Synthesis of novel chiral pyrrolidine-type (salen)Mn(III) complexes.

Zhang, Weiqiang

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By

Weiqiang Zhang

Department of Chemistry

University of Wales, Swansea

United Kingdom

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ProQuest LLC.
789 East Eisenhower Parkway
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Summary

The thesis reports the total syntheses of new chiral pyrrolidine-type salen ligands **5.4** and their corresponding Mn(III) complexes **5.5**. The salen ligands were synthesized by condensation of *trans*-(3R,4R)-diaminopyrrolidine (**3.12**) or *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine (**3.10**) with two equivalents of (R)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene [(R)-**4.9**]. The salen ligands were transformed to their corresponding Mn(III) complexes following a general procedure. The catalytic performances of the synthesized (salen)Mn(III) complexes in asymmetric epoxidation of 1,2-dihydronaphthalene were tested.

In chapter 1, a review of asymmetric epoxidation of alkenes is given. Emphasis is placed on the development and some of the important designs of chiral salen ligands and their corresponding (salen)Mn(III) complexes.

In chapter 2, the nature of the research project is outlined.

In chapter 3, the syntheses of *trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt (**3.9**), *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine (**3.10**) and its trihydrochloride salt (**3.11**) are reported. These compounds were prepared from (2R,3R)-(+)-tartaric acid *via* multi-step syntheses. Extensive studies on optimization of these transformations are reported.

Chapter 4 records the synthesis of (R)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene [(R)-**4.9**] from 2-naphthol *via* a seven-step synthetic procedure. Extensive studies on these transformations are described, especially on the oxidative coupling of 2-naphthol and on the optical resolution of racemic 2,2'-dihydroxy-1,1'-binaphthalene.

In chapter 5, the preparations of salen ligands **5.4** and their corresponding Mn(III) complexes **5.5** are reported. The applications of synthesized Mn(III) complexes in asymmetric epoxidation of 1,2-dihydronaphthalene were carried out.

In chapter 6, an overall conclusion of the work is given.

Abbreviations

1. atm	Atmospheric pressure
2. ClMOM	Chloromethyl methyl ether
3. Confign.	Configuration
4. Cp	Cyclopentadienyl
5. DCM	Dichloromethane
6. DEAD	Diethylazodicarboxylate
7. DIEA	*N,N*-diisopropylethylamine
8. DMAP	4-Dimethylaminopyridine
9. DMF	*N,N*-Dimethylformamide
10. dppe	1,2-Bis(diphenylphosphino)ethane
11. Equiv.	Equivalent(s)
12. $Eu(hfc)_3$	Europium tri[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorate]
13. HPLC	High performance liquid chromatography
14. *m*-CPBA	*m*-Chloroperbenzoic acid
15. Mesyl	Methylsulfonyl
16. NMO	*N*-methylmorpholin-*N*-oxide
17. PDMS	Polydimethylsiloxane
18. 4-PPNO	4-Phenylpyridine-*N*-oxide
19. r.t.	Room temperature
20. SM	Starting material
21. TBHP	*tert*-Butyl hydroperoxide
22. Temp.	Temperature
23. TFAA	Trifluoroacetic anhydride
24. Tf_2NPh	*N*-phenylbis(trifluoromethanesulfonimide)
25. THF	Tetrahydrofuran
26. Tlc	Thin layer chromatography
27. Tosyl	Tolylsulfonyl
28. Triflyl	Trifluoromethanesulfonyl

Contents

CHAPTER ONE

INTRODUCTION

1.1 Alkene epoxidation

Epoxides, or oxiranes, are three-membered-ring cyclic ethers (Fig. 1.1). They are found in many biologically active natural products. And, because of the strain of the three-membered ring, epoxides exhibit unique chemical reactivity.

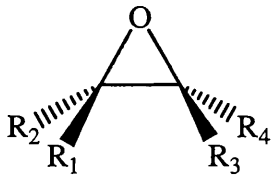
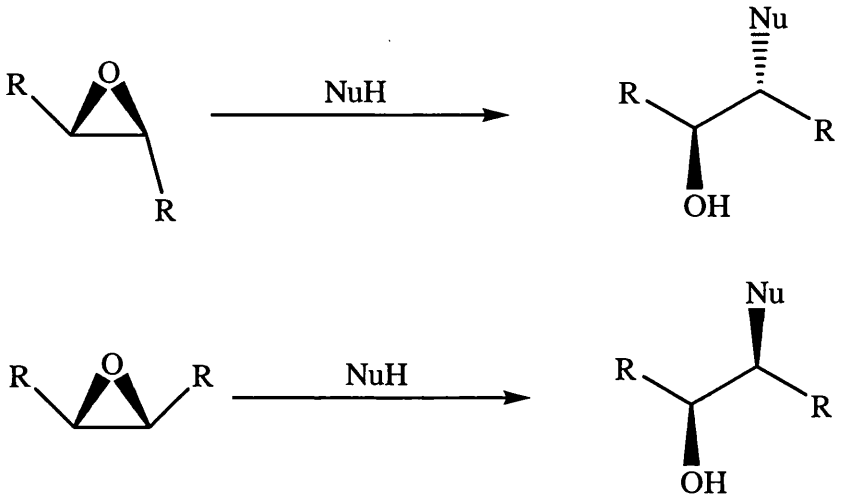


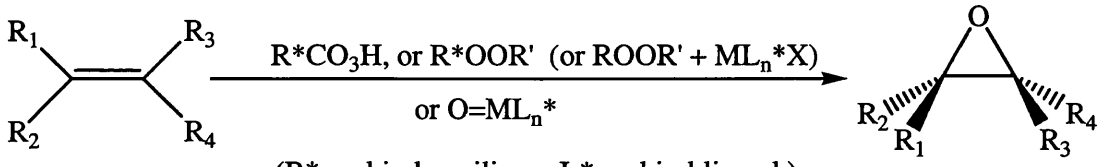
Fig. 1.1 Epoxide

Epoxides have a long history as versatile intermediates in organic synthesis[1-4] because they are readily converted into various useful functional groups under mild conditions. Both carbons of an epoxide ring are activated toward attack by nucleophiles, and in case of the unsymmetrically substituted epoxides, the regiochemistry of the nucleophilic attack is often predictable based on steric, electronic, and / or stereoelectronic considerations.[1,5-7] Ring-opening reaction of epoxides by nucleophiles is generally stereospecific or highly stereoselective, allowing for the control of one or two contiguous stereogenic centres in one synthetic scheme (Scheme 1.1).[8-11] Because of the increasing consideration given to the role of absolute stereochemistry in the function of biologically active compounds,[12] optically active epoxides are especially desirable synthetic building blocks in the synthesis of various chiral compounds, both biotic and exobiotic substrates.[13-14] For this reason, development of a general methodology for asymmetric synthesis of epoxides is a very important objective in synthetic organic chemistry.[14-17]



Scheme 1.1

Many methodologies have been developed to prepare epoxides. For example, epoxides can be synthesized from 1,2-diols, halohydrins, α-halo esters, carbonyl compounds, amides, diazoalkanes, or dihalides.[18] Among these methods, epoxidation of alkenes with electrophilic chiral oxenes or their equivalents is the most important one, especially for asymmetric epoxidation of unfunctionalized alkenes. The advantages of such a process include: a) a single-step synthesis; b) ready availability of various alkenes and oxidants; and c) mild reaction conditions with high chemoselectivities. Representative chiral oxene equivalents include optically active peroxyacids, optically active peroxides (in some cases, a combination of achiral peroxides and chiral metal complex catalysts), and oxo-metal species (metal oxenoids) bearing a chiral ligand (Scheme 1.2).[19-20]



(R* = chiral auxiliary, L* = chiral ligand)

Scheme 1.2

Since the work to be reported in this thesis focuses on preparation of chiral metal complex catalysts and their applications in asymmetric epoxidation of unfunctionalized alkenes, a brief review of the history of asymmetric epoxidation reactions is given in the next section.

1.2 Alkene asymmetric epoxidation

1.2.1 Historical overview

A listing of important discoveries reported by the end of 1993 in asymmetric epoxidation catalysis has been provided by Jacobsen (Table 1.1).[17]

Table 1.1 Historical overview of developments in catalytic asymmetric epoxidation according to Jacobsen

Year	Event
1965	Discovery of the first enantioselective epoxidation reaction
1965-1967	Development of the Halcon Oxirane process for the production of propene oxide
1967	Discovery of directing effects in metal-mediated epoxidations of allylic alcohols
1975	Report by Collman of the chemically robust class of 'picket fence' porphyrins
1979	Discovery by Groves that iron porphyrin complexes mimic the epoxidation activity of cytochrome P-450
1980	Introduction of the use of synthetic peptide polyamino acid catalysts by Juliá for enantioselective epoxidation of chalcone.
1980	Discovery by Sharpless of the titanium tartrate epoxidation of allylic alcohols
1981	First report of practical synthetic applications of the titanium tartrate technology
1981	Development of kinetic resolution of secondary allylic alcohols
1983	First report of porphyrin-catalyzed asymmetric epoxidation
1983	Proposal by Groves of the side-on approach transition state model
1983-1986	Detailed mechanistic studies by Kochi on epoxidation reactions catalyzed by achiral salen complexes
1986	Discovery that addition of molecular sieves renders titanium tartrate epoxidation reaction truly catalytic

1990-1991	Discovery and development of enantioselective epoxidation of unfunctionalized alkenes by Mn(salen) complexes
1992	Application of the asymmetric dihydroxylation reaction developed by Sharpless to the efficient synthesis of epoxides
1993	Industrial, ton scale production of the chiral Mn(salen) epoxidation catalysts

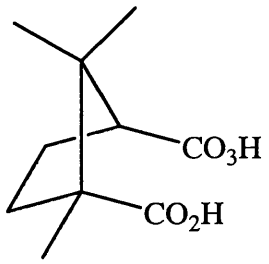
1.2.2 Asymmetric epoxidation with organic oxidants

1.2.2.1 Asymmetric epoxidation with electrophilic oxidants

Generally, asymmetric epoxidation with organic electrophiles has typically been restricted to stoichiometric processes.

1.2.2.1.1 Asymmetric epoxidation with chiral peroxy acids

In 1965, Henbest reported the first asymmetric epoxidation reaction of alkenes with a chiral peroxy acid, (+)-peroxycamphoric acid (**1.1**),[21] which, however, was later discovered to actually contain two diastereomers (Pirkle).[22] Very low enantioselectivities were obtained with the isomeric mixture of oxidants for a variety of substrates (1.0 - 2.4% ee) and even for the purified (+)-peroxycamphoric acid (< 10% ee). Since then, various other chiral peroxy acids have been used for this purpose but enantioselectivities remain low (< 20% ee).[23] Failure to obtain significant enantioselectivities with such systems might be attributable to the substrate and the asymmetric centre in the peroxy acid being far removed from each other in the transition state of the epoxidation (Fig. 1.2).[24, 25]



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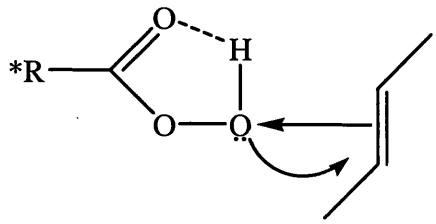
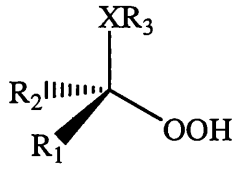


R* = asymmetric center

Fig. 1.2 Transition state model for epoxidation with optically active peroxy acids

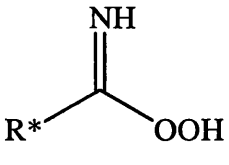
1.2.2.1.2 Asymmetric epoxidation with other chiral hydroperoxy compounds

Several different classes of chiral hydroperoxy compounds, **1.2** - **1.4**, have also been used for such purpose. Enantioselectivities obtained have not exceeded 10% ee.[26]



X= O, NH

1.2



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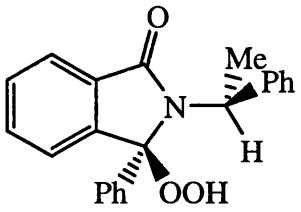

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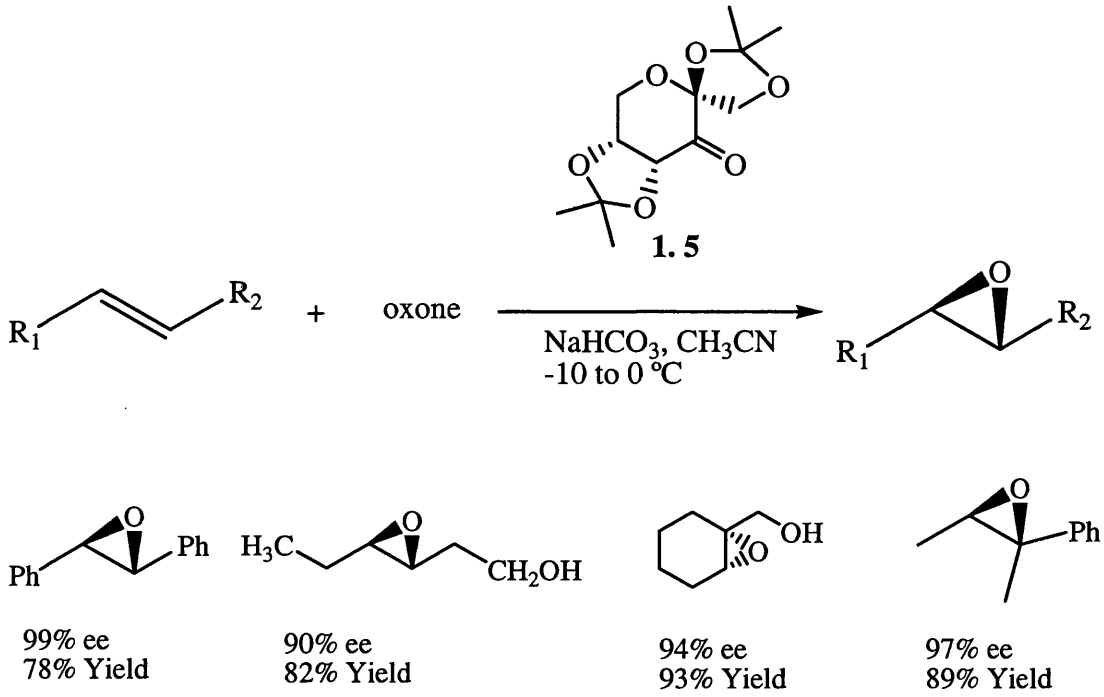
1.2.2.1.3 Asymmetric epoxidation with chiral dioxiranes and chiral oxaziridines

In contrast to optically active peroxy acids, dioxiranes and oxaziridines possess asymmetric center(s) next to the electrophilic oxygen atom, therefore, interaction between the incoming alkenes and the asymmetric center in the oxidants

would be enhanced, and higher enantioselectivity would be expected in the epoxidation.

In 1984, the first use of chiral dioxiranes for catalytic asymmetric epoxidation was reported by Curci *et al.*, in which dioxiranes were generated *in situ* from the corresponding ketones and Oxone®. The enantioselectivity obtained was low.[27] However, the ketones could be used in substoichiometirc amount (30 mol%) without appreciable loss in enantioselectivity. Later, Shi *et al.* reported the use of a fructose-derived ketone **1.5** for asymmetric epoxidation in the presence of Oxone® (Scheme 1.3). Chemoselectivities of the reaction were very high. Also, high enantioselectivities were realized in epoxidation of *trans*- di- and tri- substituted alkenes regardless of the presence or absence of functional groups.[28]

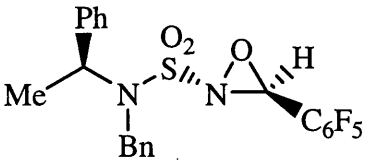


Scheme 1.3

Chiral ketone = 0.3 equiv.; Oxone® =1.4 equiv.

Epoxidation with a chiral oxaziridine was first reported by Davis *et al.* Higher enantioselectivity (65% ee) was achieved in epoxidation of *trans*-β-methylstyrene using an *N*-sulfonyloxaziridine **1.6** as the chiral oxidant.[29] Later, Davis and Przeslawski reported that chiral oxaziridine **1.7** effected epoxidation of styrene and

trans-β-methylstyrene in better than 90% ee.[30] However, these latter reactions were very slow (two weeks at 60 °C).



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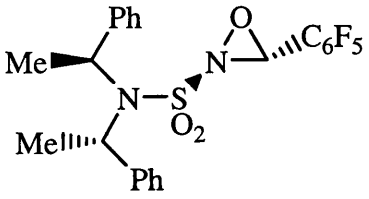

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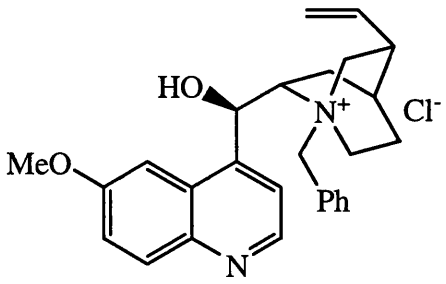
1.2.2.2 Asymmetric epoxidation of conjugated ketones with nucleophilic oxidants

In the context of non-metal-mediated asymmetric epoxidation, enantioselective catalytic epoxidation of certain α,β-unsaturated carbonyl compounds with nucleophilic oxidants has been developed with success. These reactions typically use hydrogen peroxide or an alkyl hydroperoxide under basic conditions as the stoichiometric oxidant, and an asymmetric catalyst consisting of a chiral organic phase transfer agent.

