS)

Fourier transformed infrared absorption spectra were recorded on a Perkin Elmer FT-IR Paragon 2001 instrument in the range 4000-600 cm^{-1}. Samples were prepared as potassium bromide discs or as thin films of their solution in the appropriate solvent between sodium chloride plates. Resin samples were always run as potassium bromide discs.

Mass spectra were carried out at Loughborough University and were recorded on Kratos MS-80 or Jeol-SX102 instruments using electron impact (EI), or fast atom bombardment (FAB). Electrospray (ES) mass spectrometry was carried out at OSI Pharmaceuticals using a Micromass Platform LC instrument.

3.5 Nuclear Magnetic Resonance (NMR)

Proton nuclear magnetic resonance spectra were recorded on the following NMR instruments: Varian Mercury 400 at OSI Pharmaceuticals; Bruker AC 250 and Bruker DPX 400 at Loughborough University, operating at 250.13 and 400.13 MHz respectively. All experiments were conducted at 25 °C unless otherwise stated, in deuteriated solvents. Tetramethylsilane, acetonitrile or methanol were used as the internal standard. Multiplicities were recorded as broad singlet (br.s), singlet (s), doublet (d), triplet (t), apparent triplet (app t), quartet (q), quintet (quint), apparent quintet (app quint), double doublet (dd), double triplet (dt), triple doublet (td), double double doublet (ddd), double double double doublet (dddd), and multiplet (m).

Carbon-13 nuclear magnetic resonance spectra were recorded on a Varian Mercury 400 instrument, operating at 100.58 MHz at OSI Pharmaceuticals; on Bruker AC 250 and Bruker DPX 400 instruments at Loughborough University, operating at 62.86 and 100.62 MHz respectively. Normally the ^{13}C NMR spectrum for each compound was recorded in the same deuteriated solvent as that used for the ^{1}H NMR spectrum, unless otherwise stated. Tetramethylsilane, acetonitrile or methanol were used as the internal standard. DEPT and COSY analyses were recorded on a Bruker DPX 400 instrument at Loughborough University. For resin samples, Magic Angle Spinning (MAS) ^{13}C NMR spectra were recorded at Durham University on a Varian UNITY *Inova* with a 7.05T Oxford Instruments magnet, operating at 75.43 MHz; the MAS probe was a standard 7 mm probe.

Polymer samples analysed at Loughborough University were prepared by placing 100-120 mg of resin in a 5 mm NMR tube and add small amounts of deuteriated solvents until the polymer was fully swollen, and 2-4 mm of excess solvent remained. The tube was then

sonicated or gently tapped by hand until no air bubbles were visible and the suspension appeared uniformly dispersed.

3.6 Determination of enantiomeric excesses (NMR)

Enantiomeric excesses were determined by proton nuclear magnetic resonance (^{1}H NMR) spectroscopy. The proton nuclear magnetic resonance spectra were recorded in deuteriated chloroform on Bruker AC 250 NMR instrument, in the presence of *tris*-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), [(+)-Eu(hfc)$_3$], as the chiral shift reagent, and tetramethylsilane as the internal standard. Between 3 and 5 mol% of the chiral shift reagent was used, depending on the substrate and concentration of the solution used. In no case, however, did the total mass of the chiral shift reagent used in each of the ^{1}H NMR experiments exceed 10 mg due to the paramagnetic properties of europium(III), which may compromise data through line broadening.

3.7 Agitation mode for resin beads

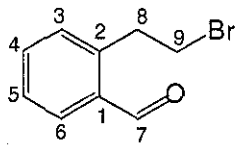
The resin beads could not be stirred using a magnetic stirrer, because this can damage the beads. The resin-mixtures were agitated on an orbital shaker; either a Stuart Scientific orbital incubator SI 50 or an Heidolph Instruments Rotamax 120.

3.8 Numbering system

The assignments of the proton and carbon-13 resonances have been made according to numbering systems indicated in the diagrams below. Some of the systems used are standard in chemical nomenclature but others were adopted by the present author in order that compounds derived from the same skeletal core retain the numbering of the parent compound. This was undertaken because, according to the IUPAC system, compounds derived from the same precursor often possess different numbering which is not convenient for comparison/recognition purposes.

3.9 Experimental procedures

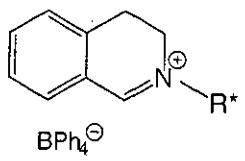
2-(2-Bromoethyl)benzaldehyde (7) [157]



Bromine (60.0 g, 0.37 mol) was added through a reflux condenser over a period of 5 min with stirring to an ice-cooled solution of isochroman (50.0 g, 0.37 mol) in carbon tetrachloride (200 mL). After the vigorous reaction subsided, (*ca.* 5 min), the cooling bath was removed and the dark brown solution was heated under reflux until the reaction mixture became pale yellow (*ca.* 1 hour). The solution was allowed to reach ambient temperature, and the solvent removed under reduced pressure. A solution of 48% aqueous hydrobromic acid (75 mL) was added to the resulting oil (yellow), and the reaction mixture was heated to reflux (dark green-blue). After approximately 10-15 min the solution was allowed to cool and extracted with diethyl ether. The combined organic extracts were washed with water, then with saturated aqueous sodium carbonate, and dried over magnesium sulfate. Filtration followed by evaporation of the solvent under reduced pressure yielded the crude 2-(2-bromoethyl)benzaldehyde as a brown oil (71.5 g, 90%). Vacuum distillation (T 150-200 °C, p 0.06-0.1 mbar) afforded the title compound as an analytically pure colourless oil.

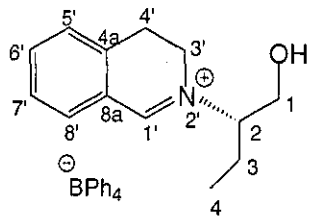
ν_{max}(neat)/cm^{-1} 2742, 1697 (C=O), 1600, 1575; δ_H (250 MHz, $CDCl_3$) 3.55-3.64 (4H, m, $2CH_2$ at C-8 and C-9), 7.35 (1H, dd, *J* 7.4, 1.4 Hz, H-3), 7.48 (1H, ddd, *J* 7.5, 7.3, 1.4 Hz, H-5), 7.52 (1H, ddd, *J* 7.4, 7.3, 1.7 Hz, H-4), 7.82 (1H, dd, *J* 7.5, 1.7 Hz, H-6), 10.15 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 193.3 (CH, HC=O), 141.0 (C quat, C-1), 134.9 (Ar-CH, C-6), 134.3 (C quat, C-2), 134.1 (Ar-CH, C-4) 132.5 (Ar-CH, C-3), 128.1 (Ar-CH, C-5), 36.7 (CH_2, C-9), 33.17 (CH_2, C-8); *m/z* (FAB) 211 (M^+, 100); exact mass calcd for C_9H_9BrO M^+ 211.9837, found M^+ 211.9837

General procedure for the synthesis of dihydroisoquinolinium salts from 2-(2-bromoethyl)-benzaldehyde and primary amines in solution phase



A flask containing distilled 2-(2-bromoethyl)-benzaldehyde (1.1 eq) was cooled by means of an ice-bath. The appropriate amine (1.0 eq) was dissolved in ethanol (15 mL/g of amine) and the solution added dropwise to the vigorously stirred cooled bromoaldehyde. After the complete addition, stirring was continued for 1 hour. The cooling bath was removed and the reaction mixture was stirred for a further 1 hour, while attaining room temperature. Sodium tetraphenylborate (1.0 eq) was added to the reaction mixture as an acetonitrile solution. After 5 min, the solvents were evaporated and the viscous oil obtained was triturated in ethanol, causing the precipitation of the organic salt. The latter was isolated by suction filtration, washed with ethanol/water (1:1), then ethanol, and finally with diethyl ether. The product was obtained as a white or yellowish solid.

(2*S*)-(3,4-Dihydroisoquinolinium-2-yl)-butan-1-ol tetraphenylborate (8)

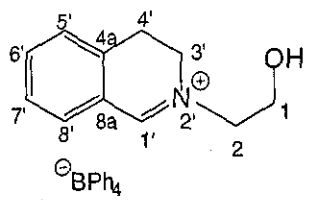


The title compound was prepared according to the general procedure, using 2-amino-1-butanol (1.0 g, 11.0 mmol) in ethanol (15 mL), bromoethylbenzaldehyde (2.78 g, 12.31 mmol) and sodium tetraphenylborate (3.83 g, 11.20 mmol), giving the title compound as a white solid (4.59 g, 78%); m.p. 164-165 °C

ν_{max}(MeCN)/cm^{-1} 3535 (OH), 2983 (CH_2), 1645 (C=N), 1603, 1574, 1478; δ_H (250 MHz, CD_3CN) 0.99 (3H, t, *J* 7.4 Hz, H-4), 1.91 (2H, app quint, *J* 7.4 Hz, H-3), 3.14 (2H, app t, *J* 7.8 Hz, H-1), 3.77 (4H, m, H-3' and H-4'), 3.87 (1H, m, CH, H-2), 6.83 (4H, t, *J*

7.2 Hz, Ar-H *para* in BPh_4), 6.98 (8H, t, *J* 7.4 Hz, Ar-H *ortho* in BPh_4), 7.28 (8H, m, Ar-H *meta* in BPh_4), 7.44 (2H, m, Ar-H-5' and Ar-H-7'), 7.75 (2H, m, Ar-H-6' and Ar-H-8'), 8.70 (1H, s, NCH, H-1'); δ_C (100 MHz, CD_3CN) 167.5 (NCH, C-1'), 164.8 (4 C quat in BPh_4), 139.3 (Ar-CH, C-8'), 138.4 (C quat, C-8a), 136.8 (8 Ar-CH *meta* in BPh_4), 134.9 (Ar-CH, C-6'), 129.5 (Ar-CH, C-7'), 129.37 (Ar-CH, C-5'), 126.6 (4 Ar-CH *ortho* in BPh_4), 125.6 (C quat, C-4a), 122.8 (4 Ar-CH *para* in BPh_4), 75.9 (CH, C-2), 61.2 (OCH_2, C-1), 47.0 (CH_2, C-3'), 25.73 (CH_2, C-4'), 22.1 (CH_2, C-3), 10.6 (CH_3, C-4); *m/z* (FAB) (cation) 204 (M^+, 100); exact mass calcd for $C_{13}H_{18}NO$ M^+ 204.1388, found M^+ 204.1389. Anal. calcd for $C_{37}H_{38}BNO$: C, 84.89; H, 7.32; N, 2.67; found: C, 84.67; H, 7.24; N, 2.77%