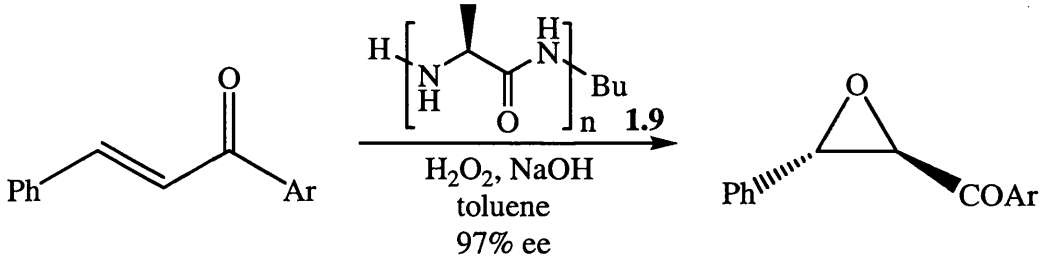
Wynberg pioneered the use of chiral ammonium salts to catalyze asymmetric epoxidation of α,β-unsaturated ketones. Enantioselectivities as high as 55% ee were obtained in epoxidation of *trans*-chalcone derivatives with basic hydrogen peroxide using quinine-derived **1.8** as the catalyst.[31]



1.8

Cyclodextrins have also been used in asymmetric epoxidation of α,β-unsaturated ketones. Low enantioselectivities have been obtained for epoxidation of a variety of substrates with α- or β-cyclodextrin using various oxidants.[32]

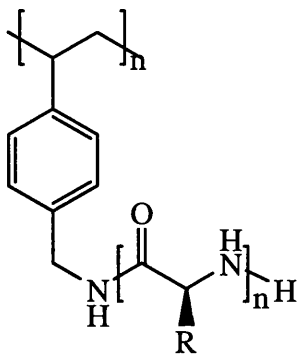
The application of synthetic peptides in asymmetric epoxidation of α,β-unsaturated ketones has led to the development of highly enantioselective catalytic systems. In 1980, Juliá introduced a poly[(S)-alanine] catalyst (**1.9**) for epoxidation of *trans*-chalcone in the presence of H_2O_2 / NaOH, with up to 97% ee (Scheme 1.4).[33] Although the substrate scope is limited to chalcone derivatives, the Juliá epoxidation reaction is one of the most effective and practical asymmetric catalytic methods.



Scheme 1.4

Other synthetic peptides, such as poly-L-leucine and poly-L-valine, have also been reported to effect the highly enantioselective epoxidation of a variety of *trans*-chalcone derivatives.[34]

Polymer-supported polyamino acids **1.10** have been used as catalysts in asymmetric epoxidation. Up to 99% ee was achieved in epoxidation of *trans*-chalcone.[35] It was reported that the catalysts could be recovered and reused without significant loss of reactivity.

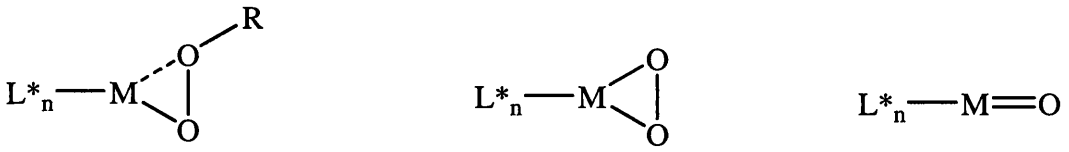


1.10

1.2.3 Metal catalyzed asymmetric epoxidation

The majority of research and progress in asymmetric epoxidation has involved metal-based catalysts.

Active species such as alkylperoxo-, peroxo- and oxo-metal species (Fig.1.3), which were thought to be the reactive intermediates in metal-based asymmetric epoxidation, can be produced by treating appropriate metal complexes with oxidants such as alkyl hydroperoxide, hydrogen peroxide, or iodosylbenzene. These epoxidation reactions take place in the coordination sphere of the metal complexes. Therefore, if the metal complex carries chiral ligand(s), epoxidation would proceed in an asymmetric environment and, in principle, should give optically active epoxides.

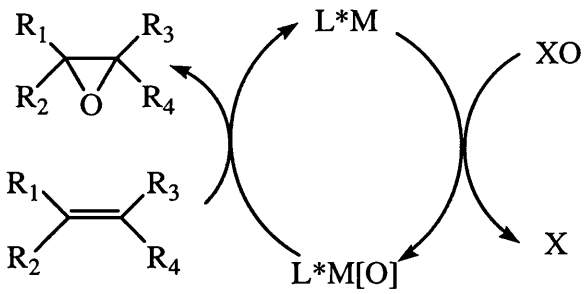


alkylperoxo-metal species peroxo-metal species oxo-metal species

L* = chiral ligand

Fig. 1.3 Active species for metal-catalyzed asymmetric epoxidation reactions

The concept of metal-catalyzed asymmetric epoxidation of alkenes is illustrated in Figure 1.4.[17]



L* = chiral ligand

Fig. 1.4 Simplified scheme for metal-catalyzed asymmetric epoxidation of alkenes

According to Jacobsen, epoxidation catalysts may best be classified by the nature of the stoichiometric oxidants that they can employ. Therefore, two classes of catalysts were distinguished: a) oxo transfer catalysts that employ oxygen atom sources such as iodosylarenes, hypochlorite, and persulfate; b) peroxo transfer catalysts that employ hydrogen peroxide or alkyl hydroperoxides as oxidants.[15]

1.2.3.1 Peroxo-based asymmetric epoxidation

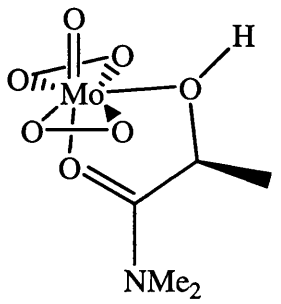
Research in the field of metal-based catalysts for asymmetric epoxidation started along two quite independent lines. The first started with the discovery and commercialization of the molybdenum-catalyzed epoxidation of propene by alkyl hydroperoxides. This work laid the foundation for the subsequent findings that molybdenum and a wide range of other metals catalyze the directed epoxidation of alkenes bearing hydroxyl directing groups. This ultimately led to the discovery of synthetically useful diastereoselctive epoxidations of unsaturated alcohols catalyzed by vanadium, and enantioselective epoxidations of allylic alcohols catalyzed by titanium tartrate complexes.[17]

1.2.3.1.1 Molybdenum-catalyzed asymmetric epoxidation

In 1979, the first catalytic enantioselective epoxidation of unfunctionalized alkenes was reported by Otsuka. Catalysts, which were prepared *in situ* from

$MoO_2(acac)_2$ and dialkyl tartrates or other carbohydrate derivatives, were found to effect asymmetric epoxidation of simple alkenes using *tert*-butyl hydroperoxide (TBHP) as oxidant. The best enantioselectivity was 14% ee in epoxidation of squalene.[36]

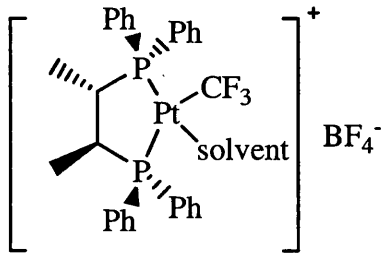
In 1979, Kagan reported that molybdenum(VI) peroxo complex **1.11** catalyzed the epoxidation of simple alkenes in 5.1 - 34.8% ee.[37] The enantioselectivities were improved up to 53% ee by a ligand variation approach.[38] High enantioselectivity (up to 95% ee) was achieved later by introducing excess chiral diol in the reaction system to induce a kinetic resolution process and by extending the reaction time.[39]



1.11

1.2.3.1.2 Platinum-catalyzed asymmetric epoxidation

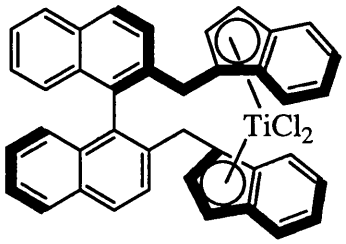
In 1987, Struckul reported that platinum(II) complexes of chiral diphosphines also catalyzed asymmetric epoxidation of simple alkenes in the presence of H_2O_2.[40] Enantioselectivities up to 41% ee were obtained in epoxidation of propene and 1-octene with the cationic catalyst **1.12.**



1.12

1.2.3.1.3 Asymmetric epoxidation with Cp-based catalysts

In 1992, Halterman reported the first application of catalysts based on chiral cyclopentadienyl (Cp) moieties in asymmetric epoxidation of simple alkenes. The highest enantioselectivity (22% ee) was obtained in epoxidation of *trans*-3-hexene using catalyst **1.13**.[41]



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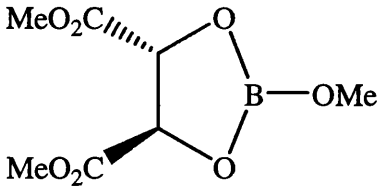
1.2.3.1.4 Main group metal-catalyzed asymmetric epoxidation

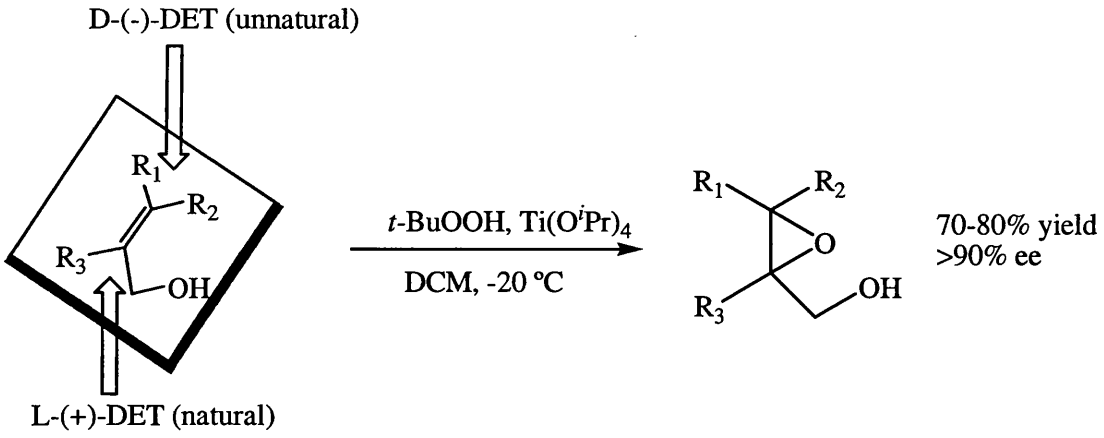
The first successful application of a main group metal in asymmetric epoxidation was for epoxidation of *trans*-stilbene using a borate-based catalyst **1.14**.[42] Enantioselectivity of 49% ee was achieved with an alkyl hydroperoxide as the oxidant.



1.14

1.2.3.1.5 Sharpless epoxidation of allylic alcohols

The titanium tartrate catalyzed epoxidation of allylic alcohols discovered by Sharpless[43] (Scheme 1.5) stands as one of the most effective, widely used, and historically important reactions in asymmetric catalysis.[44]



Scheme 1.5

There are five critical chemical components to a Sharpless epoxidation reaction: the allylic alcohol substrate, the solvent, the metal catalyst, the stoichiometric oxidant, and the chiral ligand. The only truly effective catalyst pairing for effective asymmetric epoxidation of allylic alcohols has been found to be a titanium (IV) alkoxide {the most effective source of titanium is $[Ti(OPr^{i})_4]$} in combination with a tartrate ester (DMT, DET, or DIPT). The best solvent is dry, alcohol-free CH_2Cl_2. And, the most useful oxidants are alkyl hydroperoxides such as TBHP.

The presence of water has an extremely deleterious effect on epoxidation catalyzed by titanium complexes. In 1986, it was found that addition of activated molecular sieves rendered the titanium tartrate epoxidation reaction truly catalytic. With the use of 0.3 nm or 0.4 nm sieves,[45] the catalyst levels could be reduced to 5 - 10 mol% relative to the substrate; the reaction could be run at a higher substrate concentration; and isolation of epoxy alcohol was facilitated.

Almost all allylic alcohols can be oxidized in high enantioselectivity using the titanium tartrate system. However, the scope of the substrates is almost exclusively limited to allylic alcohols. Simple alkenes do not undergo epoxidation under such conditions.

1.2.3.2 Oxo-based asymmetric epoxidation

As described above, research in the field of metal-based catalytic asymmetric epoxidation evolved along two quite independent lines. The second important line of research arose from efforts to understand and mimic the activity of oxidative enzymes such as cytochrome P-450. This led to the discovery of several classes of chiral heme-like coordination complexes that effect epoxidation of alkenes lacking directing functionality.[17]

1.2.3.2.1 P-450-catalyzed oxo transfer reaction

Cytochrome P-450 is one of the most important enzymes, and is known to catalyze various oxidations with high enantio- and regio-selectivity under mild conditions. Cytochrome P-450 possesses a porphyrin complex as the active site, wherein O_2 is activated as a form of oxo-iron species and then transferred to the substrate. The general reaction mechanism of the P-450-catalyzed oxo transfer reaction is shown in Fig. 1.5, according to Groves.[46]

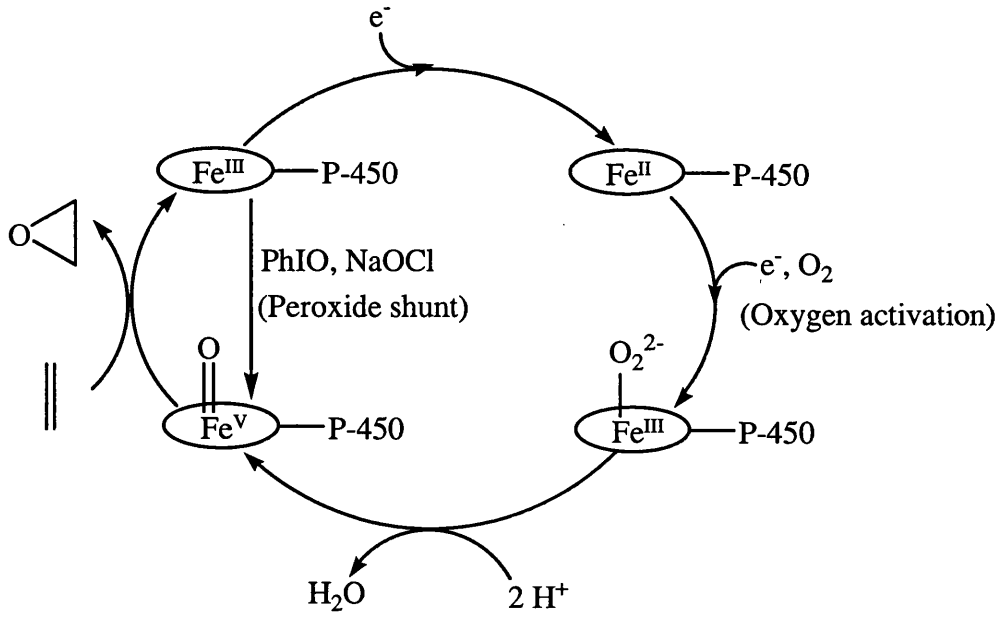
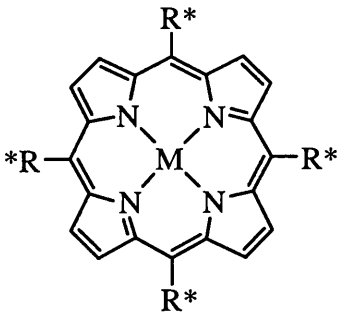


Fig. 1.5 Catalytic cycle of cytochrome P-450

1.2.3.2.2 Metalloporphyrin-based asymmetric epoxidation

Groves *et al.* reported that iron(III) porphyrin complexes could be converted into the corresponding oxo species by treatment with an oxidant such as iodosylbenzene (peroxide shunt path, see Fig. 1.5).[47] This finding suggested that simple iron(III) porphyrins could be used as model compounds for the active site of cytochrome P-450.

The generalized structure for chiral porphyrin complexes is illustrated in Fig. 1.6. The metal coordination sphere of the porphyrin ligand is sp^2 hybridized and essentially flat, and the stereochemical elements reside in positions that are relatively remote from the reaction centre. The most effective porphyrin-based epoxidation catalysts reported possess either large dissymmetric substituents on the *meso*-positions or dissymmetric bridging groups that connect two or more *meso*-positions.

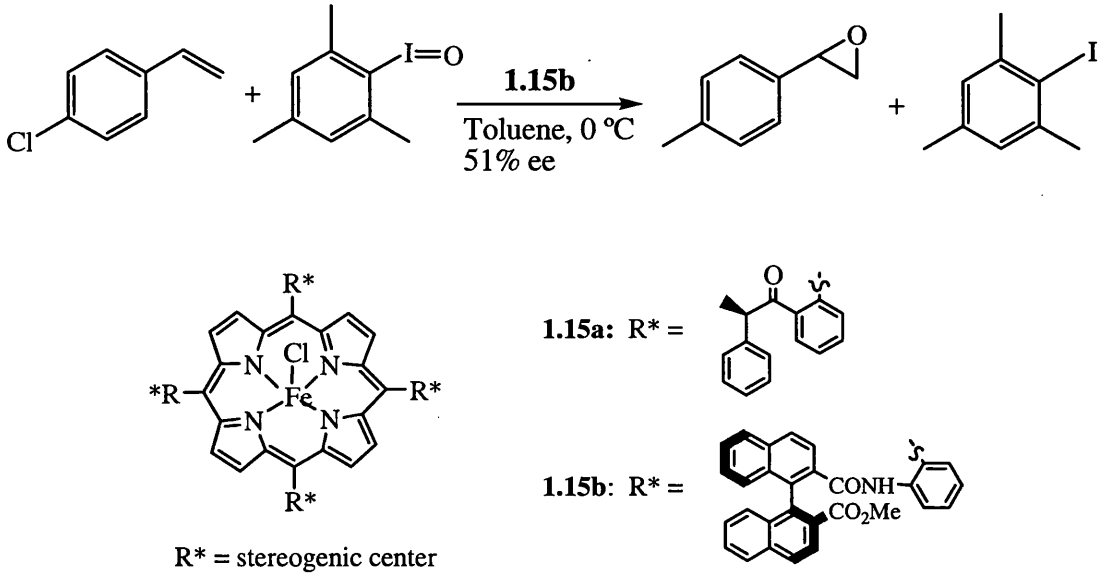


R* = Stereogenic center

Fig. 1.6 The generalized structure for chiral porphyrin complexes

The first example of asymmetric epoxidation of simple alkenes catalyzed by a chiral porphyrin complex was reported by Groves in 1983.[48] Chiral Fe(III) porphyrin complexes **1.15** were used as catalysts and iodosylmesitylene as the oxidant. Styrene derivatives were found to be good substrates and the best result (51% ee) was obtained in epoxidation of 4-chlorostyrene using complex **1.15b** as the catalyst (Scheme 1.6). To account for the observed selectivities and the general observation that *cis* alkenes are more reactive than *trans* alkenes in the reactions, Groves proposed a transition state model for oxygen atom transfer which involved a side-on approach

of an alkene to the putative iron-oxo intermediate. The proposed side-on approach is now widely accepted for the metalloporphyrin- and metallosalen-catalyzed epoxidations, which will be discussed later.