2-(3,4-Dihydroisoquinolinium-2-yl)-ethan-1-ol (9)



The title compound was prepared according to the general procedure, using 2-amino-1-ethanol (0.40 g, 6.43 mmol) in ethanol (15 mL), bromoethylbenzaldehyde (1.37 g, 6.43 mmol) and sodium tetraphenylborate (2.20 g, 6.43 mmol), giving the title compound as a yellowish solid (1.11 g, 35%); m.p. 159-160 °C

ν_{max}(MeCN)/cm^{-1} 3524 (OH), 2983 (CH_2), 1655 (C=N), 1603, 1573, 1478; δ_H (250 MHz, CD_3CN) 3.09 (2H, t, *J* 7.8 Hz, H-1), 3.33 (1H, s, OH), 3.77 (4H, s, H-3' and H-4'), 3.81(2H, t, *J* 7.5 Hz, CH_2, H-2), 6.83 (4H, t, *J* 7.2 Hz, Ar-H *para* in BPh_4), 6.97 (8H, t, *J* 7.4 Hz, Ar-H *ortho* in BPh_4), 7.28 (8H, m, Ar-H *meta* in BPh_4), 7.46 (2H, m, Ar-H-5' and Ar-H-7'), 7.75 (2H, m, Ar-H-6' and Ar-H-8'), 8.70 (1H, s, NCH, H-1'); δ_C (100 MHz, CD_3CN) 167.8 (NCH, C-1'), 164.8 (4 C quat in BPh_4), 139.3 (Ar-CH, C-7'), 137.7 (Ar-CH, C-8'), 136.7 (8 Ar-CH *meta* in BPh_4), 134.7 (Ar-CH, C-5'), 129.7 (Ar-CH, C-6'), 129.5 (Ar-CH, C-7'), 126.7 (4 Ar-CH *ortho* in BPh_4), 125.4 (C quat, C-4a), 122.8 (4 Ar-CH *para* in BPh_4), 63.7 (CH_2, C-2), 58.4 (OCH_2, C-1), 49.7 (CH_2, C-3'), 25.6 (CH_2, C-

4'); *m/z* (FAB) (cation) 176 (M^+, 100); exact mass calcd for $C_{11}H_{14}NO$ M^+ 176.10754, found M^+ 176.10748. Anal. calcd for $C_{35}H_{34}BNO$: C, 84.84; H, 6.92; N, 2.83; found: C, 84.54; H, 6.81; N, 2.84%

General procedure for the catalytic asymmetric epoxidation of 1-phenylcyclohexene mediated by iminium salts, in solution phase

Sodium carbonate (4 eq) in water (8 mL/g) was added to an ice-cooled flask containing Oxone® (2 eq) and the resulting suspension allowed to stir for 5 min so that the initial effervescence subsided. The tetrahydroisoquinolinium salt (10 mol %) was dissolved in the same volume of acetonitrile as that of water and then added to the reaction mixture. The alkene substrate was also dissolved in the same volume of acetonitrile and added to the reaction mixture. The suspension was stirred for 3 hours and transferred to a separating funnel where the acetonitrile layer was collected. The aqueous phase was diluted with water and extracted thoroughly with diethyl ether. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and the solvent evaporated to give a light brown oil which was triturated with cold petroleum ether and filtered. The organic solution was then stripped of solvent to provide the crude epoxides which were *ca.* 90% pure by ^1H NMR spectroscopy for completed or nearly completed reactions. Analytically pure epoxides can be obtained by chromatography on a short column of silica gel, eluting initially with light petroleum to remove non-polar impurities and/or parent alkene, followed by light petroleum/ethyl acetate (95:5) to afford the epoxides. These are easily identified by TLC analysis, by the quick manifestation of a deep blue stain upon exposure to an ethanolic solution of phosphomolybdic acid acidified with concentrated sulfuric acid. It must be noted that several epoxides are very volatile and when solutions of these compounds are evaporated, it is best that the water bath does not exceed 30 °C. Epoxides are very sensitive compounds and storage for prolonged periods of time (days) is best to be done under nitrogen.

General procedure for the epoxidation of various alkenes mediated by polymer-supported iminium salts using Oxone®

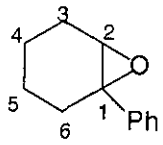
The resin was swollen in water (1 mL) prior to epoxidation reaction. Sodium carbonate (8 eq) was dissolved in water* and cooled in an ice bath before addition of Oxone® (4 eq). In an ice-cooled flask the resin** (50 and 25 mol%) was suspended in acetonitrile, and the aqueous sodium carbonate and Oxone® added. The alkene substrate was then dissolved in acetonitrile (1 mL) and added to the resin. The reaction mixture was shaken at room temperature using an orbital shaker. After reaction, the resin was filtered and rinsed with a small amount of diethyl ether. The filtrate was transferred to a separating funnel and the organic layer collected. The aqueous phase was extracted with diethyl ether and the resulting organic extracts were combined, washed with brine and dried over magnesium sulfate. Filtration and evaporation gave the expected epoxide. The epoxidations were assayed by ^{1}H NMR spectroscopy and conversions were always estimated from the integration of the H-2 signal of the alkene and the epoxide.

General procedure for the epoxidation of 1-phenylcyclohexene mediated by polymer-supported iminium salts using TPPP

Tetraphenylphosphonium monoperoxysulfate (TPPP) (2 and 4 eq) was dissolved in the desired solvent (4 mL/100 mg of oxidant). In an ice-cooled flask the resin (50 or 25 mol%) was suspended in the organic solvent (1 mL) of reaction and the solution of TPPP added. 1-Phenylcyclohexene (1 eq) was then dissolved in the organic solvent (1 mL) and added to the resin. The mixture was shaken using an orbital shaker at room temperature, and the reaction was monitored by TLC. After reaction, the resin was filtered and rinsed with a small amount of diethyl ether, which induce the precipitation of the remaining oxidant as well. The filtrate was filtered through Celite. The resulting organic extract was evaporated to give an oil. The samples were assayed by ^{1}H NMR spectroscopy and conversions were always estimated from the integration of the H-2 signal of the alkene and the epoxide.

* 0.5mL of water/0.03mmol of resin used
** All reactions were performed with between 38-500 mg of resin

1-Phenylcyclohex-1-ene oxide (10) [194]

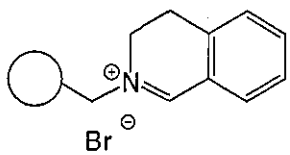


Epoxidations using soluble catalysts: 1-Phenylcyclohexene (200 mg, 1.26 mmol, 1 eq) furnished the title compound as a colourless oil (149 mg, 68%).

Epoxidations using polymer-supported catalysts: 1-Phenylcyclohexene (18 mg, 0.11 mmol, 1 eq) furnished the title compound as a colourless oil (11 mg, 60%).

ν_{max}(neat)/cm^{-1} 3084, 1602, 1495; δ_H (250MHz, $CDCl_3$) [1.22-1.35 (1H, m), 1.53-1.64 (3H, m), 1.99-2.06 (2H, m), 2.16-2.32 (1H, m), 4 CH_2 H-3 to H-6], 3.10 (1H, t, *J* 2.0 Hz, CH, H-2), 7.28-7.44 (5H, m, Ar-CH, Ph group); δ_C (62.50 MHz, $CDCl_3$) 142.8 (C quat in Ph group), 128.2 (2 Ar-CH *meta* in Ph group), 127.1 (Ar-CH *para* in Ph group), 125.3 (2 Ar-CH *ortho* in Ph group), 60.1 (C quat, Ph-C-O), [28.2 (CH_2), 24.7 (CH_2), 19.8 (CH_2), C-3 to C-6)].

General procedure for the synthesis of dihydroisoquinolinium salts from 2-(2-bromoethyl)benzaldehyde and primary amines on resins

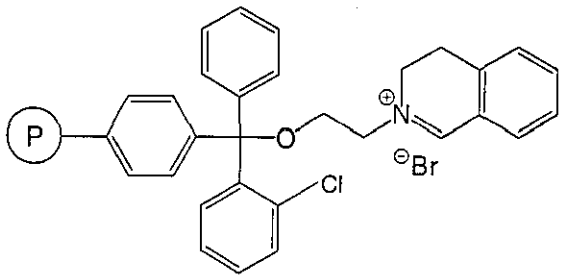


The different solvents used, the reaction times, and the temperatures tested are given in the 'Results and Discussion' section.

The aminomethyl resin (1-5 g, 1eq) was swollen in a mixture of trimethylorthoformate/ dichloromethane (1:1) for 10 min prior to reaction. The 2-(2-bromoethyl)-benzaldehyde (3 eq) was dissolved in trimethylorthoformate (0.5 mL/0.03 mmol of resin used) and added to the swollen resin. The reaction mixture was shaken overnight at room temperature using an orbital shaker. The resin was then filtered and washed successively

with dichloromethane, tetrahydrofuran, ethanol, and diethyl ether. The derivatised resin was then dried under high vacuum.

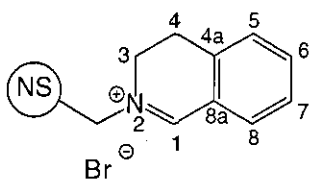
Chlorotrityl polystyrene dihydroisoquinolinium bromide salt (11)



The FT-IR spectrum of **11** did not afford the identification of the absorption band of the C-N double bond, because several peaks in this region were identical to those already present in the commercial resin.

MAS-NMR was not available at that time

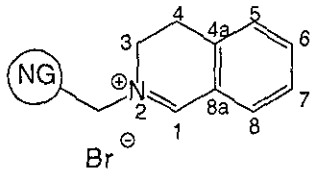
NovaSyn® TG dihydroisoquinolinium bromide salts (13)



The low loading of the resin did not allow for a good FT-IR spectrum, even though an FT-IR microspectroscopy analysis on a single bead was carried out in the Perkin Elmer main office.

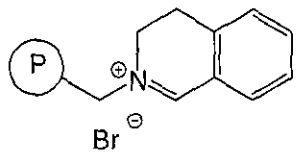
δ_C (MAS, 75 MHz, without solvent) 167.9 (NCH, C-1), 138.4 (Ar-CH, C-8), 137.8 (C quat, C-8a), 134.8 (Ar-CH, C-6), 129.1 (2 Ar-CH, C-7 and C-5), 125.7 (C quat, C-4a), 67.3 (CH_2N, C-9), 49.7 (CH_2, C-3), 25.8 (CH_2, C-4)

NovaGel® dihydroisoquinolinium bromide salt (14)



ν_{max}(KBr)/cm^{-1} 1647 (C=N), 1600; a few peaks of the ^{13}C MAS-NMR spectrum could be assigned ; δ_C (MAS, 75 MHz, $CDCl_3$) *inter alia*. 169.0 (NCH, C-1), 136.6, 126.3, 64.6 (CH_2N, C-9), 48.4 (CH_2, C-3), 26.0 (CH_2, C-4)

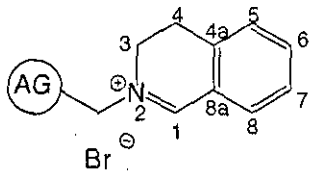
Polystyrene dihydroisoquinolinium bromide salt (15)



ν_{max}(KBr)/cm^{-1} 1647 (C=N)

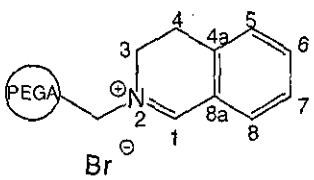
The ^{13}C MAS-NMR spectrum did not show the dihydroisoquinolinium salt

ArgoGel® dihydroisoquinolinium bromide salt (16)



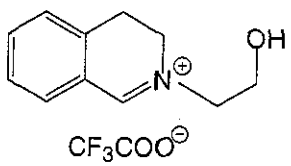
ν_{max}(KBr)/cm^{-1} 1654 (C=N); δ_C (MAS, 75 MHz, without solvent) 167.9 (NCH, C-1), 138.5 (Ar-CH, C-8), 137.4 (C quat, C-8a), 134.8 (Ar-CH, C-6), 129.2 (2 Ar-CH, C-7 and C-5), 125.7 (C quat, C-4a), 67.3 (CH_2N, C-9), 49.8 (CH_2, C-3), 25.8 (CH_2, C-4)

PEGA dihydroisoquinolinium bromide salt (17)



This resin could not be submitted to FT-IR analysis; the ^{13}C MAS-NMR spectrum showed a few charateristic peaks of the dihydroisoquinolinium salt; δ_C (MAS, 75 MHz, without solvent) *inter alia.* 167.8 (NCH, C-1), 139.1 (Ar-CH), 137.9 (C quat), 134.6 (Ar-CH), 129.0 (Ar-CH), 125.1 (C quat), 67. (CH_2N, C-9), 48.2 (CH_2, C-3), 25.7 (CH_2, C-4)

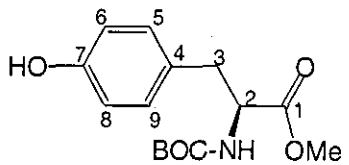
Cleavage of the iminium salt from chlorotrityl polystyrene resin (12)



A solution of 5% TFA in DCM/TIS (95:5) was added to a flask containing the polymer supported iminium salt (500 mg of resin). The suspension was shaken for 1 hour and the resin was then filtered and washed with dichloromethane. The filtrate was evaporated under reduced pressure, then dichloromethane was added to the residue and evaporated again (repeated twice).

The proton NMR spectrum of the crude cleaved product was identical to the spectrum of 2-(3,4-dihydroisoquinolinium-2-yl)-ethan-1-ol (**9**) with the exception of the anion.

***N*-(*tert*-Butyloxycarbonyl)-L-tyrosine methyl ester (19)** [195]



Method A:

Tyrosine methyl ester (5 g, 25.6 mmol) was dissolved in *tert*-butanol (10 mL) and diethyl ether (15 mL). Di-*tert*-butyl dicarbonate (5.6 g, 25.6 mmol) in diethyl ether (10 mL) was added dropwise over 30 min, and the reaction was left to stir at room temperature for a further 30 min. The mixture was diluted with diethyl ether (15 mL), washed with water, dried over magnesium sulfate, filtered and evaporated. The resulting solid was

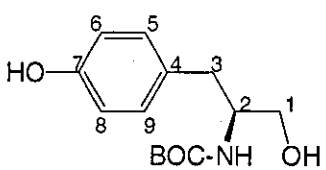
recrystallised from ethyl acetate/ petroleum ether to give of a white solid (6.8 g, 90%); m.p. 102-104 °C

$[\alpha]_D^{23}$ 11 (c 2.0, EtOH); ν_{max}(DCM)/cm^{-1} 3355 (NH, OH), 1686 (broad C=O), 1516 (CNH); δ_H (250 MHz, $CDCl_3$) 1.51 (9H, s, $3CH_3$), 2.96-3.07 (2H, m, CH_2), 3.73 (3H, s, OCH_3), 4.51-4.55 (1H, m, CH), 5.00 (1H, d, *J* 6.2 Hz, NH), 5.72 (1H, s, OH), 6.72 (2H, d, *J* 6.6 Hz, Ar-H), 6.96 (2H, d, *J* 6.6 Hz, Ar-H); δ_C (62 MHz, $CDCl_3$, 55°C) 172.8 (COO, C-1), 172.5 (COO of BOC), 155.6 (C quat, C-7), 130.5 (2 Ar-CH, C-5 and C-9), 128.0 (C quat, C-4), 116.0 (2 Ar-CH, C-6 and C-8), 80.6 (C quat of BOC), 55.4 (CH, C-2) 52.4 (OCH_3), 38.8 (CH_2, C-3), 28.6 ($3CH_3$); *m/z* (EI) 295 (M^+, 20); exact mass calcd for $C_{15}H_{21}NO_5$ M^+ 295.1419, found M^+ 295.1423. Anal. calcd for $C_{15}H_{21}NO_5$: C, 61.04; H, 7.17; N, 4.75; found: C, 60.96; H, 7.12; N, 4.31%

Method B:

To a stirred solution of di-*tert*-butyl dicarbonate (6.1 g, 28.0 mmol) in dry dichloromethane (23 mL) was added a solution of tyrosine methyl ester (5.0 g, 25.6 mmol) and dry triethylamine (3.6 mL, 26.3 mmol) in dry dichloromethane (45 mL) over 10 min. The reaction mixture was stirred at room temperature for 2 hours, after which carbon dioxide ceased to be evolved. The mixture was washed with a solution of HCl (2M) followed by water. The organic layer was dried over magnesium sulfate, filtered and evaporated to provide a white solid, which was used in the next step without further purification.

_N_-(*tert*-Butyloxycarbonyl)-tyrosinol (20) [196,197]

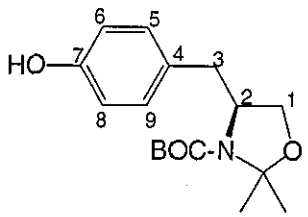


Calcium chloride (5.0 g, 4.3 mmol) was stirred in THF (50 mL) at 0 °C and sodium borohydride (3.25 g, 85.0 mmol) was added cautiously. The mixture was allowed to reach room temperature and then heated under reflux for 1 hour. After cooling, the *N*-BOC

amino ester **19** (5.0 g, 17.1 mmol) in THF (25 mL) was added very slowly. The reaction mixture was stirred overnight at room temperature and then quenched with water (200 mL). After extraction with ethyl acetate, the organic layer was dried over magnesium sulfate, filtered and evaporated to give a white solid. The resulting residue was recrystallised from dichloromethane/petroleum ether to provide the title compound as a white solid (3.9 g, 86%); m.p. 107.5-109.5 °C

$[\alpha]^{23}_D$ -26 (c 9.82, MeOH); ν_{max}(DCM)/cm^{-1} 3426 (NH, OH), 1646 (broad C=O), 1516 (CNH); δ_H (250 MHz, $CDCl_3$) 1.49 (9H, s, $3CH_3$), 2.72 (2H, d, *J* 7.1 Hz, CH_2), 3.49-3.54 (1H, m, OCH_2), 3.59-3.65 (1H, m, OCH_2), 3.74-3.79 (1H, m, CH), 4.92 (1H, d, *J* 6.2 Hz, NH), 6.74 (2H, d, *J* 6.6 Hz, Ar-H), 7.00 (2H, d, *J* 6.6 Hz, Ar-H); δ_C (62 MHz, $CDCl_3$, 55 °C) 172.4 (COO of BOC), 155.4 (C quat, C-7), 130.3 (2 Ar-CH, C-5 and C-9), 127.9 (C quat, C-4), 115.9 (2 Ar-CH, C-6 and C-8), 80.0 (C quat of BOC), 55.4 (CH, C-2) 52.6 (CH_2O, C-1), 38.8 (CH_2, C-3), 28.6 ($3CH_3$); *m/z* (EI) 267 (M^+, 25); exact mass calcd for $C_{14}H_{21}NO_4$ M^+ 267.1432, found M^+ 267.1470.