Scheme 1.6

Since then, many optically active metalloporphyrins have been synthesized and used for epoxidation of simple alkenes, including Mansuy's 'basket handle' porphyrin,[49] Naruta's 'twin coroner' porphyrins,[50] Collman's 'picnic basket' derivative and threitol-strapped manganese(III)-porphyrin complex,[51] Inoue's 'strapped' porphyrin catalyst,[52] O'Malley and Kodadek's 'chiral wall' porphyrin,[53] and Halterman's D4 symmetric metalloporphyrin.[54]

Generally, epoxidation of mono- and *cis*-disubstituted alkenes with these porphyrin complexes shows moderate to good levels of enantioselctivity, but epoxidation of *trans*-alkenes shows poor selectivity. Enantioselectivity up to 89% ee has been achieved in epoxidation of styrene derivatives. However, the scope of these reactions is rather narrow and there is considerable limitation for their use in organic synthesis.

Difficulty in construction of effective porphyrin-based catalysts might be partly attributable to its π-conjugated planar structure, which does not allow the presence of stereogenic carbons in the porphyrin ring.

As for the epoxidation method, Meunier *et al.* developed a method in which sodium hypochlorite (bleach) was used as the oxygen source and pyridine as an axial ligand.[55]The reaction rate, chemo- and stereo-selectivity were all increased. Also, high catalyst turnover numbers were realized, especially when the ligand carried electron-donating substituents on the *meso*- phenyl groups in the catalysts. The use of sodium hypochlorite as the stoichiometric oxidant constitutes an enormous improvement over the iodosylarene-based systems used formerly.

Since the work to be reported in this thesis focused on preparation of chiral salen complexes and their applications in asymmetric epoxidation of unfunctionalized alkenes, a review on metallosalen-based epoxidation reactions is reported in a separate section.

1.3 Metallosalen-based asymmetric epoxidation

1.3.1 Introduction

Metal complexes of the [*N*,*N*-ethylenebis(salicylideneaminato)] ligand (salen ligand) (Fig. 1.7) also aroused the interest of synthetic chemists as model compounds for the active site of cytochrome P-450, since they possess several structural and chemical features in common with metalloporphyrins. Both classes of coordination compounds are sterically well defined and kinetically non-labile, and thus they provide sensible matrices for rational ligand design. However, unlike the porphyrin system, in which the peripheral carbons are all sp^2 hybridized (see Fig.1.6), the salen ligand bears two sp^3 carbons at C-1″ and C-2″ positions that might be replaced with stereogenic carbons. Since these stereogenic centres are located close to the metal centre, stereochemical communication in epoxidation can be enhanced, at least in principle. Furthermore, sterically bulky and / or chiral substituents can be introduced at C-3 and C-3′ positions. All these features make the salen ligand a promising chiral template for construction of asymmetric reaction sites.[15, 17, 20]

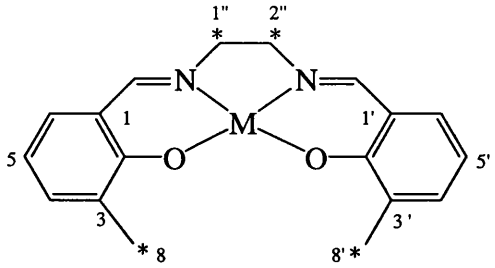
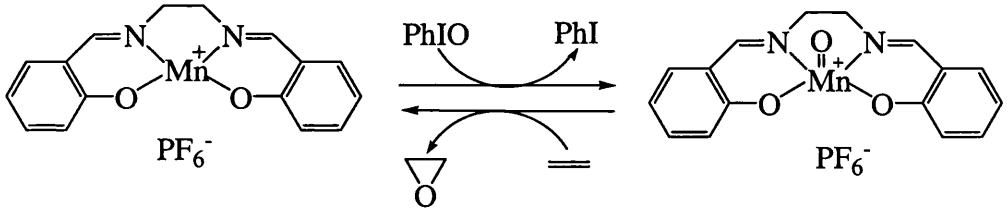


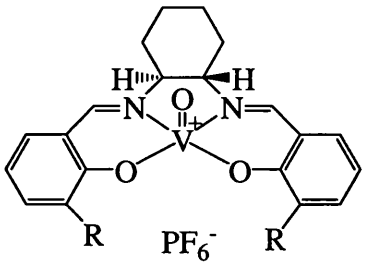
Fig. 1.7 The generalized structure for chiral salen complexes

Actually, Kochi and co-workers reported that achiral metallosalen complexes, such as (salen)Mn(III)[56] and (salen)Cr(III)[57] complexes, effected the epoxidation of unfunctionalized alkenes using iodosylbenzene as oxidant. Cationic (salen)Mn(III) complexes were found to be the most efficient catalysts (Scheme 1.7). Oxo (salen)Mn(V) complexes were postulated as the active species in the Mn-catalyzed epoxidation.[58]



Scheme 1.7

In 1986, the first application of chiral metallosalen complex in asymmetric oxidation was reported by Fujita *et al.* The reaction involved asymmetric oxidation of sulfides employing chiral (salen)vanadium complexes **1.16** as catalysts. The enantioselectivities obtained were moderate.[59]



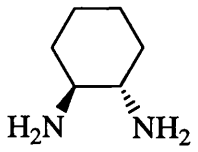
1.16 a: R = *t*-Bu
1.16 b: R = MeO

These early reports prompted the development of metallosalen-catalyzed asymmetric epoxidation of simple alkenes.

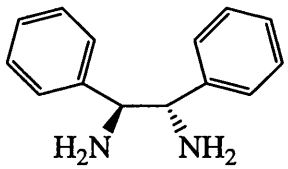
1.3.2 Preparation of chiral (salen)Mn(III) complexes

Preparation of chiral C_2 symmetric salen ligands is achieved in a general sense by condensation of an appropriately substituted 1,2-diamine with two equivalents of a salicylaldehyde derivative.

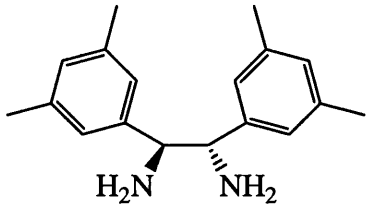
Chiral diamines can often be synthesized from optically pure tartaric acid, or resolved from the corresponding racemic diamines using optically pure tartaric acid, mandelic acid, or camphorsulfonic acid. Chiral diamines, which have been widely used in preparation of chiral metallosalen complexes and proven to be effective moieties to construct salen complexes, include 1,2-cyclohexanediamine (**1.17**), 1,2-diphenylethylenediamine (**1.18**) and 1,2-bis(3,5-dimethylphenyl)ethylenediamine (**1.19**).



1.17



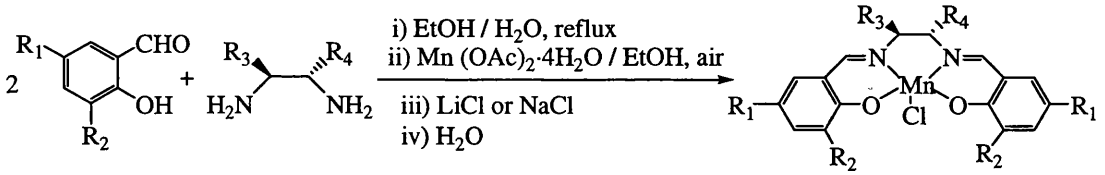
1.18



1.19

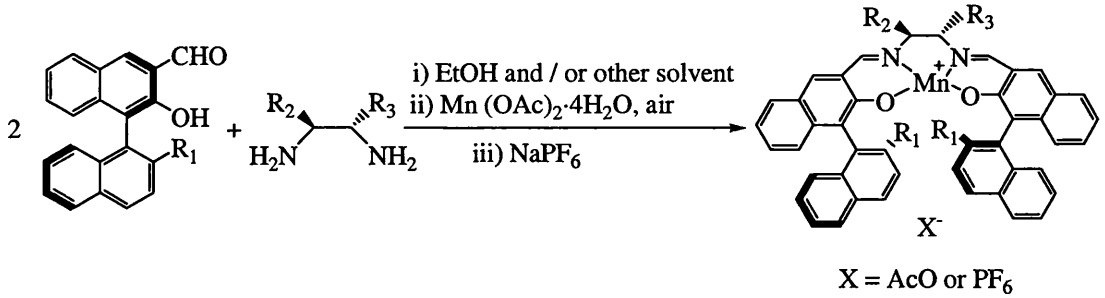
In the epoxidation reactions involving oxo intermediates, oxo transfer from metals to alkenes results in a net two-electron reduction of the metal complexes. As a result, only metals that are capable of shuttling between oxidation states are effective for oxo transfer catalysis. Metals that have been proven effective for catalytic epoxidation *via* oxo transfer include iron, manganese, ruthenium and chromium.[17,60] A wide variety of metallosalen complexes has been prepared by several research groups. Among them, the Mn(III) complexes have been proven to be the most effective catalysts in epoxidation of most alkenes.[15,56,57,61]

Preparation of Jacobsen-type (salen)Mn(III) complexes is readily accomplished by refluxing an ethanolic solution of a salen ligand with two equivalents of $Mn(OAc)_2 \cdot 4H_2O$ in air. The intermediate (salen)Mn(III)OAc complexes are usually converted into the corresponding (salen)Mn(III)Cl complexes by treatment with LiCl *in situ*. (Salen)Mn(III)Cl complexes usually precipitate as dark-brown air- and moisture-stable powder by addition of water into the reaction mixture (Scheme 1.8).[62]



Scheme 1.8

The general procedure used to prepare Katsuki-type axially chiral (salen)Mn(III) complexes is similar to the above procedure. The intermediate (salen)Mn(III)OAc complexes, however, are sometimes transformed into the corresponding (salen)Mn(III)PF_6 complexes by reaction with ferricenium hexafluorophosphate or sodium hexafluorophosphate (Scheme 1.9).[64] In some cases, the complexes were prepared in one pot from the optically pure diamine, (S)- or (R)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene and an appropriate Mn salt without isolation and purification of the corresponding salen ligands.



Scheme 1.9

1.3.3 General asymmetric epoxidation methods

Epoxidation reactions are usually carried out using a small amount of a catalyst (0.5 - 10 mol %) and 1 - 2 equivalents (molar ratio to the substrate) of a terminal oxidant in a suitable solvent at temperatures between 0 °C and room temperature.

1.3.3.1 Solvents

In addition to DCM, which is the most widely used solvent for epoxidation reactions, other solvents, such as 1,2-dichloroethane, *tert*-butyl methyl ether, ethyl acetate, acetonitrile, fluorobenzene, chlorobenzene, or toluene, can also be used as the solvent with generally little effect on the reaction rate, yield and enantioselectivity.[15,17,64,65]

1.3.3.2 Terminal oxidants

A wide variety of terminal oxidants has been used for epoxidation reactions, which include: sodium hypochlorite (NaOCl),[62b] iodosylbenzene (PhIO),[62a] molecular oxygen in combination with an aldehyde (O_2 / RCHO),[66] potassium monopersulfate (Oxone®),[67] periodates ($NaIO_4$ or *n*-Bu_4NIO_4),[68] *m*-chloroperbenzoic acid (m-CPBA)[67] and tetrabutylammonium monopersulfate (Bu_4NHSO_5), [69] etc.

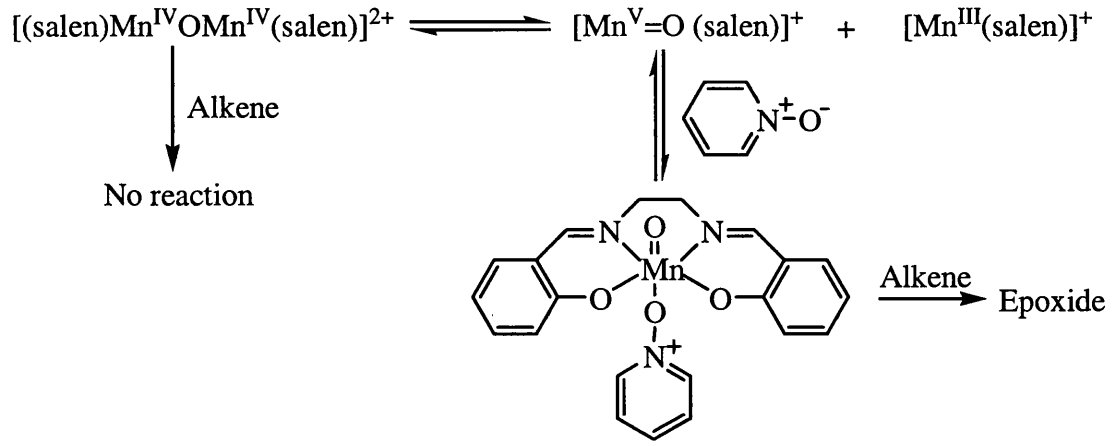
Among these oxidants, two types of terminal oxidants have been widely used. One is NaOCl solution (bleach). Epoxidation conditions using a NaOCl solution as the oxidant have been developed into a two-phase system, with an aqueous phase containing a buffered NaOCl solution and an organic phase containing a solution of the substrate and catalyst. The reactions are usually complete within a few hours at r.t. or at 0 °C. This procedure has been reported to have several significant features: a) enantioselectivities identical to those from reactions employing iodosylbenzene as the oxidant are usually obtained; b) good isolated yields of epoxides are achievable with

inexpensive reagents under mild conditions; c) no phase transfer catalyst is necessary; d) purification of solvents is unnecessary. The reactions are usually carried out in air; and e) work-up is simply accomplished by phase separation and the epoxides can be isolated by recrystallization, distillation or chromatography.[62b]

The other widely used procedure employs *m*-chloroperbenzoic acid (*m*-CPBA) as the oxidant. The reactions are usually carried out at low temperature (typically -78 ~ 0°C) under anhydrous conditions in the presence of a donor ligand, *N*-methylmorpholine-*N*-oxide (NMO). It has been found that a wide range of unfunctionalized alkenes proceed with an increase in enantioselectivity under these conditions compared to the corresponding biphasic reactions employing a buffered NaOCl solution as the oxidant. Furthermore, alkenes that are either water-soluble or decompose in the presence of a buffered NaOCl solution could be epoxidized under such reaction conditions.[67]

1.3.3.3 Donor ligands

The epoxidation reactions are usually carried out in the presence of a donor ligand. In most cases, addition of a donor ligand, which is capable of coordination to the metal centre, has been found to lead to an increase in the enantioselectivity, epoxide yield and catalyst turnover number.[70] Additives that have been proven to be useful include pyridine, imidazole derivatives, pyridine *N*-oxide derivatives (e.g. 4-phenylpyridine *N*-oxide and 4-*N*,*N*-dimethylaminopyridine *N*-oxide), and *N*-methylmorpholine *N*-oxide. The functions of the *N*-oxide additives in metallosalen-catalyzed epoxidations have been suggested to involve: a) direct complexation to the high valent oxo intermediate with rate acceleration in the subsequent epoxidation,[56,57a] b) activation of the intermediate metal-oxo complexes,[71] c) assistance to dissociation of the unreactive dimer complexes to their monomeric counterparts (Scheme 1.10),[56, 72] d) help in solubilization of the active oxidant,[73] and e) depression of the Lewis acidity of metal-oxo complexes to prevent decomposition of the acid sensitive epoxides.[74]



Scheme 1.10

4-Phenylpyridine *N*-oxide (4-PPNO) has been found to be the most effective additive in epoxidation reactions employing a buffered NaOCl solution as the oxidant. *N*-Methylmorpholine *N*-oxide (NMO) has been found to be the most effective additive in epoxidation reactions employing *m*-CPBA as the oxidant.

1.3.3.4 Reaction temperature

Epoxidation reactions are usually carried out at temperatures between 0 °C and r.t. The reactions have usually been found to proceed very slowly at a temperature as low as -78 °C, except when *m*-CPBA is used as the oxidant.[67,75] In general, enantioselectivity increases when the reaction temperature is lowered. However, some reactions show a maximum enantioselectivity at some specific temperature.[63e]

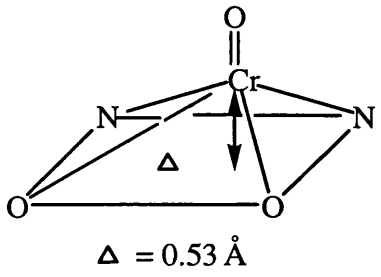
1.3.3.5 Reaction scope

In general, epoxidation of conjugated alkenes shows higher enantioselectivity than epoxidation of non-conjugated alkenes. Conjugated *cis*-disubstituted alkenes, conjugated trisubstituted alkenes and some conjugated tetrasubstituted alkenes have been found to be good substrates, whereas *trans*-disubstituted alkenes, monosubstituted alkenes, and dialkyl-substituted alkenes usually show insufficient enantioselectivities. Alkenes bearing functional groups, such as ether, ester, amide,

nitro, acetal, sily ether, nitrile, or acetylenic, could be successfully epoxidized without interference with these functional groups. However, sulfides and allylic alcohols have been found to be oxidized to the corresponding sulfoxides and aldehydes under the usual reaction conditions.

1.3.4 The mechanism of asymmetric induction and design of the optically active (salen)Mn(III) complexes

As mentioned above, Kochi and co-workers proposed that oxo (salen)Mn(V) complexes were the active species in Mn-catalyzed epoxidations, although they did not isolate them. However, they isolated an oxo (salen)Cr(V) complex **1.20** and an analogue **1.21** with pyridine *N*-oxide as an axial ligand, and characterized them by X-ray diffraction.[57a] The presence of oxo (salen)Mn(V) complexes in (salen)Mn-catalyzed epoxidation reactions was later proved by an MS / MS study of μ-oxo (salen)Mn(IV) complexes.[76]



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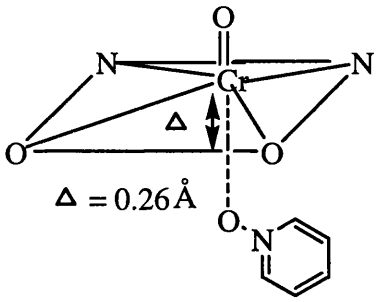


1.21

In metalloporphyrin-catalyzed epoxidation reactions, alkenes are considered to approach the metal-oxo bond from its side and parallel to the porphyrin ring (so called side-on approach) (Fig. 1.8).[48] The side-on or skewed side-on approach has also been considered to be applicable to the metallosalen-catalyzed epoxidation reactions because of the structural similarities between porphyrin and salen complexes.