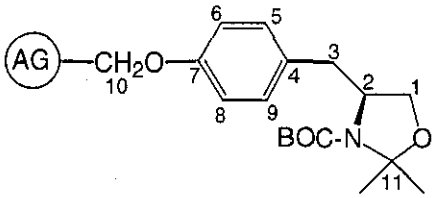
_N_-(*tert*-Butyloxycarbonyl)-_N_,_O_-isopropylidene-L-tyrosinol (21) [197]



The *N*-protected amino alcohol **20** (4 g, 15 mmol) was dissolved in dimethoxypropane (40 mL) and acetone (125 mL). Boron trifluoride etherate (0.7 mL) was added dropwise and a yellow colour change was observed. The reaction mixture was stirred for 2 hours under nitrogen, and quenched by addition of triethylamine (0.7 mL). The solvent was evaporated and the resulting oil was dissolved in ethyl acetate. This mixture was washed with aqueous sodium hydrogen carbonate, followed by brine. The organic extracts were separated and dried over magnesium sulfate, filtered and evaporated to give a browni oil. Purification of the crude oil by column chromatography using petroleum ether/ethyl acetate (5:1 then 3:1) as eluent provided the desired product as a solid(2.9 g, 63%); m.p. 87.5-89.5 °C

$[\alpha]^{23}_D$ -27 (c 1.28, $CHCl_3$); ν_{max}(DCM)/cm^{-1} 3454 (OH), 1667 (C=O); δ_H (400 MHz, DMSO, 100 °C) 1.45 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.49 (9H, s, $3CH_3$), 2.61 (1H, dd, *J* 9.3, 13.4 Hz, PhCHH), 2.97 (1H, dd, *J* 0.9,3.5, 13.4 Hz, PhCHH), 3.79 (1H, dd, *J* 2.2, 8.8 Hz, OCHH), 381-3.85 (1H, ddd, *J* 8.8 and 5.9 and 0.9 Hz, OCHH) 3.95-4.00 (1H, dddd, *J* 2.2, 3.5, 5.9, 9.3 Hz, CH), 6.73 (2H, d, *J* 6.6 Hz, Ar-H), 6.99 (2H, d, *J* 6.6 Hz, Ar-H); δ_C (100 MHz, DMSO, 100 °C) 155.3 (COO), 150.8 (C quat, Ar-C-OH), 129.3 (2 Ar-CH), 128.0 (C quat, Ar-C), 114.9 (2 Ar-CH), 92.7 (C quat, N-C-O) 78.5 (C quat of BOC), 65.5 (OCH_2), 57.9 (N-CH), 37.5 ($PhCH_2$), 27.6 ($3CH_3$), 26.2 (CH_3), 23.4 (CH_3); *m/z* (FAB) 308 (M^++H, 21), 252 (100); exact mass calcd for $C_{17}H_{25}NO_4$ M^+ 307.3910, found M^+ 307.1779. Anal. calcd for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56, found: C, 66.54; H, 8.32; N, 4.52%

Attachment of *N,O*-protected amino alcohol to the chloromethyl ArgoGel® resin (22)

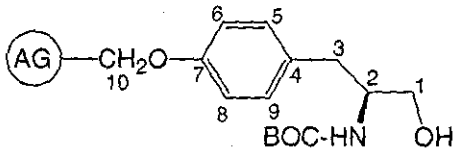


Sodium hydride (60% dispersion in mineral oil) (72 mg, 1.8 mmol) was dissolved in dry *N*-methylpyrrolidinone by stirring, and the solution turned brown and then purple. The protected amino alcohol **21** (551 mg, 1.8 mmol) was added and the mixture stirred until the evolution of hydrogen ceased. After addition of chloromethyl ArgoGel® resin (2.0 g, 0.9 mmol), the reaction mixture was shaken on an orbital shaker at room temperature for 50 hours under nitrogen. The polymer was filtered off and washed successively with diethyl ether, ethanol, THF, THF-water, THF, ethanol and diethyl ether. The resin was dried under vacuum at 50 °C.

loading: 0.1 mmol/g (from CHN); ν_{max}(KBr)/cm^{-1} 2868 (CH_2, CH_3), 1701 (C=O), 1654, 1107; at room temperature a doubling of peaks was observed for the isopropylidene group in the carbon spectrum.[173] δ_C (MAS, 75 MHz, without solvent) 157.5 (COO), 151.6 (C

quat, Ar-C-O, C-7), 130.6 (C quat, Ar-C, C-4), 130.1 (2 Ar-CH, C-5 and C-9), 114.7 (2 Ar-CH, C-6 and C-8), 93.8, 93.4 (C quat, N-C-O) 79.4 (C quat of BOC), 69.7 (CH_2O, C-10), 65.9 (CH_2O, C-1), 59.2 (N-CH, C-2), 38.7 (CH_2, C-3), 28.5 ($3CH_3$ of BOC), 27.5, 26.8 (CH_3), 24.5, 23.2 (CH_3)

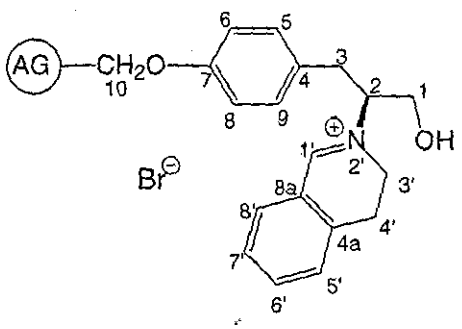
Deprotection of resin-bound protected-(L)-tyrosinol (23)



The polymer-bound protected tyrosinol **22** (1.36 g, 0.61 mmol) was shaken overnight in dichloromethane (19 mL) and TFA (3.4 mL) at room temperature. The resin was then filtered off and rinsed with dichloromethane. Triethylamine (1 mL), dissolved in dichloromethane was poured onto the resin and allowed to react for 10 min. The resin was washed with dichloromethane, tetrahydrofuran, ethanol, diethyl ether and dried under vacuum.

loading: 0.1 mmol/g (from CHN); ν_{max}(KBr)/cm^{-1} 3448 (NH_2, OH), 2926 (CH_2), 1654 (C=C polystyrene), 1560, 1098; δ_C (MAS, 75 MHz, without solvent) 157.4 (C quat, Ar-C-O, C-7), 131.0 (C quat, Ar-C, C-4), 130.1 (2 Ar-CH, C-5 and C-9), 114.7 (2 Ar-CH, C-6 and C-8), 69.7 (CH_2O, C-10), 66.2 (CH_2O, C-1), 54.3 (N-CH, C-2), 39.8 (CH_2, C-3)

Iminium salt formation derived from resin-bound (L)-tyrosinol (24)

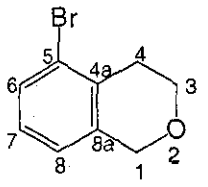


Bromoethylbenzaldehyde **7** (333 mg, 1.56 mmol) was added to the resin-bound amino alcohol **23** (1.3 g, 0.52 mmol) in a 1:1 mixture of trimethylorthoformate/dichloromethane

(9 mL), and the reaction mixture was shaken overnight at room temperature. The resin was filtered and rinsed with dichloromethane, tetrahydrofuran, ethanol, diethyl ether and dried under vacuum.

loading: 0.1 mmol/g (from CHN); ν_{max}(KBr)/cm^{-1} 3446 (OH), 2869 (CH_2), 1654 (C=C polystyrene), 1647 (C=N); δ_C (MAS, 75 MHz, without solvent) 167.2, (NCH, C-1'), 158.0 (C quat, Ar-C-O, C-7), 138.0 (Ar-CH, C-8'), 136.6 (C quat, C-8a), 134.6 (Ar-CH, C-6'), 130.1 (2 Ar-CH, C-5 and C-9), 127.8 (2 Ar-CH, C-5' and C-7' coincidient with polystyrene signal), 125.2 (C quat, C-4a), 115.2 (2 Ar-CH, C-6 and C-9), 74.9 (CH, C-2), 69.6 (CH_2O, C-10), 67.4 (CH_2O, C-1), 46.3 (CH_2, C-3'), 34.0 (CH_2, C-3), 25.2 (CH_2, C-4').

5-Bromoisochroman (27) [175]



Method A:

2-Bromophenylethanol (1.0 g, 5.0 mmol) was dissolved in dry toluene (1.8 mL) in a three necked-flask, equipped with a thermometer, and inlet and outlet tubes to allow the gas to bubble through the reaction medium. The solution was cooled down to between -5 and -10 °C and paraformaldehyde (150.0 mg, 5.0 mmol) added to the mixture. HCl gas was then bubbled through the mixture for 4 hours, while the reaction was stirred. Ground calcium chloride was stirred into the mixture and the latter was then filtered. The solvent was evaporated to give crude bromophenethyl chloromethyl ether as an oil, which was used without further purification.

Concentrated sulfuric acid (53 μL, 1 mmol) was added to the bromophenethyl chloromethyl ether and the mixture was stirred for 3 hours at 80-90 °C. After cooling to room temperature, a solution of sodium hydroxide (20%) was added and the mixture was stirred for a further 1 hour. The reaction mixture was extracted with diethyl ether and the

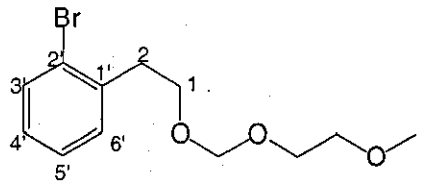
combined organic layers were washed with water. The organic phase was dried over magnesium sulfate, filtered and evaporated under vacuum. The yellow residue was purified by column chromatography using petroleum ether/ethyl acetate (9:1) as the eluent. The resulting compound was recrystallised from ethyl acetate/petroleum ether to yield the title compound as a white solid (580 mg, 55%).

ν_{max}(DCM)/cm^{-1} 2959 (CH_2), 1557, 1462, 1441, 1107, 770, 648; δ_H (250MHz, $CDCl_3$): 2.81 (2H, t, *J* 5.8 Hz, CH_2, H-4), 4.00 (2H, t, *J* 5.8 Hz, CH_2, H-3), 4.73 (2H, s, CH_2, H-1), 6.93 (1H, d, *J* 7.6 Hz, Ar-H, H-8), 7.10 (1H, app t, *J* 7.6, 7.9 Hz, Ar-H, H-7), 7.43 (1H, d, *J* 7.9 Hz, Ar-H, H-6); δ_C (100 MHz, $CDCl_3$) 138.0 (C quat, C-5), 133.5 (C quat, C-4a), 130.7 (1C, Ar-CH), 127.7 (1C, Ar-CH), 125.7 (C quat, C-8a), 123.9 (1C, Ar-CH), 68.2 (CH_2, C-1), 55.5 (CH_2, C-3), 29.6 (CH_2, C-4); *m/z* (FAB) 212-214 (M^+, 100), 182-184 (100); exact mass calcd for C_9H_9BrO M^+ 211.9837, found M^+ 211.9838.

Method B:

To a dried flask were added the MEM ether compound **30** (698 mg, 2.42 mmol) in dry dichloromethane (15 mL). The stirred solution was cooled to 0 °C and titanium tetrachloride (0.32 mL, 2.90 mmol) in dry dichloromethane (3 mL) was added dropwise. The yellow solution was stirred for an additional 2 hours at 0 °C, whereupon the reaction was quenched with the slow addition of water (5 mL). The two-phase system was allowed to reach room temperature, and was stirred until the organic layer was clear. The organic phase was collected and the aqueous layer was washed with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and evaporated giving a yellow oil. The latter was purified by column chromatography using petroleum ether/ethyl acetate (5:1) and provided the title compound as a white solid (348 mg, 68%).