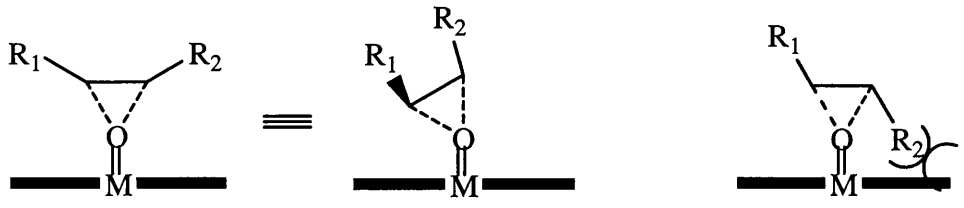


Fig. 1.8 The side-on approach model for oxygen transfer showing the less-hindered approach of *cis*-alkenes than *trans*-alkenes. The porphyrin ligand is symbolized by the heavy line.

As can be seen from Fig. 1.9, alkenes can approach an oxo (salen)Mn(V) complex in a side-on manner from various directions.[17]

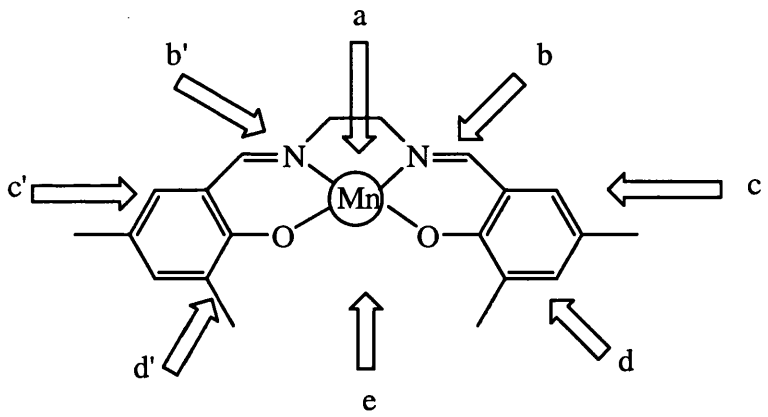
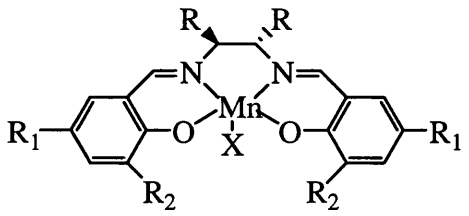


Fig. 1.9 The side-on approaches of an alkene to an oxo (salen)Mn(V) complex. The oxo ligand is oriented out of the plane of the page.

To achieve a high enantioselectivity in metallosalen-catalyzed epoxidation reactions, two factors, the pathway of the incoming alkene and its conformational orientation, must be strictly controlled. The problem of how to control the direction of an alkene's approach is solved by appropriately introducing substituents onto the salen ligand. That is, the substituents on the salen ligand interact sterically and electronically with the incoming alkene, and interfere with the alkene's approach from the side of the substituent.

A wide variety of salen ligands and the corresponding (salen)Mn(III) complexes has been developed since the 1990s. It is impossible and unnecessary to cover them all here. Therefore, only some of the important designs and achievements are reviewed below.

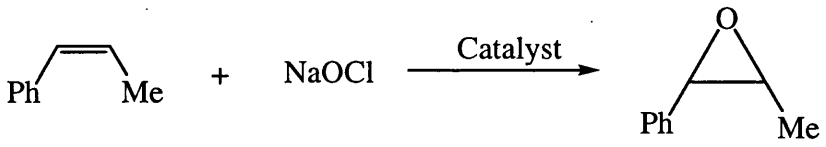
In the 1990s, Jacobsen and co-workers reported asymmetric epoxidation of conjugated alkenes using (salen)Mn(III) complexes **1.22**.[62a,72,77]



X= Cl, AcO^-

1.22a: R, R = Ph, Ph; $R_1 = R_2 = H$
1.22b: R, R = Ph, Ph; $R_1 = H$; $R_2 = t$-Bu
1.22c: R, R = -$(CH_2)_4$-; $R_1 = R_2 = t$-Bu
1.22d: R, R = -$(CH_2)_4$-; R_1 = OMe; $R_2 = t$-Bu
1.22e: R, R = -$(CH_2)_4$-; $R_1 = NO_2$; $R_2 = t$-Bu
1.22f: R, R = -$(CH_2)_4$-; $R_1 = Pr^i_3SiO$; $R_2 = t$-Bu

These complexes have stereogenic carbon atoms on the ethylenediimine moiety. The C-3 and C-3' substituents are achiral but their presence has been found to be essential to achieve a high enantioselectivity. Complex **1.22a**, which has no substituents at C-3 and C-3' positions, catalyzed epoxidation reactions with poor enantioselectivities, e.g., with <10% ee in epoxidation of *cis*-β-methylstyrene (Scheme 1.11). Introduction of bulky *tert*-butyl substituents at C-3 and C-3' positions, as in the complex **1.22b**, improved the enantioselectivity dramatically to 84% ee. The presence and identities of the substituents at C-5 and C-5' positions can also have significant, although generally less important, effects on the epoxidation enantioselectivity. In general, electron-donating or sterically demanding substituents improve the enantioselectivity (see catalyst **1.22c** - **1.22f**). A happy combination of steric and electronic substituents properties was achieved in complex **1.22f**[77d]. However, complex **1.22c**, which has the advantage of greater synthetic accessibility, is almost as good (Scheme 1.11)[17,77a] and has been the most widely used catalyst in this class. It has become commercially available.



Catalyst	ee (%)
1.22a	<10
1.22b	84
1.22c	90
1.22d	86
1.22e	46
1.22f	92

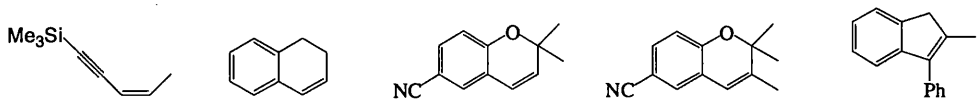
Scheme 1.11 Asymmetric epoxidation of *cis*-β-methylstyrene using (salen)Mn(III) complexes 1.22

Some of the epoxidation results using (salen)Mn(III) complexes **1.22c**, **1.22f,** or their corresponding enantiomers (named as **ent-1.22c** and **ent-1.22f**) are summarized in Table 1.2.

Table 1.2 Asymmetric epoxidation of alkenes using (salen)Mn(III) complexes 1.22c, 1.22f or their enantiomers as the catalyst [62c-d, 67,77e]

Entry	Substrate[a]	Catalyst	Oxidant	Temp. (°C)	Yield (%)	ee (%)	Confign.
1	A	**1.22c**	NaOCl	r. t.	84 (2.5:1)[b]	90[c]	3R, 4R
2	B	**1.22c**	NaOCl	0	67	86	1S, 2R
3	C	**1.22f**	*m*-CPBA[d]	-78	91	97	-
4	D	**ent-1.22c**	NaOCl	0	82	>98	3R, 4R
5	E	**ent-1.22f**	NaOCl[e]	0	90	90	-

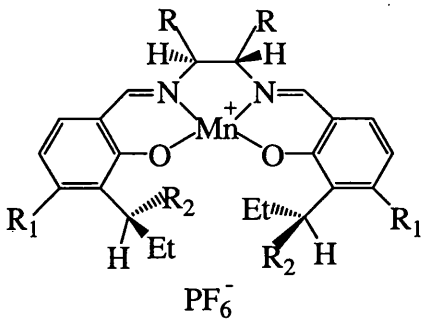
a) Substrates:



A B C D E

b) The product is a mixture of *trans*- and *cis*-epoxides. Numbers in parentheses are a ratio of *trans*- and *cis*-epoxides.
c) The number stands for the ee of *trans*-epoxide.
d) Reaction was carried out in the presence of excess NMO under anhydrous conditions. The solvent was DCM.
e) Reaction was carried out in the presence of 4-PPNO under a two-phase solvent system. The organic solvent used was DCM.

Katsuki and co-workers reported asymmetric epoxidation of alkenes using (salen)Mn(III) complexes **1.23**, which bear stereogenic centers at C-8 and C-8' positions as well as at C-1" and C-2" positions.[63a,70b,78] The chiral and bulky C-3 and C-3' substituents were expected not only to prevent alkenes from approaching the metal-oxo bond from undesired directions, but also to control the orientation of the incoming alkenes. Indeed, the conformations of C-3 and C-3' chiral substituents were found to have a considerable influence on the asymmetric induction. For instance, the catalyst **1.23b,** which has methyl groups at C-4 and C-4' positions and therefore would fix the conformation of C-3 and C-3' substituents to a hydrogen atom-in-aromatic-plane conformation, was found to be better than catalyst **1.23a** which has no C-4 and C-4' methyl groups. The catalyst **1.23c,** which has more bulky 4-*t*-butylphenyl groups at C-8 and C-8' positions, afforded even higher asymmetric induction.[78c,d] In contrast to Jacobsen-type catalysts which usually afford very low enantoselectivities (<20% ee) with *trans*-disubstituted substrates, Katsuki's catalysts exhibited moderate enantioselectivities with certain *trans*-alkenes, e.g. epoxidation of *trans*-stilbene proceeded with a 62% ee using catalyst **1.23d** (Table 1.3, Entry 1). It could be concluded from this observation that the stereochemical elements at the C-3 and C-3' positions have little influence on epoxidation of *cis*-alkenes, but have significant influence on epoxidation of *trans*-alkenes.[78e]



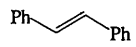
1.23a: R, R = Ph, Ph; R_1 = H; R_2 = Ph
1.23b: R, R = Ph, Ph; R_1 = Me; R_2 = Ph
1.23c: R, R = Ph, Ph; R_1 = Me; R_2 = 4-*t*-Bu-Ph
1.23d: R, R = -$(CH_2)_4$-; R_1 = Me; R_2 = 4-*t*-Bu-Ph

Some of the epoxidation results using (salen)Mn(III) complex **1.23c** are summarized in Table 1.3.

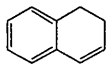
Table 1.3 Asymmetric epoxidation of alkenes using (salen)Mn(III) complex 1.23c as the catalyst[78c]

Entry	Substrate[a]	Solvent	Oxidant	Temp. (°C)	Yield (%)	ee (%)	Confign.
1	A	CH_3CN	PhIO	r. t.	65	62	1R, 2R
2	B	CH_2Cl_2	NaOCl[b]	r. t.	38	91	1S, 2R
3	C	CH_3CN	PhIO	r. t.	78	96	-

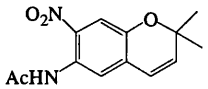
a) Substrates:



A



B

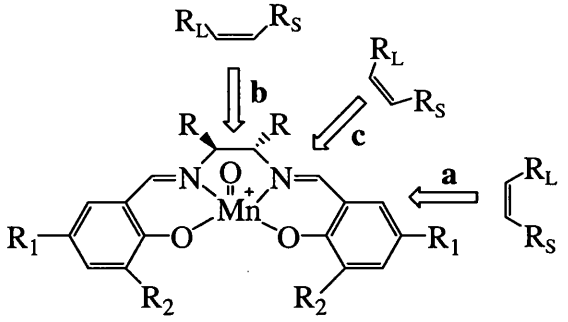


C

b) Reaction was carried out in the presence of 4-PPNO in a two-phase solvent system.

The ligand substituent effects outlined above might be rationalized qualitatively within the side-on approach transition state model. The presence of bulky substituents at C-3, C-3', C-5, and C-5' positions presumably blocks several competing pathways and dictates the orientation of the incoming alkene. For catalysts **1.22b** and **1.23,** the incoming alkene was proposed to approach the metal-oxo bond *via* pathway **a** (Fig. 1.10), with its bulkier substituent away from the C-3 substituent to avoid steric repulsion between them.[62a,78a] For catalysts **1.22c - 1.22f**, Jacobsen and co-workers proposed the pathway **b** where the incoming alkene passes between the two nitrogen atoms.[77c] However, Katsuki and co-workers proposed a new pathway **c** for alkenes' approach.[78b,78f] They suggested that the incoming alkene's approach along the pathway **c** would be subjected to a different electronic environment at either side of the bond axis due to the salicylaldehyde moiety being rich in π-electrons and the ethylenediimine part having no π-electrons. As a result, not only the repulsive steric interaction, but the repulsive π-π electronic interaction between the benzene ring of the salen ligand and the unsaturated alkene

substituent plays an important role in dictating the orientation of the incoming alkenes.[78f]

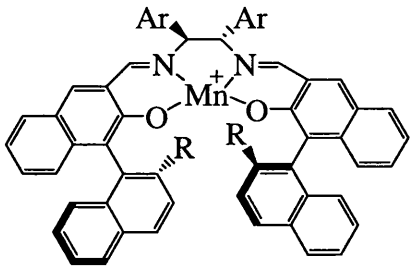


R_L = larger substituent

R_S = smaller substituent

Fig. 1.10 The proposed pathway by which an incoming alkene approaches the oxo-metal bond

The hypothesis that π-π repulsion plays an important role in asymmetric induction using (salen)Mn(III) complexes has led to the development of a new type of (salen)Mn(III) complex. Katsuki *et al.* introduced (salen)Mn(III) complexes **1.24,** which possess asymmetric centres in the ethylenediimine moiety and binaphthyl groups of axial chirality.[63b-c,79] The sterically bulky and π electron rich binaphthyl moiety with a phenyl group protruding toward the space above C-3' was incorporated, which was expected to intensify the steric and electronic repulsion between the salen ligand and the alkene substituents, and therefore enhance asymmetric induction. Replacement of phenyl groups at C-1" and C-2" positions in complex **1.24b** with more bulky 3,5-dimethylphenyl groups, which were expected to suppress the access of alkenes along the disfavoured pathway (**ent-c**), provided a more effective catalyst **1.24c** (Table 1.4, Entry 3 and 4). (Salen)Mn(III) complex **1.24c** afforded extremely high enantioselectivities in epoxidation of conjugated *cis*-alkenes and trisubstituted alkenes.



AcO $^-$ or PF_6^-

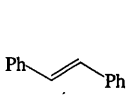
1.24a: Ar, Ar = Ph, Ph; R = Me
1.24b: Ar, Ar = Ph, Ph; R = Ph
1.24c: Ar, Ar = 3,5-$Me_2C_6H_3$, 3,5-$Me_2C_6H_3$; R = Ph

Some of the epoxidation results using (salen)Mn(III) complexes **1.24b** or **1.24c** are summarized in Table 1.4.

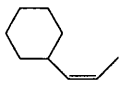
Table 1.4 Asymmetric epoxidation of alkenes using (salen)Mn(III) complex 1.24b or 1.24c as the catalyst[63c,79b-c]

Entry	Substrate[a]	Catalyst	Solvent	Oxidant	Temp. (°C)	Yield (%)	ee (%)	Confign.
1	A	1.24b	CH_3CN	PhIO	-40	17	81	1R, 2R
2	B	1.24c	CH_2Cl_2	NaOCl[b,c]	-18	23	82	1S, 2R
3	C	1.24b	CH_2Cl_2	NaOCl	0	96	93	1S, 2R
4	C	1.24c	CH_2Cl_2	NaOCl[c]	0	78	98	1S, 2R
5	D	1.24c	CH_2Cl_2	NaOCl[c]	0	80 (2:1)[d]	96[e] (94)[f]	3R, 4R
6	E	1.24c	CH_2Cl_2	NaOCl[c]	0	80	>99	3S, 4S
7	F	1.24c	CH_2Cl_2	NaOCl	0	88	>99	-
8	G	1.24c	CH_2Cl_2	NaOCl[b]	-18	5	70	-

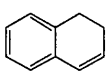
a) Substrates:



A

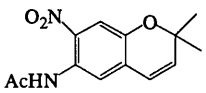


B

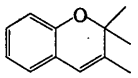


C

D



E



F

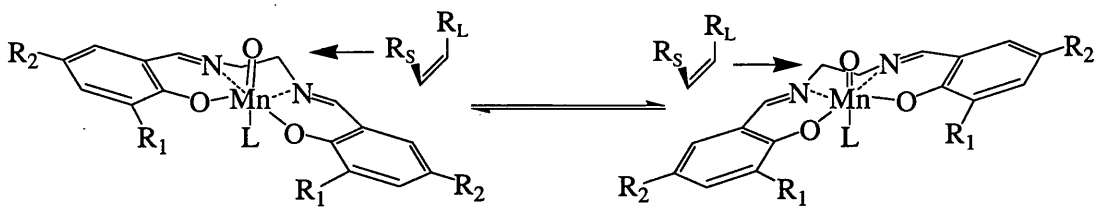
G

b) An aqueous solution of NaOCl saturated with sodium chloride was used.

c) Reaction was carried out in the presence of 4-PPNO in a two-phase solvent system.
d) The product is a mixture of *trans*- and *cis*-epoxides. Numbers in parentheses are a ratio of *trans*-and *cis*-epoxides.
e) The number stands for the ee of *trans*-epoxide.
f) The number in parentheses stands for the face selectivity. Face selectivity = ee *trans* × % *trans* + ee *cis* × % *cis*

All the above discussions about the mechanism of asymmetric induction are based on the hypothesis that the ligands of oxo (salen)Mn(V) complexes have planar structures. However, Katsuki also proposed that the ligands of oxo (salen)Mn(V) complexes might take a non-planar stepped conformation. As a result, an alkene might approach the metal-oxo bond from one side of the salen ligand more readily than from the other. [80-82]

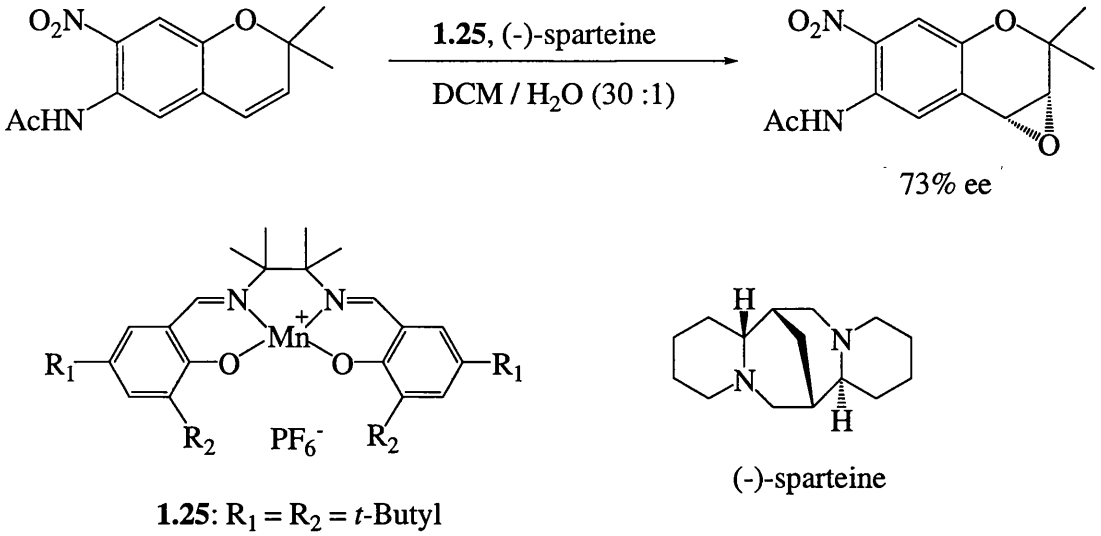
Based on this hypothesis, achiral oxo (salen)Mn(V) complexes were proposed to exist in an equilibrium mixture of two enantiomeric stepped conformers (**A** and **ent-A**, Fig. 1.11), and an alkene approaches these enantiomeric metal-oxo species from their downward benzene ring sides to give the racemic epoxide. If this equilibrium is shifted to one side by some means, epoxides should be formed in an optically active form. Indeed, Katsuki reported that a combination of an achiral (salen)Mn(III) complex **1.25** and a chiral ligand, (-)-sparteine, afforded a good enantioselectivity (73% ee) in epoxidation of 6-acetamido-2,2-dimethyl-7-nitro-2H-chromene (Scheme 1.12).[83]