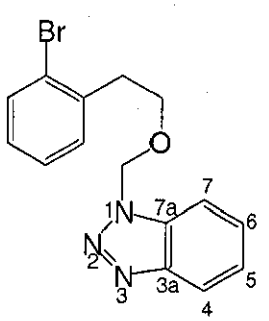
Methoxyethoxymethyl-2-(2-bromo-phenyl)ethylether (30)



To a stirred solution of commercial 2-bromophenylethanol (2.43 g, 12.1 mmol) in dry dichloromethane (24 mL) was added *N,N*-diisopropylethylamine (DIPEA, 3.16 mL, 18.1 mmol), followed by MEM-Cl (2.1 mL, 17.9 mmol). The reaction was stirred at room temperature overnight, then diluted with dichloromethane, and washed with aqueous HCl (1 M). The organic extracts were dried over magnesium sulfate, filtered and evaporated to give a yellow oil. The crude compound was purified by column chromatography (petroleum ether/ethyl acetate 95:5) to provide the title compound as a colourless oil (2.79 g, 80%).

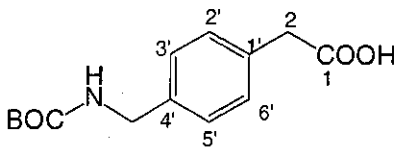
ν_{max}(DCM)/cm^{-1} 2928, 2877 (CH_2, CH_3), 1471 (CH_2, CH_3), 1113, 1068, 1024 (C-O), 751 (C-Br); δ_H (250 MHz, $CDCl_3$) 3.04 (2H, t, *J* 6.9 Hz, CH_2, H-2), 3.37 (3H, s, CH_3O), 3.48-3.52 (2H, m, $OCH_2\underline{CH_2}O$), 3.59-3.63 (2H, m, $O\underline{CH_2}CH_2O$), 3.80 (2H, t, *J* 6.9 Hz, H-1), 4.71 (2H, s, OCH_2O),7.07 (1H, m, Ar-H), 7.24 (2H, m, Ar-H) 7.52 (1H, d, *J* 7.8 Hz, Ar-H); δ_C (100 MHz, $CDCl_3$) 138.0 (C quat, C-1'), 132.7, 131.0, 127.9, 127.2, (4 Ar-CH), 124.5 (C quat, C-2'), 95.2 (OCH_2O), 71.7 ($OCH_2\underline{C}H_2O$), 66.6 ($O\underline{C}H_2CH_2O$), 66.5 (OCH_2, C-1), 58.9 (CH_3O), 36.3 (CH_2, C-2); *m/z* (FAB) 289 (M^+, 8), 183 (100); exact mass calcd for $C_{12}H_{17}BrO_3$ M^+ 289.0439, found M^+ 289.0439.

Benzotriazolylmethyl 2-(2-bromophenyl)ethyl ether (29)



Sodium hydride (264 mg, 11 mmol) was added to a stirred solution of bromophenyl ethanol (2 g, 10 mmol) and 1-(chloromethyl)benzotriazole (1.67 mg, 10 mmol) in dry toluene (20 mL). The mixture was stirred and heated at reflux under nitrogen for 6 hours. After being cooled to room temperature, the reaction mixture was poured into water and the organic layer was separated. The toluene solution was washed twice with ice-cold 10% sodium hydroxide, followed by water. The solution was dried over anhydrous potassium carbonate and the solvent was evaporated to give the desired product as a solid. The crude product was purified by column chromatography using petroleum ether/ethyl acetate (3:1) as the eluent, and afforded the desired product a solid (3.32 g, 54%); m.p. 88-89 °C ν_{max}(KBr)/cm^{-1} 1474, 1450, 1160, 1102, 1003, 753, 744; δ_H (250 MHz, $CDCl_3$) 2.94 (2H, t, *J* 7.0 Hz, CH_2O), 3.74 (2H, t, *J* 7.0 Hz, $C\underline{H_2}CH_2O$), 5.99 (2H, s, OCH_2N), 7.00-7.13 (3H, m, 3 Ar-H of PhBr), 7.39-7.52 (3H, m, H-5, H-6, H-3 of PhBr), 7.58 (1H, d, *J* 8.1 Hz, H-7), 8.07 (1H, d, *J* 8.3 Hz, H-4); δ_C (100 MHz, $CDCl_3$) 146.8 (C quat, C-3a), 137.6 (C quat, C-Br), 133.1 (C quat, C-7a), 131.4 (1C, Ar-CH of PhBr), 128.5 (1C, Ar-CH of PhBr), 128.3 (1C, Ar-CH of PhBr), 127.7 (Ar-CH, C-6), 124.8 (Ar-CH, C-5), 120.4 (Ar-CH, C-4), 110.3 (Ar-CH, C-7), 77.6 (OCH_2N), 68.7 ($\underline{C}H_2CH_2O$), 36.3 (CH_2O); *m/z* (EI) 333-331 (M^+, 9), 301-303 (6), 273 (7), 250 (17), 222 (54), 194 (12), 184 (22), 167 (28), 132 (23), 104 (47), 77 (100), 51 (25)); exact mass calcd for $C_{15}H_{14}BrN_3O$ M^+331.0320, found M^+331.0321. Anal. calcd for $C_{15}H_{14}BrN_3O$: C, 54.23; H, 4.25; N, 12.65; found: C, 54.48; H, 4.19; N, 12.46%

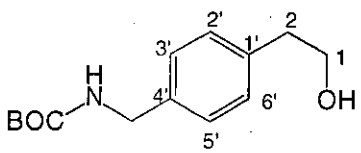
2-{4-[(*tert*-Butyloxycarbonyl)aminomethyl]phenyl} ethanoic acid (35) [185]



Bromomethylphenylacetic acid (1.5 g, 6.55 mmol) was added in small portions to a mixture of ethanol (170 mL) and a solution of concentrated ammonium hydroxide (50 mL). The mixture was stirred at room temperature for 1 hour and the solvents were evaporated to give a white solid. The latter was treated with a solution of sodium

hydroxide (1M, 20 mL), followed by the evaporation of the water under reduced pressure. The solid obtained was dissolved in a 1:1 mixture of 1,4 dioxane and water (34 mL), and a solution of sodium hydroxide (1M, 6.5 mL) was added, before the mixture was cooled to 0 °C in an ice-water bath. Di-*tert*-butyl dicarbonate (1.57 g, 7.2 mmol) was slowly added. After 0.5 hour the reaction mixture was allowed to warm to room temperature and stirred overnight. Dioxane was removed under vacuum and the aqueous mixture was chilled in an ice-water bath and acidified to pH 3 using a solution of HCl (2M). The reaction mixture was extracted with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered, and evaporated to give a white residue. The resulting crude product was recrystallised from ethyl acetate/petroleum ether to yield the title compound as a white solid (1.0 g, 57%); m.p. 108-110 °C (litt. m.p. 110 °C (hexane))
ν_{max}(DCM)/cm^{-1} 3345 (NH, OH), 1682 (broad C=O), 1517 (CNH), 1248; δ_H (400 MHz, CD_3OD) 1.44 (9H, s, $3CH_3$), 3.56 (2H, s, CH_2COO), 4.19 (2H, s, CH_2N), 4.81 (1H, s, NH), 7.17-7.21 (4H, br.s, Ar-H); δ_C (100 MHz, CD_3OD) 174.3 (COOH), 157.3 (OCON), 138.4 (C quat, C-4'), 133.6 (C quat, C-1'), 129.2, 127.1 (2 Ar-CH), 79.0 (C quat of BOC), 43.6 (CH_2N), 40.4 ($\underline{C}H_2COO$), 27.6 ($3CH_3$) ; *m/z* (ES) 531 ($2M^+$+H, 70), 283 (M^++NH_3, 80), 210 (M^+-^{t}Bu, 100). Anal. calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 55.28; found: C, 63.27; H, 7.19; N, 5.19%

2-{4-[(*tert*-Butyloxycarbonyl)aminomethyl]phenyl} ethan-1-ol (36)

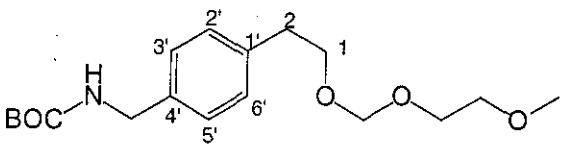


N-BOC aminomethylphenyl acetic acid (35) (1.0 g, 3.77 mmol) was dissolved in dry THF (12.6 mL) at 0 °C and was treated dropwise with a 1M solution of BH_3.THF (9.5 mL, 9.5 mmol) under nitrogen. The mixture was stirred for 2 hours at 0 °C and the reaction quenched by the dropwise addition of brine. The layers were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to provide a white solid, which was purified

by chromatography (petroleum ether/ethyl acetate 2:1), to afford the title compound as a white solid (677 mg, 74%); m.p. 57-58 °C

ν_{max}(DCM)/cm^{-1} 3343 (OH, NH), 2977 (CH_2), 2933 (CH_3), 1691 (C=O), 1515 (CNH), 1252 (C-O); δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, $3CH_3$), 2.84 (2H, t, *J* 6.5 Hz, PhC$\underline{H_2}$), 3.83 (2H, t, *J* 6.5 Hz, CH_2O), 4.28 (2H, d, *J* 5.8 Hz, CH_2N), 4.86 (1H, br.s, NH), 7.1-7.19 (4H, br.s, Ar-H); δ_C (100 MHz, $CDCl_3$) 156.4 (COO of BOC), 138.4 (C quat, C-4'), 133.6 (C quat, C-1'), 129.6 (2 Ar-CH), 128.0 (2 Ar-CH), 79.8 (C quat of BOC), 63.9 (CH_2O), 44.7 (CH_2N), 39.2 (CH_2, C-2), 28.8 ($3CH_3$); *m/z* (ES) 252 (M^++H, 20), 196 (100), 178 (62), 165 (39), 154 (65), 135 (98); exact mass calcd for $C_{14}H_{21}NO_3$ M^+ 252.1599, found M^+ 252.1604. Anal. calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N,5.57; found: C, 66.82; H, 8.46; N, 5.45%

2-{4-[(*tert*-Butyloxycarbonyl)-aminomethyl]-2-phenyl}ethyl-*O*-methoxyethoxymethyl ether (37)

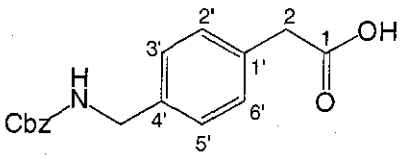


To a stirred solution of the *N*-BOC amino alcohol (**36**) (339 mg, 1.35 mmol) in dry dichloromethane(4.2 mL) was added *N,N*-diisopropylethylamine (0.30 mL, 1.69 mmol), followed by MEM-Cl (0.19 mL, 1.62 mmol). The reaction was stirred at room temperature overnight, then diluted with dichloromethane, and washed with aqueous HCl. The organic extracts were dried over magnesium sulfate, filtered and evaporated to give a yellow oil. The crude oil was purified by column chromatography (petroleum ether/ethyl acetate 3:1) to provide the title compound as a colourless oil (240 mg, 75%).

ν_{max}(DCM)/cm^{-1} 3351 (NH), 2975, 2929 and 2878 (CH_2, CH_3), 1714 (C=O), 1515 (CNH), 1249 (C-O); δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, $3CH_3$), 2.80 (2H, t, *J* 6.7 Hz, CH_2, H-2), 3.30 (3H, s, CH_3O), 3.41-3.43 (2H, m, $OCH_2C\underline{H_2}O$), 3.51-3.53 (2H, m, $OC\underline{H_2}CH_2O$), 3.70 (2H, t, *J* 6.7 Hz, CH_2, H-1), 4.20 (2H, *J* 6.2 Hz, CH_2N), 4.62 (2H, s, OCH_2O), 7.12 (4H, s, Ar-H); δ_C (100 MHz, $CDCl_3$) 155.9 (COO of BOC), 138.2 (C

quat, C-4'), 136.9 (C quat, C-1'), 129.2 (2 Ar-CH), 127.7 (2 Ar-CH), 95.6 (OCH_2O), 72.0 (CH_2, C-1), 68.7 ($OCH_2\underline{C}H_2O$), 67.0 ($O\underline{C}H_2CH_2O$), 59.3 (CH_3O), 44.8 (CH_2N), 36.3 (CH_2, C-2), 28.8 ($3CH_3$); *m/z* (FAB) 339 (M^+, 50), 282 (72), 238 (68), 208 (100), 181 (100); exact mass calcd for $C_{18}H_{29}NO_5$ M^+ 339.24457, found M^+ 339.24414.

2-{4-[(Benzyloxycarbonyl)aminomethyl]phenyl} ethanoic acid (38)



Method A:

Commercial bromomethylphenylacetic acid (2.0 g, 8.73 mmol) was added in small portions to a mixture of ethanol (210 mL) and concentrated aqueous ammonium hydroxide (50 mL). The mixture was stirred at room temperature for 1 hour and the solvents were evaporated to give a white solid. The latter was treated with a solution of sodium hydroxide (1M, 26 mL), followed by the evaporation of the water under reduced pressure. The solid obtained was dissolved in a 1:1 mixture of 1,4 dioxane and water (43 mL), and a solution of sodium hydroxide (1M, 8.7 mL) was added, before the mixture was cooled to 0 °C in an ice-water bath. Benzylchloroformate (1.79 g, 10.47 mmol) was slowly added. After 0.5 hour the reaction mixture was allowed to reach room temperature and stirred overnight. Dioxane was removed under vacuum and the aqueous layer chilled in an ice-water bath and acidified to pH 2 using a solution of HCl (5M). The aqueous phase was extracted with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered, and evaporated to give a white residue. The resulting crude product was recrystallised from ethyl acetate/petroleum ether to yield the title compound as a white solid (1.5 g, 58%).

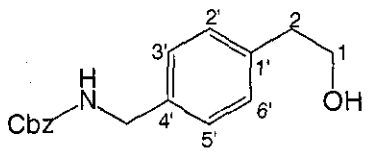
Method B:

Commercial bromomethylphenylacetic acid (5.0 g, 21.83 mmol) was added in small portions to concentrated aqueous ammonium hydroxide (460 mL). The mixture was

stirred at room temperature for 1 hour and the solvent was evaporated to give a white solid. The latter was treated with a solution of sodium hydroxide (2M, 33 mL), followed by the evaporation of the water under pressure. The solid obtained was dissolved in 1,4 dioxane (22 mL), and a solution of sodium hydroxide (2M, 42 mL) added, before the mixture was cooled to 0 °C in an ice-water bath. Benzylchloroformate (4.47 g, 26.20 mmol) was slowly added. After 0.5 hour the reaction mixture was allowed to reach room temperature and stirred overnight. Dioxane was removed under vacuum and the aqueous layer was chilled and acidified to pH 2 using a solution of HCl (5M). The aqueous phase was extracted with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered, and evaporated to give a white solid. The resulting crude product was recristallised from ethyl acetate/petroleum ether to yield the title compound as a white solid (5.3 g, 81%); m.p. 149-152 °C

ν_{max}(DCM)/cm^{-1} 3419 (NH, OH), 1638 (broad C=O); δ_H (400 MHz, CD_3OD) 3.59 (2H, s, CH_2COOH), 4.29 (2H, s, CH_2N), 5.11 (2H, s, OCH_2Ph), 7.24-7.36 (9H, m, Ar-H); δ_C (100 MHz, CD_3OD) 176.0 (COOH), 159.4 (OCON), 139.6 (C quat, C-4'), 138.8 (C quat of Bn), 135.3 (C quat, C-1'), 130.9, 129.8, 129.4, 129.2, 128.8 (5 Ar-CH), 67.9 (OCH_2Ph), 45.6 (CH_2N), 42.0 (CH_2, C-2); *m/z* (ES) 599 ($2M^+$+H, 94), 300 (M^++H, 61), 341 (70), 256 (22), 201 (25), 149 (30); exact mass calcd for $C_{17}H_{17}NO_4$ M^+ 299.1157, found M^+ 299.1164. Anal. calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68, found: C, 67.92; H, 5.53; N, 4.34%

2-{4-[(Benzyloxycarbonyl)aminomethyl]phenyl} ethan-1-ol :

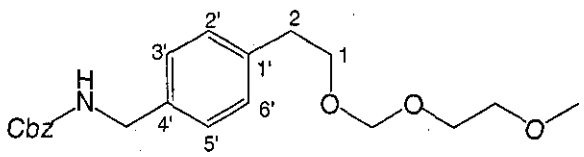


The N-Cbz aminomethylphenylacetic acid (38) (5.28 g, 17.66 mmol) was dissolved in dry THF (58.9 mL) at 0 °C and was treated dropwise with a 1M solution of BH_3.THF (44.1 mL, 44.1 mmol) under nitrogen. The mixture was stirred for 2 hours at 0° C and the reaction quenched by the dropwise addition of brine. The layers were separated and the

aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, concentrated, and purified by chromatography using a gradient of eluents: (petroleum ether/ethyl acetate 2:1, then 1:1), giving the title compound as a white solid (4.42 g, 88%); m.p. 83-86 °C

ν_{max}(DCM)/cm^{-1} 3319 (OH, NH), 1688 (C=O), 1538 (CNH); δ_H (250 MHz, $CDCl_3$) 1.90 (1H, s, OH), 2.82 (2H, t, *J* 6.5 Hz, CH_2, H-2), 3.81 (2H, t, *J* 6.5 Hz, CH_2, H-1), 4.36 (2H, d, *J* 6.0 Hz, CH_2N), 5.12 (2H, s, CH_2 of Bn), 7.15-7.35 (9H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 156.9 (OCON), 138.3 (C quat, C-4'), 136.9 (C quat of Bn), 136.8 (C quat, C-1'), 129.6, 128.9, 128.5, 128.2, 128.1 (5 Ar-CH), 67.2 (CH_2 of Bn), 63.9 (CH_2O), 45.2 (CH_2N), 39.1 (CH_2, C-2); *m/z* (ES) 286 (M^++H, 95), 268 (68), 242 (21), 207 (37), 135 (94), 91 (27); exact mass calcd for $C_{17}H_{19}NO_3$ M^+ 285.1365, found M^+ 285.1361. Anal. calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.90; found: C, 71.56; H, 6.71; N, 4.91%

2-{4-[(Benzyloxycarbonyl)aminomethyl]phenyl}ethyl-*O*-methoxyethoxymethyl ether (40)

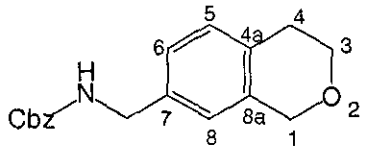


To a stirred solution of the *N*-protected amino alcohol (**39**) (1.6 g, 5.61 mmol) in dry dichloromethane(17.5 mL) was added *N,N*-diisopropylethylamine (1.37 mL, 7.86 mmol), followed by MEM-Cl (0.87 mL, 7.58 mmol). The reaction was stirred at room temperature overnight, then diluted with dichloromethane, and washed with aqueous HCl. The organic extracts were dried over magnesium sulfate, filtered and evaporated to give a yellow oil. The crude compound was purified by column chromatography (petroleum ether/ethyl acetate 2:1) to provide the title compound as a colourless oil (1.7 g, 82%).

ν_{max}(DCM)/cm^{-1} 3333 (NH), 2928 (CH), 2879 (CH), 1721 (C=O), 1516 (CNH), 1245 (C-O); δ_H (250 MHz, $CDCl_3$) 2.82 (2H, t, *J* 6.9 Hz, CH_2, H-2), 3.37 (3H, s, CH_3O), 3.48-3.51 (2H, m, $OCH_2\underline{CH_2}O$), 3.57-3.59 (2H, m, $OCH_2\underline{CH_2}O$), 3.77 (2H, t, *J* 6.9 Hz, CH_2, H-1), 4.34 (2H, d, J 6.2 Hz, CH_2N), 4.69 (2H, s, OCH_2O), 5.13 (2H, s, CH_2 of Bn), 7.15-

7.35 (9H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 156.8(OCON), 138.6 (C quat, C-4'), 137.0 (C quat of Bn), 136.8 (C quat, C-1'), 129.5, 129.3, 128.9, 128.5, 128.0 (5 Ar-CH), 95.7 (OCH_2O), 72.1 ($OCH_2\underline{C}H_2O$), 68.8 ($O\underline{C}H_2CH_2O$), 67.2 (CH_2 of Bn), 69.1 (CH_2, C-1), 59.3 (CH_3O), 45.2 (CH_2N), 36.3 (CH_2, C-2); *m/z* (ES) 374 (M^++H, 40), 298 (100), 254 (49), 164 (33), 146 (52); exact mass calcd for $C_{21}H_{27}NO_5$ M^+ 373.1889, found M^+ 373.1883.