A **ent-A**

R_L = Large substituent
R_S = Small substituent

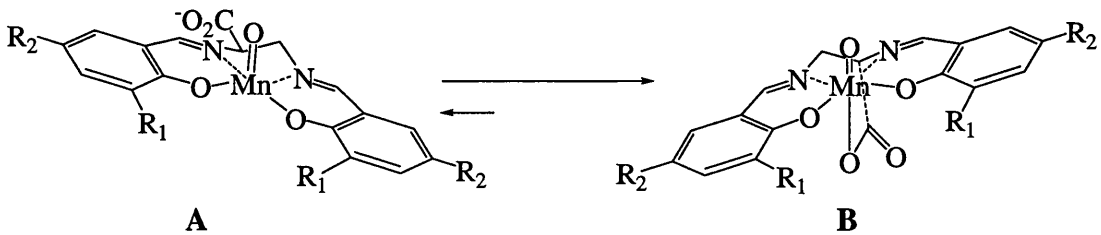
Fig. 1.11 An equilibrium mixture of enantiomeric conformers A and ent-A for achiral oxo (salen)Mn(V) complexes



1.25: $R_1 = R_2 = t$-Butyl

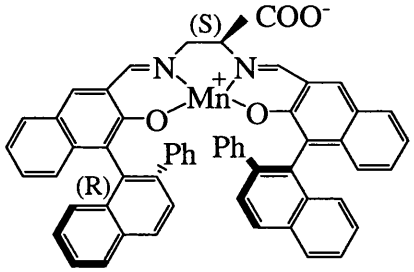
Scheme 1.12

As to chiral oxo (salen)Mn(V) complexes, they would exist in one of the two stepped conformers due to the regulation by the chirality of the ethylenediimine part. The salen ligands would usually fold in such a manner that the substituents (R) at the ethylenediimine part take a sterically favourable pseudo-equatorial orientation (Fig. 1.12 **A**). However, if (R) is a coordinating group, such as a carboxylato group, it would coordinate to the metal ion in an axial orientation and cause the inversion of the ligand conformation (Fig. 1.12 **B**).[81-82] A new type of (salen)Mn(III) complex **1.26** was synthesized by Kastuki based on this idea.[80] The epoxidation reaction system using complex **1.26** as the catalyst was reported to have several significant features: a) high levels of enantioselectivities can be achieved without adding an axial ligand; b) the catalyst can be recovered by column chromatography and reused; c) the quantity of the catalyst can be reduced from 2 % to 0.01 % (mol / mol to the substrate) while still maintaining the high yield and high enantioselectivity (Table 5, Entry 4); and d) high turnover number of the catalyst (up to 9200 times) has been realized.



A **B**

Fig. 1.12 An equilibrium mixture of conformers A and B for chiral oxo (salen)Mn(V) complexes with a carboxylato group on the ethylenediimine moiety



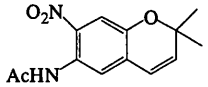
1.26

Some of the epoxidation results using complex **1.26** as the catalyst are summarized in Table 1.5.[81]

Table 1.5 Asymmetric epoxidation of alkenes using (salen)Mn(III) complex 1.26 as the catalyst[a,b]

Entry	Catalyst (mol %)[c]	Solvent	Temp. (°C)	Time	Yield[d] (%)	ee (%)	Confign.
1	5	CH_2Cl_2	r. t.	2 h	92	96	3S, 4S
2	2	CH_3CN	0	6 h	100	98	3S, 4S
3	0.2	CH_3CN	0	6 h	95	98	3S, 4S
4[e]	0.01	CH_3CN	0	10 d	92	99	3S, 4S

a) All reactions were carried out using iodosylbenzene as the terminal oxidant.
b) The substrate is:

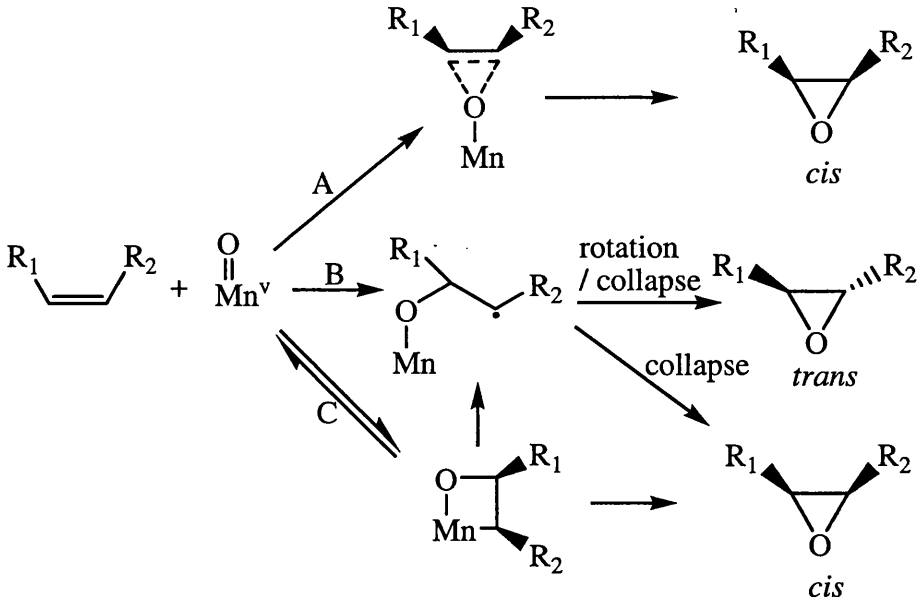


c) mol % to the substrate.
d) Isolated yield.
e) Turnover number of the catalyst up to 9200 was achieved.

1.3.5 Mechanism of single oxygen atom transfer from oxo (salen)Mn(V) complexes to alkenes

The mechanism of single oxygen atom transfer from an oxo (salen)Mn(V) complex to an alkene is still in controversy. Several proposals have been made for this process, which include: concerted mechanism, stepwise mechanism through

radical intermediates, and stepwise mechanism through metallaoxetane intermediates (Scheme 1.13).



Scheme 1.13 **Proposed mechanisms for Mn-salen catalyzed epoxidation reactions: A. concerted reaction (R_1 = R_2 = alkyl); B. reaction *via* a radical intermediate (R_1 = alkyl, R_2 = aryl, alkenyl, alkynyl); C. reaction *via* a metallaoxetane intermediate (R_1 = alkyl, R_2 = aryl, alkenyl, alkynyl).**

Jacobsen *et al.* suggested that epoxidation of conjugated alkenes follows **pathway B**, in which a radical intermediate undergoes competitive collapse to *cis*-epoxide and rotation / collapse to *trans*-epoxide.[15,17,84] This proposal is supported by the fact that both *cis*- and *trans*-epoxides can be formed as primary products from acyclic *cis*-alkenes (Table 1.2, Entry 1) and the fact that these reactions show remarkable absence of solvent effects.

Jacobsen *et al.* also suggested that epoxidation of alkyl-substituted alkenes follows a concerted mechanism (**pathway A**).[15,17,84] The existence of such a mechanistic divergence is supported by the phenomenon that very low enantioselectivities are usually obtained in epoxidations of alkyl-substituted alkenes and these substrates react more slowly than the sterically similar conjugated alkenes.

However, Katsuki *et al.* proposed a stepwise mechanism, in which oxygen transfer proceeds through a metallaoxetane intermediate (**pathway C**) that decomposes to give the epoxide directly or by the way of a radical intermediate.[63e] This proposal is supported by the observation that a non-linear relationship between reaction temperature and enantioselectivity exists in Mn-salen catalyzed epoxidations.

Norrby *et al.* also proposed that Mn-salen catalyzed epoxidation proceeds by way of a metallaoxetane intermediate. The proposal is based on a calculation using the Macromodel / MM3 program.[85]

1.3.6 Immobilisation of chiral (salen)Mn(III) complexes

Shortly after the discovery of salen-Mn catalyzed asymmetric epoxidation of unfunctionalized alkenes, attempts have been made to design heterogeneous solid-supported versions of these metal complexes. Due to the readily synthetic accessibility of Jacobsen-type catalysts, especially complex **1.22c**, most of the work has been directed towards immobilisation of Jacobsen-type (salen)Mn(III) complex.

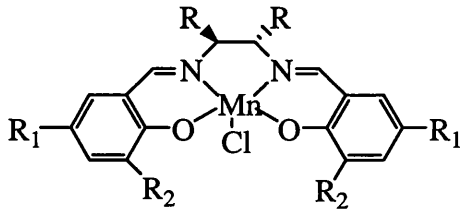
1.3.6.1 Polymer-supported chiral (salen)Mn(III) complexes

Application of polymer-supported catalysis in organic transformations has been receiving extraordinary attention during the past several decades. Immobilization of a homogeneous catalyst on a polymeric carrier would offer several practical benefits of the heterogeneous catalysis, while retaining the advantages of the homogeneous catalytic reactions.[86] Some of the attractive features of polymer-supported catalysis include: a) the catalysts could be separated easily from the reagents and products; b) the methods for recycling expensive catalysts could be simplified; c) certain catalyst deactivation pathways could be minimized by site isolation; and, d) the polymeric catalysts could possibly help in developing high throughput discovery applications as well as in developing continuous catalytic processes for industrial scale syntheses.[87]

Two different approaches have been used to attach chiral (salen)Mn(III) complexes covalently to polymer supports. These include: a) synthesis of appropriate salen-type functional monomers and then copolymerization of these functional monomers with other monomers to form catalytically active polymers; b) attachment of the metal complexes to preformed functional polymer supports by chemical modification.

1.3.6.1.1 Crosslinked polymeric chiral (salen)Mn(III) complexes prepared by copolymerization of appropriate functional monomers

Dhal[88] and Salvadori[89] independently reported the syntheses of crosslinked macroporous polymer-supported catalysts **1.27** (Complexes **1.27a-b** were prepared by Dhal; complexes **1.27c-e** were prepared by Salvadori) and their applications in epoxidation of unfunctionalized alkenes. Although some of the supported catalysts displayed good activity, the enantioselectivities were low; the best result (62% ee) was obtained in asymmetric epoxidation of β-methylstyrene with catalyst **1.27d** using *m*-CPBA / NMO system.[89] Both groups reported that the recovery and reuse of their polymeric catalysts were possible. However, no data were given.



1.27a: R, R = Ph, Ph; R_2 = H; R_1=

1.27b: R, R = Ph, Ph; R_2 = *t*-Bu; R_1=

1.27c: R, R = -$(CH_2)_4$-; R_2 = *t*-Bu; R_1=

1.27d: R, R= -$(CH_2)_4$-; R_2 =*t*-Bu; R_1=

1.27e: R, R = Ph, Ph; R_2 = *t*-Bu; R_1=

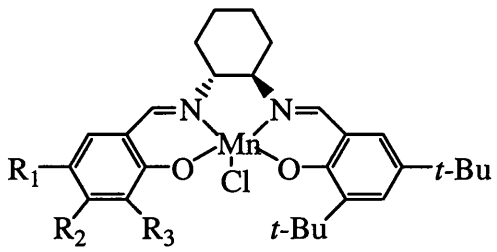
As can be seen from the structures, the salen units in these polymer-supported complexes are all localized in a cross-linked network. This would result in steric

crowding and conformational rigidity of the complexes and therefore might account for the low levels of asymmetric induction.[90]

1.3.6.1.2 Crosslinked polymeric chiral (salen)Mn(III) complexes prepared by chemical modification

In an attempt to overcome the shortcomings of the above-mentioned polymer-supported catalysts [so-called *first generation polymeric chiral (salen)Mn(III) catalysts*], some research groups adopted chemical modification approach to prepare polymeric chiral (salen)Mn(III) complexes.

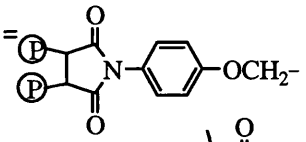
Sherrington and co-workers reported the preparation of polymeric chiral (salen)Mn(III) complexes **1.28** by attaching homogeneous chiral (salen)Mn(III) complex moieties to polymer supports through a single point linkage.[91] The most effective polymer-supported catalyst was found to be **1.28c**, in which the polymer support was a porous methacrylate-based resin. A high enantioselectivity (91% ee) was realized in asymmetric epoxidation of phenylcyclohexene using *m*-CPBA / NMO system. The low loading of manganese sites and the high surface area of the polymer support were considered to be the key factors for the good result.

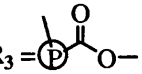


1.28a: R_1=Ⓟ-C$_6$H$_4$-OCH_2- ; R_2 = H, R_3 = *t*-Bu; **Porous styrene-based resin**

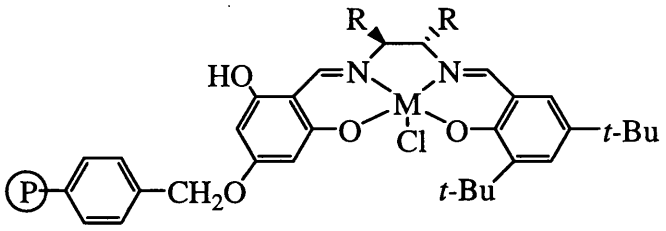
1.28b: R_1 = Ⓟ-C$_6$H$_4$-OCH_2- ; R_2 = H, R_3 = *t*-Bu; **Gel-type styrene-based resin**

1.28c: R_1 =Ⓟ-C$_6$H$_4$-OCH_2- ; R_2 = H, R_3 = *t*-Bu; **Porous methacrylate-based resin**

1.28d: R_1 =  ; R_2 = H, R_3 = *t*-Bu; **Porous styrene-based resin**

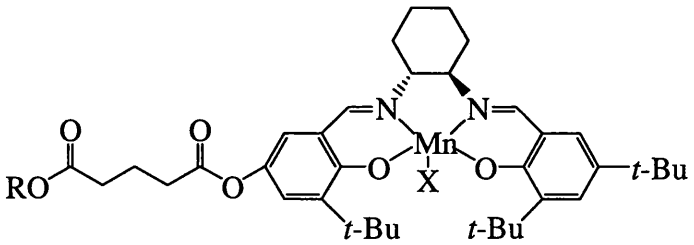
1.28e: R_1 = H; R_2 = H, R_3 =  ; **Porous methacrylate-based resin**

Laibinis and co-workers developed an analogous polymer modification approach to prepare the polymeric catalyst **1.29,** in which Merrifield resin was used as the functional polymer support.[92] A modest enantioselectivity (79% ee) was obtained in epoxidation of *cis*-β-methylstyrene with catalyst **1.29a** using NaOCl solution as oxidant under biphasic conditions. Reuse of the catalyst was found to be unsuccessful; the enantioselectivities dropped significantly upon catalyst recycling. Fracture of the imine portions of the salen framework was proposed for the degradation.



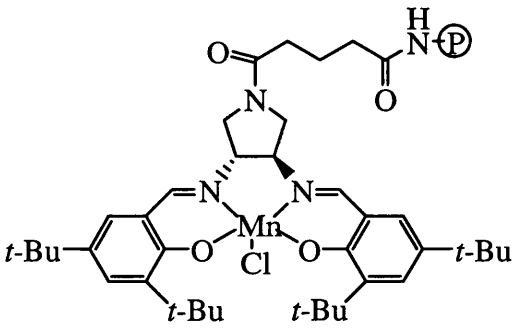
1.29a: R, R = -$(CH_2)_4$-; M = Mn
1.29b: R, R = -$(CH_2)_4$-; M = Cr

The polymeric chiral (salen)Mn(III) complexes **1.30** were prepared by Reger and Janda using a chemical modification approach.[93] The complexes exhibited improved enantioselectivities. Both Merrifield resin and *JandaJel* were used as the functional polymer supports. The five-carbon linker between the polymer and the salen ligand was expected to place the catalyst sufficiently away from the polymer backbone and allow the unimpeded access of alkenes to the active metal center. The highest enantioselectivity was achieved in epoxidation of β-methylstyrene (~ 88% ee) with catalyst **1.30b** using *m*-CPBA / NMO system, which is comparable to the corresponding homogeneous system. It was reported that these catalysts could be recycled and reused up to three times without significant losses of activity. However, a gradual degradation of the salen ligand was also reported.



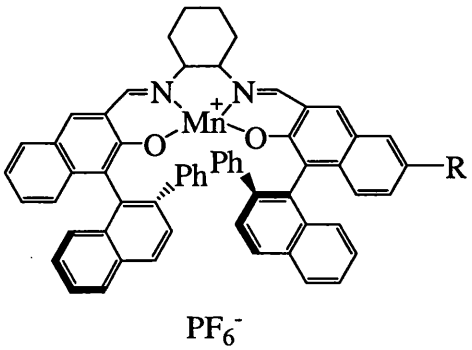
1.30a: R = Merrifield resin
1.30b: R = JandaJel

Song reported the preparation and applications of a polymer-supported (pyrrolidine salen)Mn(III) complex **1.31**.[94] The salen complex moiety was linked to *TentaGel* resin through the nitrogen atom of the pyrrolidine ring. The best result was obtained in epoxidation of 2,2-dimethylchromene (92% ee) using *m*-CPBA / NMO system. The catalyst was found to undergo partial decomposition under the epoxidation conditions.



1.31

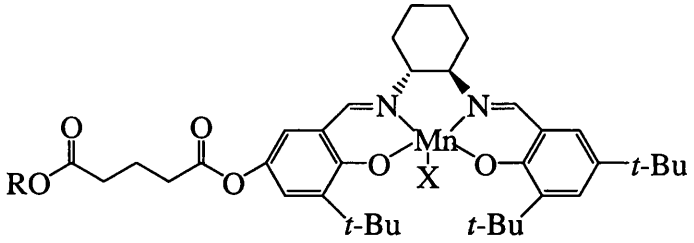
Smith[95] reported the synthesis of a polymer-supported unsymmetrical Katsuki-type (salen)Mn(III) complex **1.32,** in which the salen complex moiety was attached to Merrifield resin through a single flexible linkage by formation of an ester functional group between the alkylhydroxyl group at the C-6 position of the salen ligand and the functional group of Merrifield resin. The catalyst produced high enantioselectivity in epoxidation of 1,2-dihydronaphthalene (94% ee) using a buffered NaOCl solution / 4-PPNO system under biphasic conditions. Also, the catalyst could be recovered and reused up to six times without significant change in enantioselectivity.



1.32: R = $CH_2CH_2CH_2OCOC_6H_4$-Ⓟ

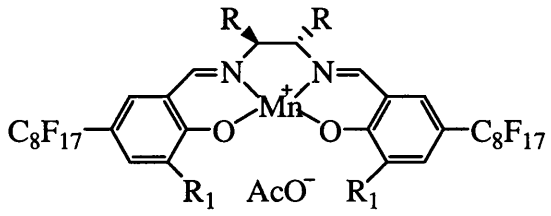
1.3.6.1.3 Soluble polymeric chiral (salen)Mn(III) complexes

Janda and co-workers also reported the preparation and application of PEG-based soluble (salen)Mn(III) complexes **1.33**.[93a] Enantioselectivities and chemical yields obtained in epoxidation reactions are comparable to the analogous heterogeneous system, e.g. high enantioselectivity (90% ee) and yield (79%) were realized in epoxidation of *cis*-β-methylstyrene with catalyst **1.33b** using the *m*-CPBA / NMO system. It was reported that the catalysts could be reused up to three times without losing their chemo- and enantio-selective activities.



1.33a: R = MeO-PEG$_{5000}$
1.33b: R = non-crosslinked poly(styrene-co-hydroxymethyl styrene)

Another interesting approach to prepare soluble, phase separable immobilized chiral (salen)Mn(III) complexes **1.34** was reported by Pozzi *et al.*[96] This approach is based on the technique of Fluorous Biphasic System (FBS). High enantioselectivity (~ 92 % ee) was achieved in epoxidation of indene using molecular oxygen / pivalaldehyde as the oxidant system under fluorous two-phase conditions.



1.34a: R, R = Ph, Ph; R_1 = H
1.34b: R, R = Ph, Ph; R_1 = C_8F_{17}
1.34c: R, R = -$(CH_2)_4$-; R_1 = C_8F_{17}
1.34d: R, R = -$(CH_2)_4$-; R_1 = H

1.3.6.2 Inorganic solid-supported chiral (salen)Mn(III) complexes

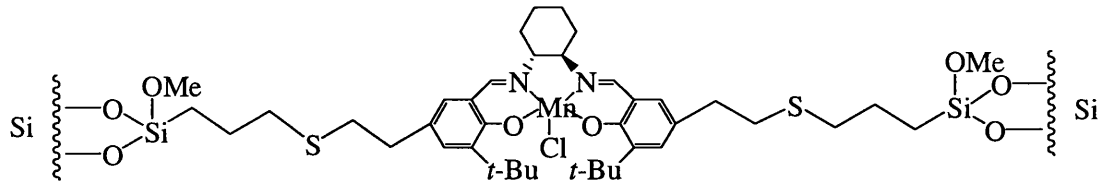
Desirable physical characteristics of inorganic supports (silica gels, zeolites, etc.) have been the driving forces to explore these materials as the carriers to prepare solid-phase catalysts and reagents. Some of these characteristics include: a) superior mechanical and thermal properties; b) well-defined pore sizes; and c) compatibility to a wide range of solvents. Immobilization of chiral metal complexes to inorganic matrices has been carried out by methods such as gel entrapment, covalent linkage and electrostatic interactions.

Vankelecom and co-workers[97] reported the physical entrapment of Jacobsen's catalyst and of a novel dimeric chiral (salen)Mn(III) complex in polydimethylsiloxane (PDMS) membranes. Chemoselectivities and enantioselectivities of these two immobilized catalysts were reported to be comparable to the corresponding homogeneous systems in epoxidation of alkenes. This approach appears to be a general and facile way to prepare catalytically active immobilized metal complexes.

Sabater *et al.* reported the preparation of a chiral (salen)Mn(III) complex of simple structure within the supercages of zeolite Y (13Å)[98] (so-called '*ship-in-a-bottle*' approach). The complex was found to have similar catalytic activity to the corresponding soluble complex in epoxidation of unfunctionalized alkenes.

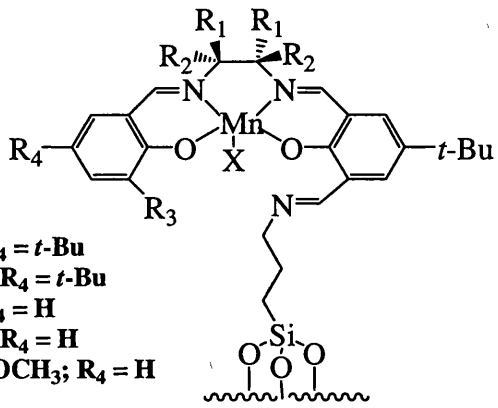
Ogunwumi and Bein used a similar strategy to prepare heterogeneous chiral (salen)Mn(III) complexes in which zeolite EMT was used as the support.[99] The heterogeneous catalysts exhibited high enantioselectivities in epoxidation of aromatic alkenes using a buffered NaOCl solution as the terminal oxidant.

Salvadori and co-workers reported the preparation of silica gel-supported chiral (salen)Mn(III) complex **1.35**, in which the salen moiety was covalently linked to silica gel by a two-point attachment.[100] As mentioned above, this type of attachment would result in restricted mobility of the metal-complex moieties and unfavourable steric restriction for the substrates to approach the catalytic sites. Indeed, only modest enantioselectivities have been obtained in epoxidation reactions using this complex as the catalyst.



1.35

Kim and Shin reported the preparation of siliceous MCM-41 supported chiral (salen)Mn(III) complexes **1.36**, in which the Mn(III) complexes were attached to the solid support through a single flexible linkage.[101] High yields and enantioselectivities (~70%) were achieved in epoxidation of styrene and α-methylstyrene. It was reported that the immobilized catalyst could be recycled and reused four times without significant change in selectivities.



1.36a: R_1, R_1 = Ph, Ph; R_2 = H; R_3 = R_4 = *t*-Bu
1.36b: R_1, R_1 = -$(CH_2)_4$-; R_2 = H; R_3 = R_4 = *t*-Bu
1.36c: R_1, R_1 = Ph, Ph; R_2 = H; R_3 = R_4 = H
1.36d: R_1, R_1 = -$(CH_2)_4$-; R_2 = H; R_3 = R_4 = H
1.36e: R_1, R_1= -$(CH_2)_4$-; R_2 = H; R_3 = OCH_3; R_4 = H

Kim *et al.*[102] reported the preparation of heterogeneous chiral (salen)Mn(III) complexes immobilized on mesoporous MCM-41. The Mn complexes were introduced into MCM-41 using an ion-exchange method. The immobilized catalysts showed high enantioselectivity (up to 86% ee) in epoxidation of styrene. It was reported that the catalysts could be reused up to three times without significant change in their activity and selectivity.

1.4 Conclusions

Asymmetric epoxidation has become one of the most important reactions in organic synthesis. Many approaches have been developed for this purpose. Among

those, a fairly good level of enantioselectivity has been achieved in the epoxidation of conjugated alkenes catalyzed by salen complexes, though further improvement is still required.

1.5 References for *Chapter 1*

1. R. E. Parker and N. S. Isaacs. *Chem. Rev.*, 1959, 59,737.
2. J. G. Smith. *Synthesis*, 1984, 629.
3. G. Berti. In: *Topics in Stereochemistry*, Eds. N. L. Allinger and E. L Eliel. Wiley: New York, 1973, Vol. 7, pp. 93.
4. R.C. Larock. *Comprehensive Organic Transformations*, VCH: New York, 1989, pp. 505.
5. A. Fürst and P. A. Plattner. *Helv. Chim. Acta*, 1949, 32, 275.
6. G. H. Alt and D. H. R. Barton. *J. Chem. Soc.,* 1954, 4284.
7. G. Stork, L. D. Cama and D. R. Coulson. *J. Am. Chem. Soc.,* 1974, 96, 5268.
8. A. S. Rao. In: *Comprehensive Organic Syntheses*, Eds. B. M. Trost and I. Fleming. Pergamon: Oxford, 1991, Vol. 7, pp. 357.
9. A. Gansäuer. *Angew. Chem. Int. Ed. Engl.*, 1987, 36, 2591.
10. B. E. Rossiter. In: *Asymmetic Synthesis*, Ed. J. D. Morrison. Academic Press: Orland, 1985, Vol. 5, pp. 193.
11. N. Hosoya, A. Hatayama, R. Irie, H. Sasaki and T. Katsuki. *Tetrahedron*, 1994, 50, 4311.
12. W. A. Nugent, T. V. RajanBabu and M. J. Burk. *Science*, 1993, 259, 479.
13. A. S. Rao, S. K. Paknikar and J. G. Kirtane. *Tetrahedron*, 1983, 39, 2323.
14. T. Katsuki. *J. Synth. Org. Chem. Jpn.*, 1995, 53, 940.
15. E. N. Jacobsen. In*: Catalytic Asymmetric Synthesis,* Ed. I. Ojima. VCH: New York, 1993, pp. 159.
16. R. A. Johnson and K. B. Sharpless. In*: Catalytic Asymmetric Synthesis,* Ed. I. Ojima. VCH: New York, 1993, chap. 4.1.
17. E. N. Jacobsen. In: *Comprehensive Organometallic Chemistry II,* Eds. G. Wilkinson, F. G. Stone and E. W. Abel. Pergamon: New York, 1995, Vol. 12, pp. 1098.

18. M. B. Smith and J. March. *Advanced Organic Chemistry: Reactions, mechanisms and Structure,* 5th Ed. Wiley & Sons: New York, 2001, 2000.
19. B. M. Trost (Ed). *Comprehensive Organic Synthesis*, Pergamon Press: Oxford, 1999, 7.
20. T. Katsuki. In: *Asymmetric Synthesis*, 2nd Ed., Ed. Iwao Ojima. Wiley-VCH, Inc.: New York, 2000, 287.
21. H. B. Henbest. *Chem. Soc., Spec. Publ.*, 1965, 19, 83.
22. W. H. Pirkle and P. L. Rinaldi. *J. Org. Chem.*, 1977, 42, 2080.
23. a) F. Montanari. *J. Chem. Soc., Chem. Commun.,* 1969, 135; b) R. M. Bowman, J. F. Collins and M. F. Grundon. *J. Chem. Soc., Perkin Trans,.* 1973, 1, 626.
24. K. B. Sharpless and T. R. Verhoeven. *Aldrichimica Acta*, 1979, 12, 63.
25. M. G. Finn, K. B. Sharpless. In: Asymmetric Synthesis, Ed. J. D. Morrison. Academic Press: New York, 1985, Vol. 5, chap. 8.
26. a) J. Jr. Rebek and R. McCready. *J. Am. Chem. Soc.,* 1980, 102, 5602; b) K. Nanjo, K. Suzuki and M. Sekiya. *Chem. Lett.,* 1978, 1143; c) J. Jr. Rebek, S. Wolf and A. Mossman. *J. Org. Chem.*, 1978, 43, 180.
27. R. Curci, M. Fiolentino and M. R. Seri. *J. Chem. Soc., Chem. Commun.,* 1984, 155.
28. a) Y. Tu, Z. X. Wang and Y. Shi. *J. Am. Chem. Soc.,* 1996, 118, 9806; b) Z. X. Wang, Y. Tu, M. Frohn, J. R. Zhang and Y. Shi, *J. Am. Chem. Soc.,* 1997, 119, 11224; c) Z. X. Wang, Y. Tu, M. Frohn and Y. Shi. *J. Org. Chem.*, 1997, 62, 2328.
29. a) F. A. Davis, M. E. Harakal and S. B. Awad. *J. Am. Chem. Soc.,* 1983, 105, 3123; b) F. A. Davis and S. Chattopadhyay. *Tetrahedron Lett.,* 1986, 27, 5079; c) F. A. Davis and A. C. Sheppard. *Tetrahedron*, 1989, 45, 5703.
30. F. A. Davis and R. M. Przeslawski. *Abstracts of Papers,* 201st National Meeting of the American Chemical Society. Atlanta, American Chemical Society: Washington, DC. 1991: ORGN 0105.
31. a) R. Helder, J. C. Hummelen, R. W. P. W. Laane, J. S. Wiering and H. Wynberg. *Tetrahedron Lett.,* 1976, 1831; b) H. Wynberg and B. Gerijdanus. *J. Chem. Soc., Chem. Commun.* 1978, 427; c) B. Marsman and H. Wynberg. *J. Org. Chem.*, 1979, 44, 2312.
32. a) S. Banfi, S. Colonna and S. Juliá. *Synth. Commun.*, 1983, 13, 1049; b) S. Colonna, S. Banfi and A. Papagni. *Gazz. Chim. Ital.*, 1985, 115, 81; c) S.

Colonna, A. Manfredi, R. Annunziata and N. Gaggero. *J. Org. Chem.*, 1990, 55, 5862.

33. S. Juliá, I. Masana and C.Vega. *Angew. Chem. Int. Ed. Engl.*, 1980, 19, 929.
34. a) S. Colonna, H. Molinari and S. Banfi. *Tetrahedron*, 1983, 39, 1635; b) S. Banfi, S. Colonna and H. Molinari. *Tetrahedron*, 1984, 40, 5207; c) C. B. Bezuidenhoudt, A. Swanepoel and A. N. Augustyn. *Tetrahedron Lett.,* 1987, 28, 4857.
35. S. Itsuno, M. Sakakura and K. Ito. *J. Org. Chem.*, 1990, 55, 6047.
36. K. Tani, M. Hanafusa and S. Otsuka. *Tetrahedron Lett.,* 1979, 3017.
37. H. B. Kagan, H. Mimoun, C. Mark and V. Schurig. *Angew. Chem. Int. Ed. Engl.*, 1979, 18, 485.
38. a) E. Broser, K. Krohn, K. Hintzer and V. Schurig. *Tetrahedron Lett.,* 1984, 25, 2463; b) W. Winter, C. Mark and V. Schurig. *Inorg. Chem.*, 1980, 19, 2045.
39. V. Schurig, K. Hintzer, U. Leyrer, C. Mark, P. Pitchen and H. B. Kagan. *J. Organomet. Chem.*, 1989, 370, 81.
40. R. Sinigalia, R. A. Michelin, F. Pinna and G. Struckul. *Organometallics*, 1987, 6, 728.
41. S. L. Colletti and R. L. Halterman. *Tetrahedron Lett.,* 1992, 33, 1005.
42. E. Manoury, H. Ait Haddou Mouloud and G. G. A. Balavoine. *Tetrahedron: Asymmetry,* 1993, 4, 2339.
43. T. Katsuki, K. B. Sharpless. *J. Am. Chem. Soc.,* 1980, 102, 5974.
44. a) R. A. Johnson, K. B. Sharpless. In: *Comprehensive Organic Syntheses*, Eds. B. M. Trost and I. Fleming. Pergamon: Oxford, 1991, Vol. 7, pp. 389; b) R. A. Johnson, K. B. Sharpless. In: *Catalytic Asymmetric Synthesis*, Ed. I. Ojima. VCH: New York, 1993, pp. 101; c) T. Katsuki, V. S. Martin. *Org. React.*, 1996, 48, 1; d) Y. E. Raifel'd and A. M. Vaisman. *Russ. Chem. Rev.*, 1991, 60, 123.
45. R. M. Hanson and K. B. Sharpless. *J. Org. Chem.*, 1986, 51.
46. J. T. Groves and T. E. Nemo, *J. Am. Chem. Soc.*, 1983, 105, 5786.
47. J. T. Groves, T. E. Nemo and R.S. Myers. *J. Am. Chem. Soc.*, 1979, 101, 1032.
48. a) J. T. Groves and T. E. Nemo. *J. Am. Chem. Soc.*, 1983, 105, 5786; b) J. T. Groves and R. S. Myers. *J. Am. Chem. Soc.*, 1983, 105, 5791.
49. D. Mansuy, P. Battioni, J. -P. Renaud and P. Guerin. *J. Chem. Soc. Chem. Commun.,* 1985, 155.
50. a) Y. Naruta, F. Tani and K. Maruyama, *Chem. Lett.*, 1989, 1269; b) Y. Naruta, F.

Tani, N. Ishihara and K. Maruyama. *J. Am. Chem. Soc.,* 1991, 113, 6865.