7-[(Benzyloxycarbonyl)aminomethyl]isochroman(41)



Method A:

The MEM ether derivative **40** (500 mg, 1.34 mmol) was dissolved in dry dichloromethane (8.4 mL) and stirred in a flame-dried flask. The solution was cooled to 0 °C and titanium tetrachloride (0.18 mL, 1.6 mmol) in dry dichloromethane (1.68 mL) was added dropwise. The yellow solution was stirred for 2 hours at 0 °C under nitrogen, whereafter the reaction was quenched with the slow addition of water (2 mL). The two-phase system was allowed to reach room temperature and stir until the organic layer was clear. The organic layer was collected, and the aqueous layer extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to provide a solid. The latter was purified by flash chromatography using petroleum ether/ethyl acetate (2:1) and yielded the desired product as a white solid (260 mg, 65%).

Method B:

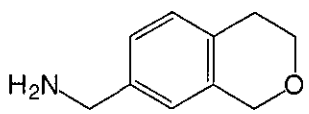
A solution of the MEM ether derivative **40** (3.66 g, 9.83 mmol) in dry dichloromethane (9.84 mL) was added to a cooled (0 °C) solution of titanium tetrachloride (2.15 mL, 19.65 mmol) in dry dichloromethane (98 mL). This mixture was stirred at 0 °C for 2 hours and then quenched by the successive addition of methanol (2 mL) and 3N HCl saturated with NaCl (55 mL). The organic phase was dried over magnesium sulfate, filtered and

evaporated to produce a white solid. The purification of this residue by column chromatography (petroleum ether/ethyl acetate (4:1) afforded the title compound as a white solid (1.99 g, 68%). m.p. 93.5-95.5 °C

ν_{max}(DCM)/cm^{-1} 3322 (NH), 2930 (CH_2), 2852 (CH_2), 1704 (C=O), 1530 (CNH);

δ_H (400 MHz, $CDCl_3$) 2.75 (2H, t, *J* 6.5 Hz, CH_2, H-4), 3.88 (2H, t, *J* 6.5 Hz, CH_2, H-3), 4.25 (2H, d, *J* 6.0 Hz, CH_2N), 4.66 (2H, s, OCH_2, H-1), 5.06 (2H, s, CH_2 of Bn), 6.82 (1H, s, Ar-H, H-8), 7.0 (2H, s, Ar-H, H-5, H-6), 7.15-7.35 (5H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 156.8 (OCON), 136.9 (C quat, C-7), 136.7 (C quat of Bn), 135.7 (C quat, C-8a), 132.9 (C quat, C-4a), 129.6, 128.9, 128.5, 126.0, 123.9 (8 Ar-CH), 67.5 (CH_2, C-1), 67.2 (CH_2 of Bn), 65.7 (CH_2, C-3), 45.3 (CH_2N), 28.5 (CH_2, C-4); *m/z* (ES) 298 (M^++H, 100), 223 (29), 147 (65), 91 (21); exact mass calcd for $C_{18}H_{19}NO_3$ M^+ 297.1365, found M^+ 297.1364. Anal. calcd for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71; found: C, 72.38; H, 6.37; N, 4.69%

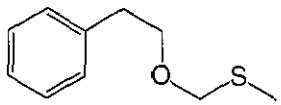
7-Aminomethyl isochroman (32)



The *N*-Cbz substituted isochroman **41** (98 mg, 0.26 mmol) was dissolved in a mixture of methanol/dichloromethane (1:1) (4 mL), and the solution was degassed. Palladium on charcoal (10%w/w, 10 mg), was added to the mixture which was stirred under an atmosphere of hydrogen (balloon) at room temperature for 1.5 hours, then filtered through a celite pad. The filtrate was concentrated and gave the title compound as a yellowish solid (50 mg, 100%), which was analysed by proton NMR spectroscopy, and subsequently used without further purification for the next step.

δ_H (400 MHz, CD_3OD) 2.74 (2H, t, *J* 6.5 Hz, CH_2, H-4), 3.80 (2H, d, *J* 6.0 Hz, CH_2N), 3.85 (2H, t, *J* 6.5 Hz, CH_2, H-3), 4.64 (1H, s, CH_2, H-1), 6.93 (1H, s, Ar-H H-8), 7.06 (4H, m, Ar-H, H-5, H-6); *m/z* (ES) 205 (M^++MeCN, 100), 164 (M^++H, 50), 147 (52).

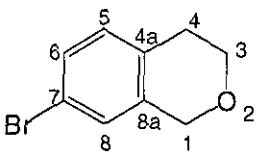
O-Methylthiomethyl-2-phenethyl ether (44) [198]



To a stirred suspension of sodium hydride (196.4 mg (60% in mineral oil), 4.91 mmol) in 1.4 mL of dimethoxyethane, was added phenylethanol (300 mg, 2.45 mmol) at 0 °C under nitrogen. To the mixture was added sodium iodide (368.1 mg, 2.45 mmol) followed by chloromethyl methyl sulfide (273.2 mg, 2.45 mmol). After 1 hour ar 0 °C, the reaction mixture was allowed to reach room temperature over a 4 hour period, poured into 6 mL of water, and extracted with diethyl ether. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude product was filtered through a short column of silica gel using pentane/ether (4:1), to afford the title compound as a colourless oil (83 mg, 18%)

ν_{max}(DCM)/cm^{-1} 2918 and 2861 (CH_2, CH_3), 1078 (C-O-C), 699 (Ar-CH, monosubstituted Ph); δ_H (250 MHz, $CDCl_3$) 2.12 (3H, s, CH_3), 2.97 (2H, t, *J* 6.9 Hz,Ph CH_2), 3.83 (2H, t, *J* 6.9 Hz, CH_2O), 4.69 (2H, s, OCH_2S), 7.30 (5H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 140.0 (C quat, Ar-C) 129.9 (2C, Ar-CH), 129.4 (2C, Ar-CH), 127.7 (1C, Ar-CH), 76.2 (OCH_2S), 69.7 (CH_2O), 37.0 ($PhCH_2$), 14.7 (SCH_3); *m/z* (EI) 182 (M^+, 20), 152 (13), 105 (100); exact mass calcd for $C_{10}H_{14}OS$ M^+182.0765, found M^+182.0763.

7-bromoisochroman (47) [192]



To a stirred solution of commercial 4-bromophenylethanol (500 mg, 2.48 mmol) in dry dichloromethane (5 mL) was added *N,N*-diisopropylethylamine (DIPEA, 0.65 mL, 3.73 mmol), followed by MEM-Cl (0.43 mL, 3.73 mmol). The reaction was stirred at room temperature for 2 hours, then diluted with dichloromethane, and washed with aqueous HCl

(1 M). The organic extracts were dried over magnesium sulfate, filtered and evaporated to give an oil. The crude oil was analysed by proton NMR spectroscopy and proved to correspond to the MEM ether derivative. This oily compound was subsequently used without further purification for the next step. A solution of the crude MEM ether (718 mg, 2.48 mmol) in dry dichloromethane (1.94 mL) was added to a cooled (0 °C) solution of titanium tetrachloride (0.55 mL, 4.96 mmol) in dry dichloromethane (25 mL). This mixture was stirred at 0 °C for 2 hours and then quenched by the successive addition of methanol (1 mL) and 3N HCl saturated with NaCl (25 mL). The organic phase was dried over magnesium sulfate, filtered and evaporated to produce an oil. The purification of this residue by column chromatography (petroleum ether/ethyl acetate (4:1) afforded the title compound as a colourless oil (370 g, 70%)

ν_{max}(DCM)/cm^{-1} 2920 (CH_2), 1557, 1462, 1441, 1107, 650; δ_H (250 MHz, $CDCl_3$) 2.79 (2H, t, *J* 5.8 Hz, CH_2, H-4), 3.95 (2H, t, *J* 5.8 Hz, CH_2, H-3), 4.72 (2H, s, OCH_2, H-1), 7.00 (1H, d, *J* 8.0 Hz, Ar-H), 7.13 (1H, s, Ar-H, H-8), 7.28 (1H, d, *J* 8.0 Hz, Ar-H); δ_C (100 MHz, $CDCl_3$) 137.2 (C quat, C-7), 132.3 (C quat, C-8a), 130.7 (1C, Ar-CH), 129.6 (1C, Ar-CH), 127.5 (1C, Ar-CH), 119.6 (C quat, C-4a), 67.7 (CH_2, C-1), 65.4 (CH_2, C-3), 28.2 (CH_2, C-4); *m/z* (FAB) 212-214 (M^+, 100), 182-184 (100); exact mass calcd for C_9H_9BrO M^+ 211.98368, found M^+ 211.98384.