51. a) J. P. Collman, X. Zhang, R. T. Hembre and J. I. Brauman. *J. Am. Chem. Soc.*, 1990, 112, 5356; b) J. P. Collman, V. J. Lee, X. Zhang, J. A. Ibers and J. I. Brauman. *J. Am. Chem. Soc.,* 1993, 115, 3834; c) J. P. Collman, V. J. Lee, C. J. Kellen-Yuen, X. Zhang, J. A. Ibers and J. I. Brauman. *J. Am. Chem. Soc.,* 1995, 117, 692; d) J. P. Collman, Z. Wang, A. Straumanis, M. Quelquejeu. *J. Am. Chem. Soc.,* 1999, 121, 460.
52. K. Konishi, K. Oda, K. -I. Nishida, T. Aida and S. Inoue. *J. Am. Chem. Soc.,* 1992, 114, 1313.
53. S. O'Malley and T. Kodadek. *J. Am. Chem. Soc.,* 1989, 111, 9176.
54. R. L. Halterman and S. T. Jan. *J. Org. Chem.*, 1991, 56, 5253.
55. B. Meunier, E. Guilmet, M. -E. De Carvalho and R. Poilblanc. *J. Am. Chem. Soc.,* 1984, 106, 6668.
56. K. Srinivasan, P. Michaud and J. K. Kochi. *J. Am. Chem. Soc.,* 1986, 108, 2309.
57. a) E. G. Samsel, K. Srinivasan and J. K. Kochi. *J. Am. Chem. Soc.,* 1985, 107, 7606; b) T. L. Sidall, N. Miyaura, J. C. Huffmann and J. K. Kochi. *J. Chem. Soc., Chem. Commun.,* 1983, 1185.
58. K. Srinivasan, P. Michaud and J. K. Kochi. *J. Am. Chem. Soc.,* 1986, 108, 2309.
59. K. Nakajima, M. Kojima and J. Fujita. *Chem. Lett.,* 1986, 1483.
60. K. A. Jørgensen. *Chem. Rev.,* 1989, 89, 431.
61. W. Zhang. Ph D thesis: University of IIIinois, USA, 1991.
62. a) W. Zhang, J. L. Loebach, S. R. Wilson and E. N. Jacobsen. *J. Am. Chem. Soc.,* 1990, 112, 2801; b) W. Zhang and E. N. Jacobsen. *J. Org. Chem.,* 1991, 56, 2296; c) H. N. Lee, A. R. Muci and E. N. Jacobsen. *Tetrahedron Lett.,* 1991, 32, 5055; d) H. N. Lee and N. E. Jacobsen. *Tetrahedron Lett.,* 1991, 32, 6533.
63. a) H. Sasaki, R. Irie and T. Katsuki. *Synlett,* 1993, 300; b) H. Sasaki, R. Irie and T. Katsuki. *Synlett,* 1994, 356; c) H. Sasaki, R. Irie, T. Hamada, K. Suzuki and T. Katsuki. *Tetrahedron,* 1994, 50, 11827; d) H. Naoki, A. Hatayama, R. Irie, H. Sasaki and T. Katsuki. *Tetrahedron,* 1994, 50, 4311; e) T. Hamada, T. Fukuda, H. Imanishi and T. Katsuki. *Tetrahedron*, 1996, 52, 515.
64. T. Katsuki. *J. Synth. Org. Chem., Jpn.*, 1995, 53, 940.
65. T. Katsuki. *Journal of Molecular Catalysis A: Chemical,* 1996, 113, 87.
66. T. Yamada, K. Imagawa, T. Nagata and T. Mukaiyama. *Chem. Lett.,* 1992, 2231.
67. M. Palucki, G. J. McCormick and E. N. Jacobsen, *Tetrahedron Lett.,* 1995, 36,

5457.

68. P. Pietikäinen. *Tetrahedron Lett.,* 1995, 36, 319.
69. a) P. Pietikäinen. *Tetrahedron Lett.,* 1999, 40, 1001; b) P. Pietikäinen. *Tetrahedron,* 2000, 56, 417.
70. a) L. Deng and E. N. Jacobsen. *J. Org. Chem.,* 1992, 57, 4320; b) R. Irie, K. Noda, Y. Ito, N. Matsumoto and T. Katsuki. *Tetrahedron: Asymmetry*, 1991, 2, 481.
71. N. S. Finney, P. J. Pospisil, S. Chang, M. Palucki, R. G. Konsler, K. B. Hansen and E. N. Jacobsen. *Angew. Chem., Int. Ed. Engl.,* 1997, 36, 1720.
72. E. N. Jacobsen, L. Deng, Y. Furukawa and L. E. Martinez. *Tetrahedron,* 1994, 50, 4323.
73. D. L. Hughes, G. B. Smith, J. Liu, G. C. Dezeny, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven and P. J. Reider. *J. Org. Chem.,* 1997, 62, 2222.
74. Y. Yamashita and T. Katsuki. *Synlett,* 1995, 829.
75. M. Palucki, P. J. Pospisil, W. Zhang and E. N. Jacobsen. *J. Am. Chem. Soc.,* 1994, 116, 9333.
76. D. Feichtinger and D. A. Plattner. *Angew. Chem., Int. Ed. Engl.,* 1997, 36, 1718.
77. a) J. F. Larrow, E. N. Jacobsen, Y. Gao, Y. Hong, X. Nie and C. M. Zepp. *J. Org. Chem.,* 1994, 59, 1939; b) S. B. Chang, R. M. Heid and E. N. Jacobsen. *Tetrahedron Lett.,* 1994, 35, 669; c) E. N. Jacobsen, W. Zhang, L. C. Muci, J. R. Ecker and L. Deng. *J. Am. Chem. Soc.,* 1991, 113, 7063; d) S. Chang, R. M. Reid and E. N. Jacobsen. *Tetrahedron Lett.,* 1994, 35, 669; e) B. D. Brandes and E. N. Jacobsen. *Tetrahedron Lett.,* 1995, 5123.
78. a) R. Irie, K. Noda, Y. Ito, N. Matsumoto and T. Katsuki. *Tetrahedron Lett.,* 1990, 31, 7345; b) R. Irie, K. Noda, Y. Ito and T. Katsuki. *ibid.*, 1991, 32, 1055; c) N. Hosoya, R. Irie and T. Katsuki. *Synlett.*, 1993, 261; d) N. Hosoya, A. Hatakeyama, K. Yanai, H. Fujii, R. Irie and T. Katsuki. *Synlett.*, 1993, 641; e) N. Hosoya, R. Irie, Y. Ito and T. Katsuki. *Synlett.*, 1991, 691; f) T. Hamada, R. Irie and T. Katsuki. *Synlett.*, 1994, 479.
79. a) N. Hosoya, A. Hatakeyama, R. Irie, H. Sasaki and T. Katsuki. *Tetrahedron,* 1994, 50, 4311; b) T. Fukuda, R. Irie and T. Katsuki. *Synlett.*, 1995, 197; c) D. Mikame, T. Hamada, R. Irie and T. Katsuki. *Synlett.*, 1995, 827.
80. Y. N. Ito and T. Katsuki. *Tetrahedron Lett.,* 1998, 39, 4325.
81. Y. N. Ito and T. Katsuki. *Bull. Chem. Soc. Jpn.,* 1999, 72, 603.

82. T. Katsuki. In*: Catalytic Asymmetric Synthesis,* 2nd Ed., Ed. I. Ojima. Wiley-VCH: New York, 2000, pp. 287.

83. a) T. Hashihayata, Y. N. Ito and T. Katsuki. *Synlett.*, 1996, 1079; b) T. Hashihayata, Y. N. Ito and T. Katsuki. *Tetrahedron,* 1997, 53, 9541; c) K. Miura and T. Katsuki. *Synlett.*, 1999, 783.

84. a) H. Fu, G. C. Look, W. Zhang, E. N. Jacobsen and C-H. Wong. *J. Org. Chem.,* 1991, 56, 6497; b) W. Zhang, N. H. Lee and E. N. Jacobsen. *J. Am. Chem. Soc.,* 1994, 116, 425; c) S. Chang, J. M. Galvin and E. N. Jacobsen. *J. Am. Chem. Soc.,* 1994, 116, 6937.

85. P.-O. Norrby, C. Linde and B. Åkermark. *J. Am. Chem. Soc.,* 1995, 117, 11035.

86. a) H. R. Hartley. *Supported Metal Catalysis*, Reidel: Dordrecht, 1985; b) J. H. Clark, A. P. Kybett and D. J. Macquarie. *Supported Reagents: Preparation, Analysis and Applications*, VCH: Weinheim, 1992.

87. P. K. Dhal, B. B. De and S. Sivaram. *Journal of Molecular Catalysis A: Chemical*, 2001, 177, 71.

88. a) B. B. De, B. B. Lohray, S. Sivaram and P. K. Dhal. *Tetrahedron: Asymmetry,* 1995, 6, 2105; b) B. B. De, B. B. Lohray, S. Sivaram and P. K. Dhal. *J. Polym. Sci. A: Polym. Chem.,* 1997, 35, 1809.

89. a) F. Minutolo, D. Pini and P. Salvadori. *Tetrahedron Lett.,* 1996, 37, 3375; b) F. Minutolo, D. Pini, A. Petri and P. Salvadori. *Tetrahedron: Asymmetry,* 1996, 7, 2293.

90. B. Clapham, T. S. Reger and K. D. Janda. *Tetrahedron,* 2001, 57, 4637.

91. a) L. Canali, E. Cowan, H. Deleuze, C. L. Gibson and D. C. Sherrington. *Chem. Commun.,* 1998, 2561; b) L. Canali, D. C. Sherrington, H. Deleuze. *React. Funct. Polym.,* 1999, 40, 155; c) L. Canali, E. Cowan, H. Deleuze, C. L. Gibson and D. C. Sherrington. *J. Chem. Soc., Perkin Trans.,* 2000, 1, 2055.

92. a) M. D. Angelino and P. E. Laibinis. *Macromolecules,* 1998, 31, 7581; b) M. D. Angelino and P. E. Laibinis. *J. Polym. Sci. A: Polym. Chem.,* 1999, 37, 3888.

93. a) T. S. Reger and K. D. Janda. *J. Am. Chem. Soc.,* 2000, 122, 6929; b) P. H. Toy and K. D. Janda. *Tetrahedron Lett.,* 1999, 40, 6329.

94. C. E. Song, E. J. Roh, B. M. Yu, D. Y. Chi and S. C. Kim and K. -J. Lee. *Chem. Commun.,* 2000, 615.

95. K. Smith and C. H. Liu. *Chem. Commun.,* 2002,886.

96. G. Pozzi, M. Cavazzini, F. Cinato, F. Montanari and S. Quici. *Eur. J. Org. Chem.,*

1999, 1947.

97. a) I. F. J. Vankelecom, D. Tas, R. F. Parton, V. V. de Vyver and P. A. Jacobs. *Angew. Chem. Int. Ed. Engl.*, 1996, 35, 1346; b) K. B. M. Janssen, I. Laquiere, W. Dehaen, R. F. Parton, I. F. J. Vankelecom and P. A. Jacobs. *Tetrahedron: Asymmetry,* 1997, 8, 3481.
98. M. J. Sabater, A. Corma, A. Domenech, V. Fornes and H. Garcia. *J. Chem. Soc., Chem. Comm.,* 1997, 1285.
99. S. B. Ogunwumi and T. Bein. *J. Chem. Soc., Chem. Comm.,* 1997, 901.
100. D. Pini, A. Mandoli, S. Orlandi and P. Salvadori. *Tetrahedron: Asymmetry,* 1999, 10, 3883.
101. G. -J, Kim and J. -H, Shin. *Tetrahedron Lett.,* 1999, 40, 6827.
102. G. -J. Kim and S. -H. Kim. *Catal. Lett.*, 1999, 57, 139.

CHAPTER TWO

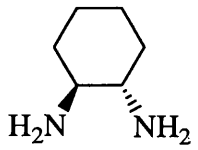
THE RESEARCH PROJECT

2.1 Introduction

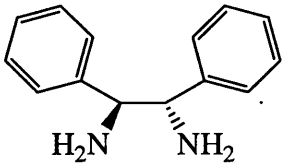
As described in *Chapter 1*, optically active epoxides serve as desirable synthetic building blocks in synthesis of various chiral compounds. For this reason, development of a general methodology for asymmetric synthesis of epoxides is one of the important objectives in synthetic organic chemistry. Among many catalytic systems developed, chiral (salen)Mn(III) complexes have been found to be effective catalysts for asymmetric epoxidation of a wide variety of substrates, especially for *cis* cyclic alkenes. During the past decades, many chiral salen ligands have been synthesized and used as their Mn(III) complexes in asymmetric alkene epoxidations.

The homogeneous Jacobsen-type and Katsuki-type chiral (salen)Mn(III) complexes afforded high level of enantioselectivities in epoxidation of *cis* cyclic unfunctionalized alkenes. However, the catalysts were not always easy to remove from the product and were sometimes found to be unstable under the epoxidation conditions, and therefore had to be used in a carefully controlled experimental protocol and could not be recycled.[1] Another drawback of the homogeneous catalysts is the formation of inactive μ-oxo-Mn(IV) dimer intermediates that limits the possibility for catalyst recycling.[2] Not surprisingly, there has been a number of attempts to develop the heterogeneous versions of chiral (salen)Mn(III) complexes, especially Jacobsen-type catalysts which have relatively simple structures, to facilitate recycling of the catalysts and isolation of the product. However, only limited success has been achieved so far. Some of the important developments on heterogenisation of chiral (salen)Mn(III) complexes are reported in *Chapter 1*.

Optically pure six-membered-ring cyclic diamines, such as 1,2-cyclohexanediamine (**2.1**), and open-chain diamines, such as 1,2-diphenylethylenediamine (**2.2**), have been widely used for construction of salen complexes (Section 1.32 in *Chapter 1*). However, less attention has been paid to the use of optically pure five-membered-ring diamines for such purpose. As a result, the chemistry of salen ligands and the corresponding Mn(III) complexes that bear a chiral five-membered-ring diimine bridge has not been fully explored.

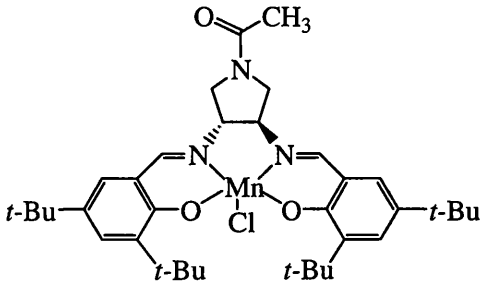


2.1

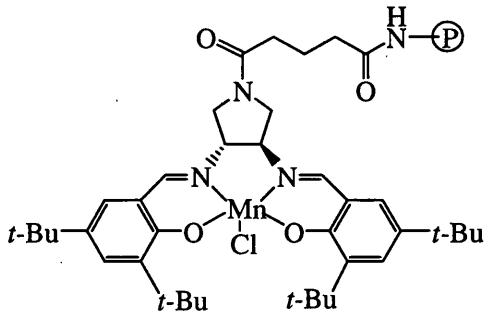


2.2

Song *et al* have reported the synthesis of a (pyrrolidine salen)Mn(III) complex **2.3** and a polymer-bound (pyrrolidine salen)Mn(III) complex **2.4.** In both cases, optically pure five-membered-ring diamine (diaminopyrrolidine and *N*-substituted diaminopyrrolidine) was used as the chiral diamine to construct the salen ligand.[3] Both catalysts showed high enantioselectivities in epoxidation of several unfunctionalized alkenes, e.g. high enantioselectivities were achieved in epoxidation of 2,2-dimethylchromene using catalyst **2.3** (95% ee) and catalyst **2.4** (92% ee). The results suggested that the optically pure diaminopyrrolidine derivatives were appropriate components for construction of salen ligands and the corresponding (salen)Mn(III) complexes.



2.3

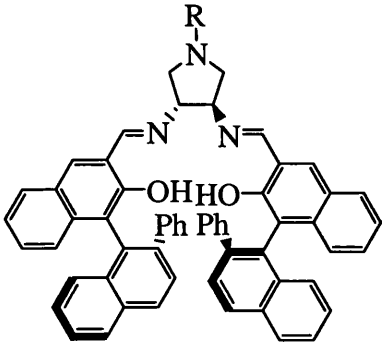


2.4

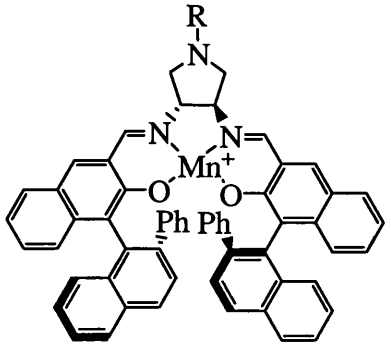
When 1,2-cyclohexanediamine (**2.1**) or 1,2-diphenylethylenediamine (**2.2**) was used to construct the salen ligands, there would be no functional group in the chiral diimine moiety on the resulting salen ligands. As a result, immobilization of a chiral (salen)Mn(III) complex onto a functional solid support, especially by means of covalent linking to a polymer support, has to be fulfilled by attachment *via* the benzene ring of the substituted salicylaldehyde moiety. This meant that synthesis of substituted salicylaldehyde derivatives, which have a functional group (a handle) on the benzene ring, had to be carried out (Section 1.35 in *Chapter 1*). In order to avoid cross-linking, it would also be necessary to construct a salen ligand from two different

salicylaldehydes, only one of which possessed the linker functionality. The supported catalysts designed by this or similar methodology have achieved only limited success so far.[1a,2a,4] An alternative strategy for attachment of a homogeneous catalyst to a solid support is to avoid attachment *via* the benzene rings. Synthesis of enantiomerically pure diamines with a functional handle convenient for attachment to a resin or other supports would be an attractive option. As described above, Song utilized this methodology to prepare a polymer-supported (pyrrolidine salen)Mn(III) complex **2.4**, in which the (salen)Mn(III)moiety was linked to *TentaGel* resin through the nitrogen atom of the pyrrolidine ring.[3]

We decided to synthesize a new type of chiral salen ligands **2.5**, which would incorporate several significant features: a) the presence of a chiral five-membered-ring pyrrolidine type diimine moiety; b) the presence of a secondary amino functional group in salen ligand **2.5a**, which could be used as a handle for attachment to a solid support if desired; b) incorporation of optically pure binaphthalene salicylaldehyde derivative having axial chirality, which have been proven to be better components than simple substituted salicylaldehyde derivatives for construction of salen ligands. Salen ligands **2.5** would then be converted into the corresponding Mn(III) complexes **2.6**, which would be used as the catalysts to explore their catalytic performances in asymmetric epoxidation of unfunctionalized alkenes.