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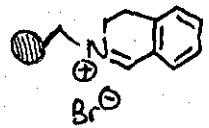
APPENDICES

APPENDIX 1



NovaSyn TG
iminium salt

Sample B Iminium resin

Date Sep 29 1999
User vnmr1 Probe 7 mm
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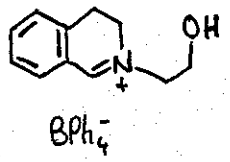
Pulse sequence s2pul

Observe C13
Frequency 75.430 MHz
Spectral width 30007.5 Hz
Acquisition time 200.0 ms
Relaxation delay 1.0 sec
No. repetitions 6000

Direct polarisation
Pulse angle 30.0 degrees
Spin-rate 4300 Hz

Line broadening 5.0 Hz
FT size 16384
Ambient temperature

APPENDIX 1'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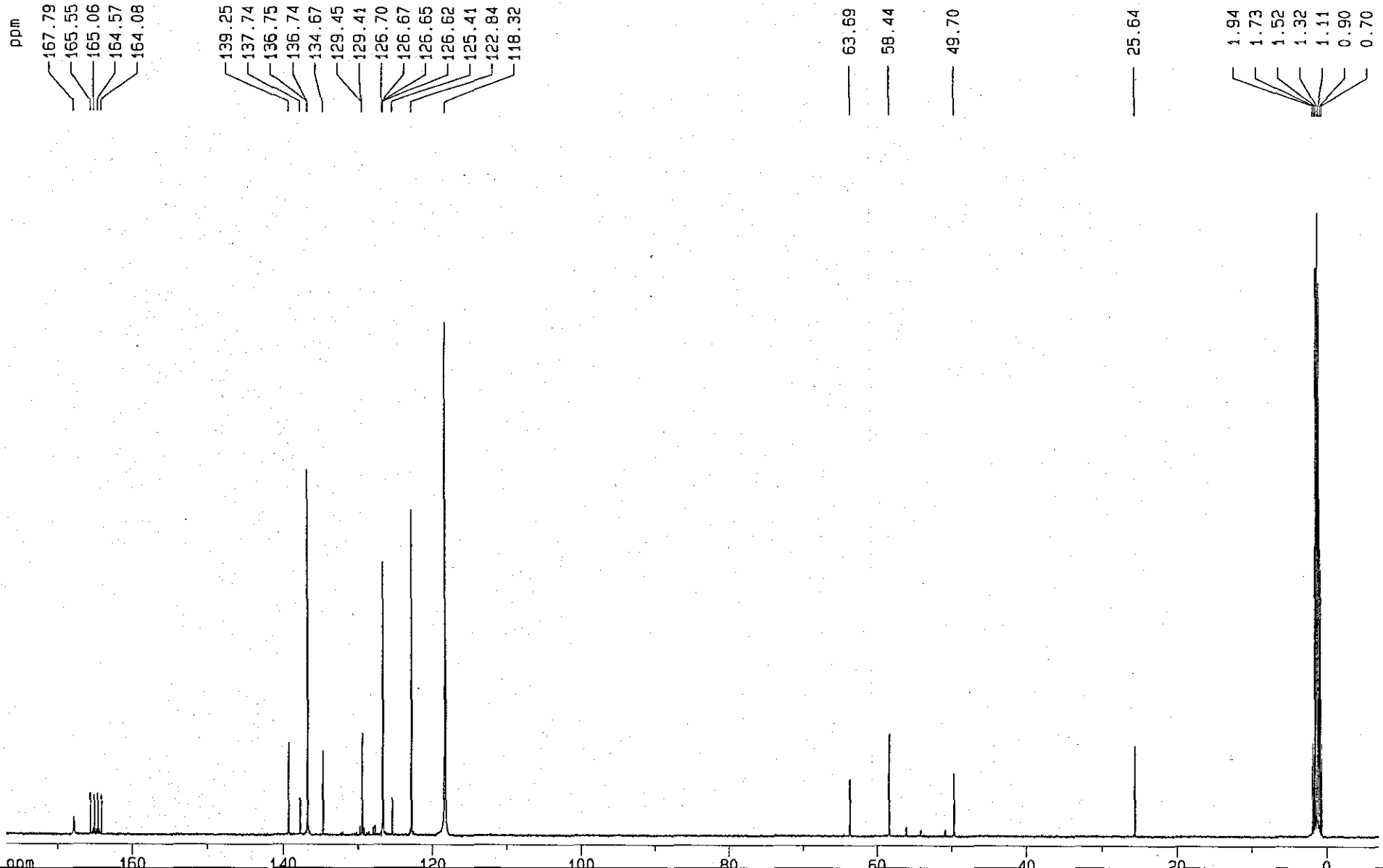
+
BPh4-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126.70
126.67
126.65
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125.41
122.84
118.32
63.69
58.44
49.70
25.64
1.94
1.73
1.52
1.32
1.11
0.90
0.70
ppm
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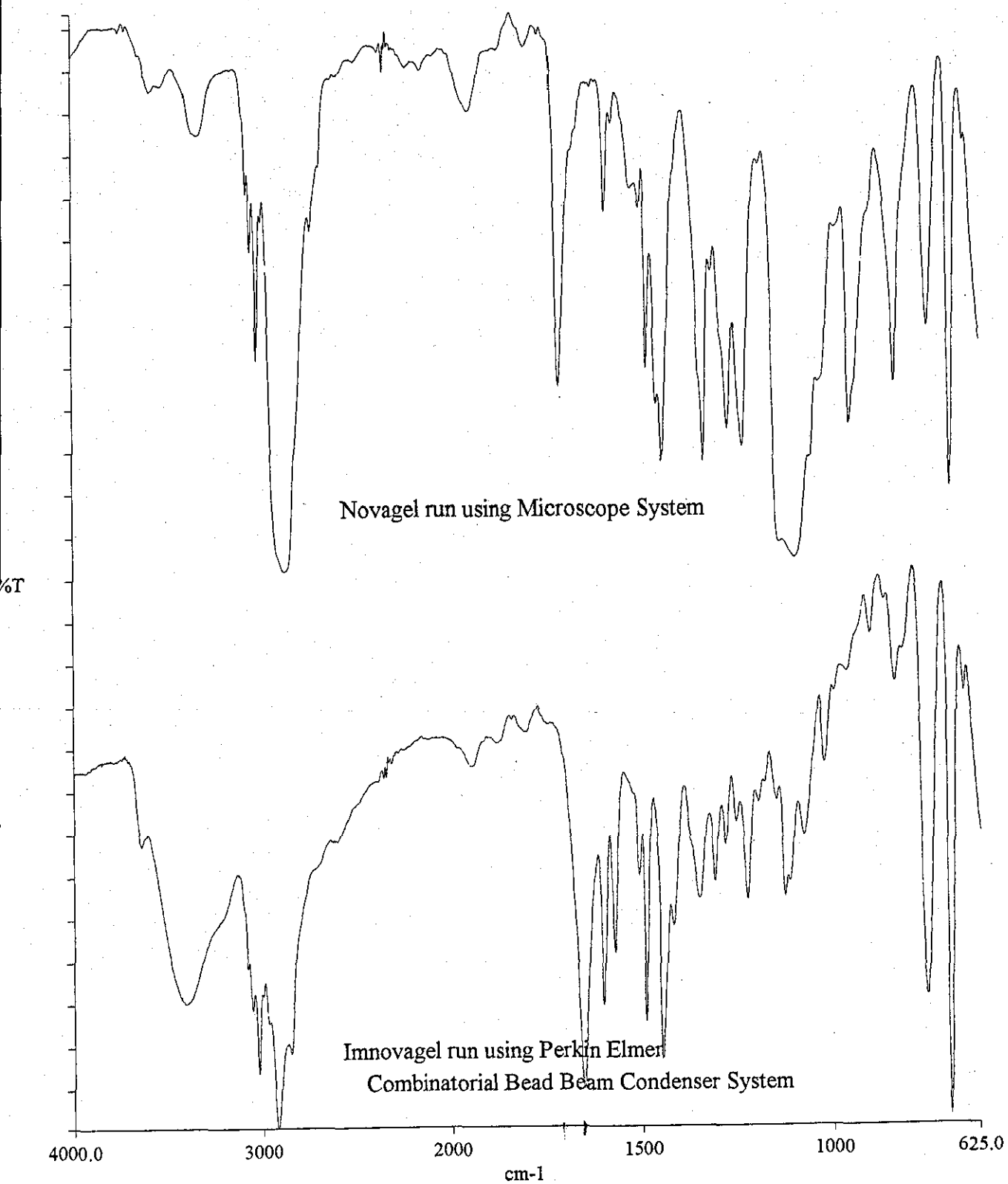
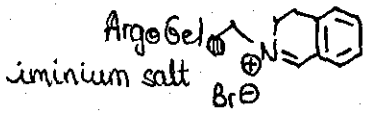
Spectra of Combinatorial Beads using Microscope and Combinatorial Bead Accessory

Date: 22-11-99



APPENDIX 2

APPENDIX 3



Sample D: Iminium Argogel

Date Dec 10 1999
User vnmr1 Probe 7 mm
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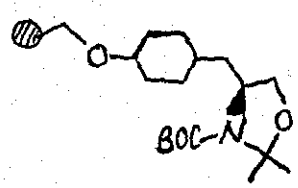
Pulse sequence s2pul

Observe C13
Frequency 75.430 MHz
Spectral width 30007.5 Hz
Acquisition time 200.0 ms
Relaxation delay 1.0 sec
No. repetitions 10000

Direct polarisation
Pulse angle 30.0 degrees
Spin-rate 3000 Hz

Line broadening 2.0 Hz
FT size 65536
Ambient temperature

APPENDIX 4



Sample 2

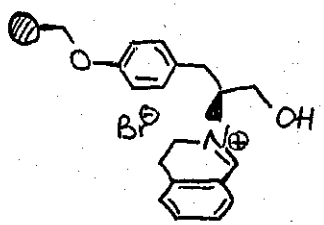
Date May 30 2000
User vnmr1 Probe 7 mm
File data12/pcp30May0002
Pulse sequence s2pul

Observe C13
Frequency 75.430 MHz
Spectral width 30007.5 Hz
Acquisition time 200.0 ms
Relaxation delay 1.0 sec
No. repetitions 4544

Direct polarisation
Pulse angle 90.0 degrees
Spin-rate 2500 Hz

Line broadening 5.0 Hz
FT size 65536
Ambient temperature

APPENDIX 5



Sample A Iminium argogel

Date Jun 21 2000
User vnmr1 Probe 7 mm
File data12/pcp21Jun0002.fid
Pulse sequence s2pul

Observe C13
Frequency 75.430 MHz
Spectral width 30007.5 Hz
Acquisition time 200.0 ms
Relaxation delay 1.0 sec
No. repetitions 15000

Direct polarisation
Pulse angle 90.0 degrees
Spin-rate 2800 Hz

Line broadening 5.0 Hz
FT size 65536
Ambient temperature

167.272
164.710
157.995
145.173
137.972
136.613
134.597
130.092
127.846
125.539
115.206
107.738
107.240
77.856
77.431
74.893
74.177
72.625
71.299
70.510
69.624
67.450
61.464
60.857
46.347
42.729
40.397
34.047
29.518
25.183
19.245
16.696

180 160 140 120 100 80 60 40 20 ppm