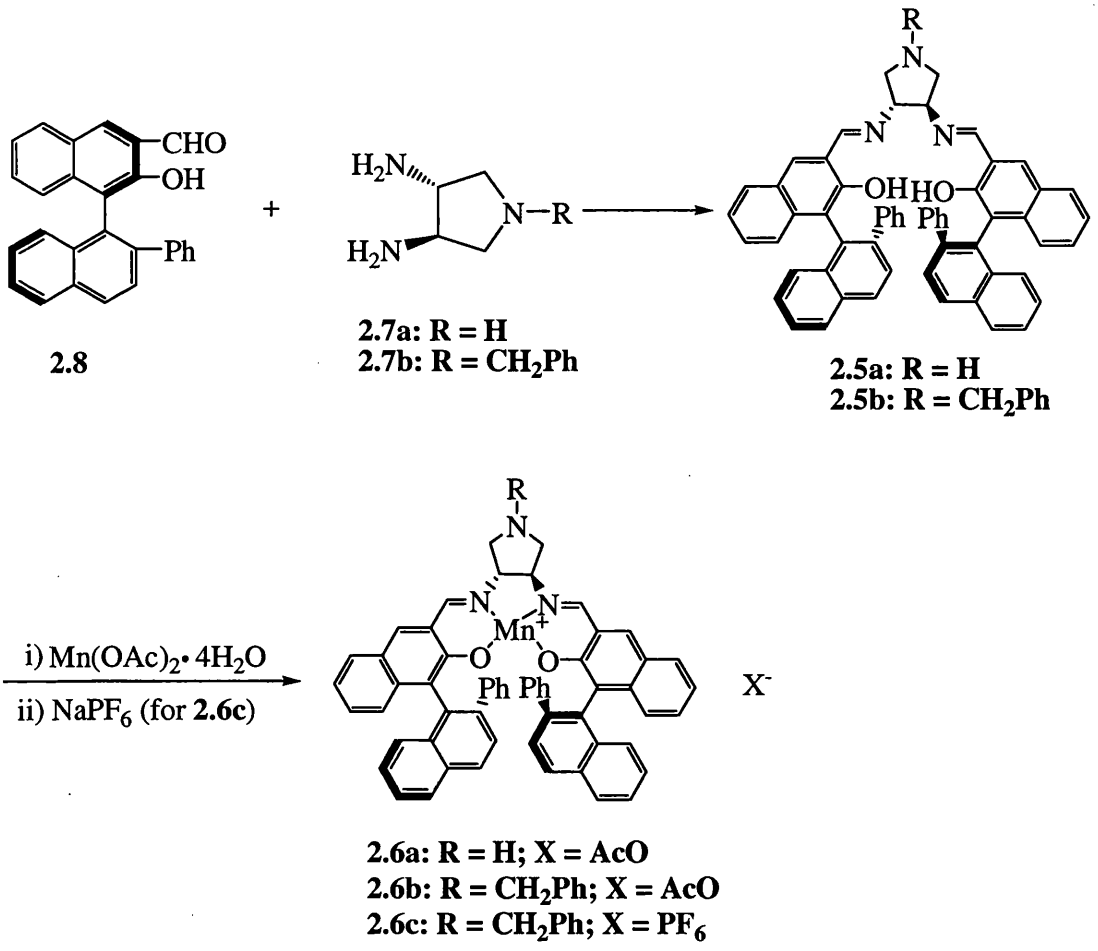
2.5a: R = H
2.5b: R = CH_2Ph



2.6a: R = H; X = AcO
2.6b: R = CH_2Ph; X = AcO
2.6c: R = CH_2Ph; X = PF_6

2.2 Approach to the synthesis

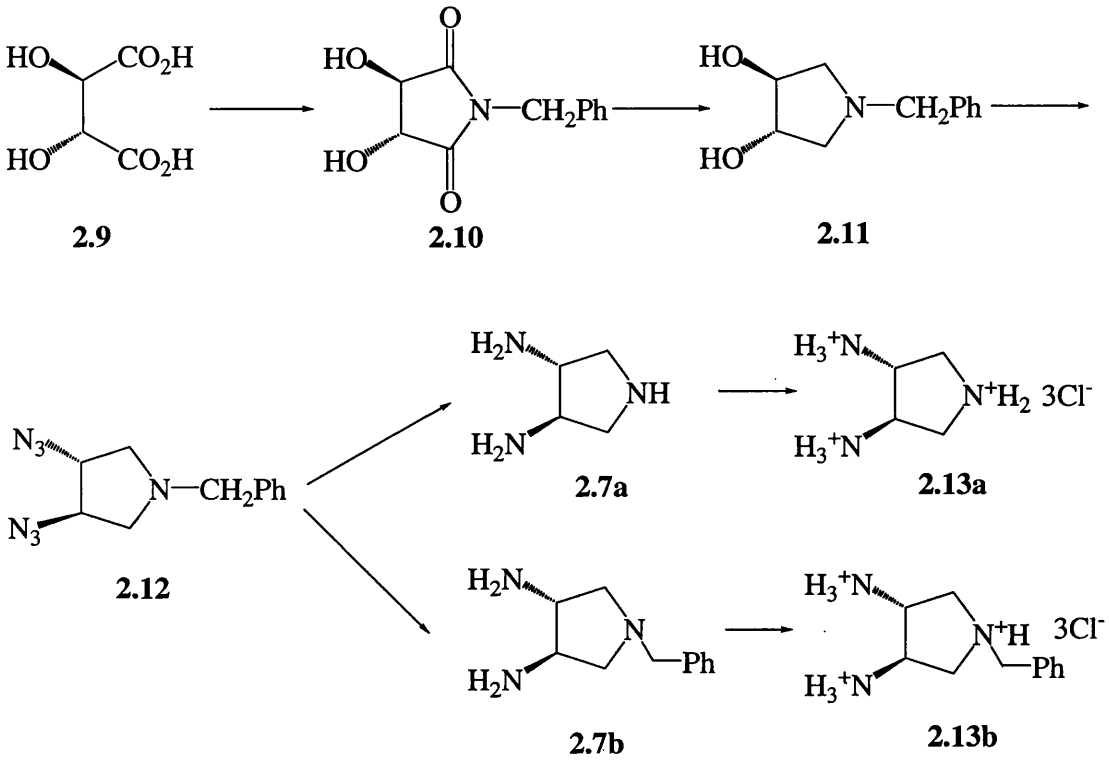
Salen ligands **2.5** would be synthesized by condensation of *trans*-(3R,4R)-diaminopyrrolidine (**2.7a**) or *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine (**2.7b**) with two equivalents of (R)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthyl (**2.8**) (Scheme 2.1). The corresponding (salen)Mn(III)OAc complexes would be prepared by reaction of the salen ligands with one or two equivalents of $Mn(OAc)_2{\cdot}4H_2O$ in air. (Salen)Mn(III)PF_6 complex **2.6c** would be prepared by reaction of (salen)Mn(III)OAc complex **2.6b** with $NaPF_6$ (Scheme 2.1)



Scheme 2.1

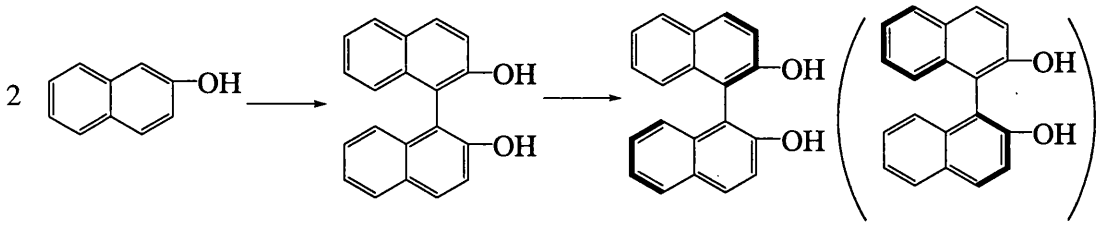
The proposed synthetic route to optically pure *trans*-(3R,4R)-diaminopyrrolidine(**2.7a**) and *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine (**2.7b**) is shown in Scheme 2.2. (2R,3R)-(+)-tartaric acid (**2.9**) would be used as the starting material. Since most polyamines are unstable and

difficult to handle and store, the target compounds would be transformed into their trihydrochloride salt **2.13**. These syntheses are to be reported in *Chapter 3* of this thesis.

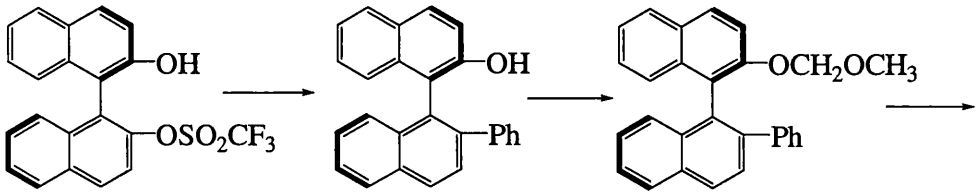


Scheme 2.2

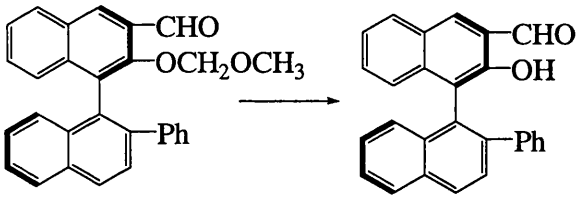
The proposed synthetic route to optically pure (R)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthyl (**2.8**) is shown in Scheme 2.3. 2-Naphthol (**2.14**) would be used as the starting material. The syntheses are to be reported in *Chapter 4* of this thesis.



2.14 **Rac-2.15** **(R)-2.15** **(S)-2.15**



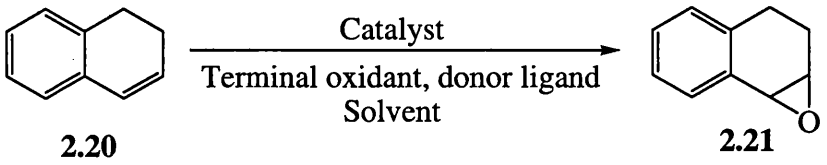
(R)-2.16 **(R)-2.17** **(R)-2.18**



(R)-2.19 **2.8**

Scheme 2.3

Upon successful preparation of these complexes, their catalytic performances in asymmetric epoxidation of unfunctionalized alkenes would be tested using 1,2-dihydronaphthalene (**2.20**) as the substrate (Scheme 2.4).



2.20 **2.21**

Scheme 2.4

2.3 References for *Chapter 2*

1. a) D. C. Sherrington. *Catalysis Today*, 2000, 57, 87; b) W. Zhang and E. N. Jacobsen. *J. Org. Chem.,* 1991, 56, 2296.
2. a) P. K. Dhal, B. B. De and S. Sivaram. *Journal of Molecular Catalysis A: Chemical*, 2001, 177, 71; b) K. Srinivasan, P. Michaud and J. K. Kochi. *J. Am. Chem. Soc.,* 1986, 108, 2309.
3. C. E. Song, E. J. Roh, B. M. Yu, D. Y. Chi and S. C. Kim and K. -J. Lee. *Chem. Commun.,* 2000, 615.
4. B. Clapham, T. S. Reger and K. D. Janda. *Tetrahedron,* 2001, 57, 4637.

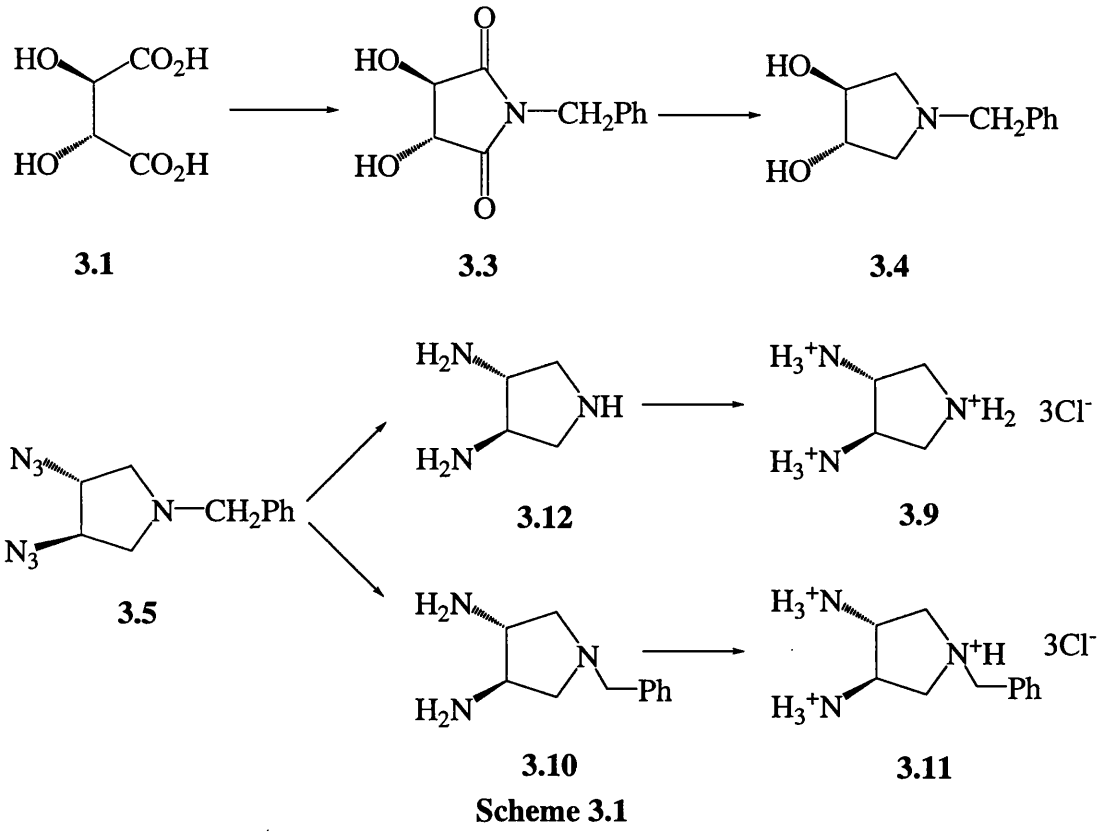
CHAPTER THREE

SYNTHESIS OF *TRANS*-(3R,4R)-DIAMINOPYRROLIDINE TRIHYDROCHLORIDE SALT AND *TRANS*-(3R,4R)-1-BENZYL-3,4-DIAMINOPYRROLIDINE TRIHYDROCHLORIDE SALT

3.1 Introduction

As described in *Chapter 2*, optically pure *trans*-(3R,4R)-diaminopyrrolidine (named as **2.7a** in *Chapter 2*) and *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine (named as **2.7b** in *Chapter 2*) would be used as the chiral diamine for construction of the target salen ligands and the corresponding (salen)Mn(III) complexes.

These two chiral vicinal diamines are not commercially available. The established synthetic routes involve a multi-step synthesis using optically pure (2R,3R)-(+)-tartaric acid as the starting material (Scheme 3.1).



Scheme 3.1

We decided to adopt such synthetic routes to prepare the target compounds. Compound **3.3** would be synthesized by treatment of (2R,3R)-(+)-tartaric acid (**3.1**) with benzylamine. Compound **3.3** would be then reduced to give the corresponding diol **3.4**. Diol **3.4** would be converted into the corresponding diazide **3.5**, which would be reduced to give the target compound **3.10** or **3.12**. Since most polyamines are

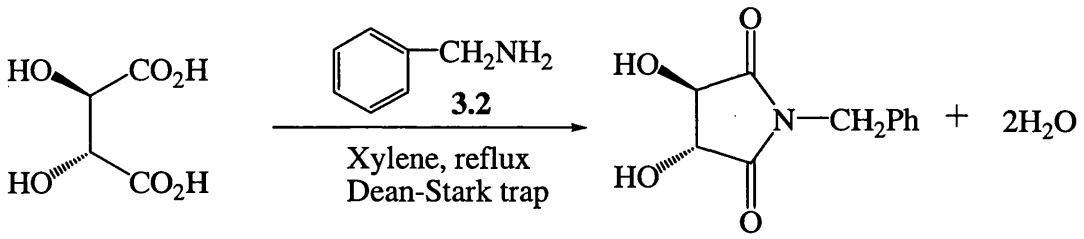
unstable and difficult to handle and store, the target compounds would therefore be transformed to their trihydrochloride salt **3.11** and **3.9**.

Although some of the transformations have been reported by several research groups,[1,12a,26] the detailed experimental procedures were sometimes not reported. We decided to adopt such synthetic routes and to work out the optimal reaction conditions for these transformations. The results are reported in this chapter.

3.2 Discussion and results

3.2.1 Synthesis of (3R,4R)-1-benzyl-3,4-dihydroxy-2,5-pyrrolidinedione (3.3)

Compound **3.3** has been synthesized by treatment of natural (2R,3R)-(+)-tartaric acid (**3.1**) with benzylamine (**3.2**) (Scheme 3.2).[1-3]



3.1 **3.3**

Scheme 3.2

Xylene, which can form an azeotrope with water generated within the reaction system, was used as solvent. A Dean-Stark trap was used to remove the azeotrope from the reaction system continuously to drive the equilibrium to the right, and it was also used as a means to monitor the progress of the reaction by recording the volume of water produced or by waiting until the characteristically milky heterogeneous azeotrope was no longer produced.

In the present work, two experiments were conducted. In an attempt to prevent the formation of diamide, an equimolar amount of benzylamine with respect to tartaric acid was employed. The reaction mixture was heated under reflux until no more

azeotrope was produced. The product was isolated according to the reported procedure and recrystallised from ethanol. The reaction conditions and the results are listed in Table 3.1.

Table 3.1 Synthesis of (3R,4R)-1-benzyl-3,4-dihydroxy-2,5-pyrrolidinedione (3.3) according to Scheme 3.2

Entry	Quantities (mol)		Temp.	Yield (%) [a]
	Tartaric acid	Benzylamine		
1	0.3	0.3	reflux	61
2	1	1	reflux	71

a: Isolated yield after recrystallization from ethanol.

The first experiment was carried out on a small scale. It was reasonably successful (Entry 1). Therefore, the reaction was next carried out on a larger scale in order to produce enough material to continue with the synthesis. The reaction was successful; the product was obtained in 71% yield after recrystallization from ethanol (Entry 2). The detailed experimental procedure and characterization of the product are reported in the *Experimental Section* of this chapter.

Having successfully synthesized compound **3.3** in large quantity, the next step would be to reduce it to the diol **3.4**.

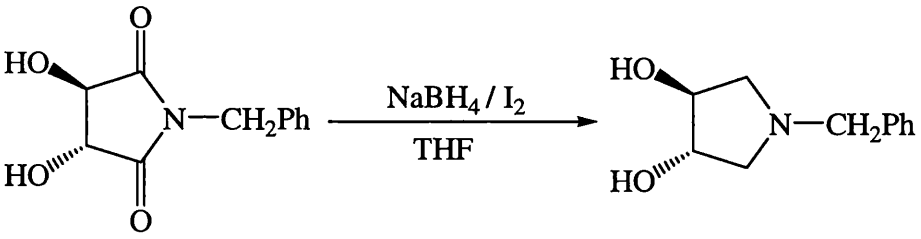
3.2.2 Synthesis of (3S,4S)-1-benzyl-3,4-dihydroxypyrrolidine (3.4) from compound 3.3

Reduction of carboxylic acid amides to the corresponding amines has been examined with a variety of complex and simple metal hydrides, such as $LiAlH_4$, $LiAlH(OMe)_3$, and AlH_3. However, diborane, borane-tetrahydrofuran (BH_3·THF) and borane-dimethyl sulfide (H_3B·SMe_2, BMS) have proven to be the reagents of choice over any complex metal hydride. The advantages include: a) the reaction is usually rapid, quantitative, and clean; b) the reaction can tolerate many functional groups such as nitro, halogen, ester, sulfone, carbamate, etc.[4] Compound **3.3** has been reduced to

the corresponding diol **3.4** [(3S,4S)-1-benzyl-3,4-dihydroxypyrrolidine] by using different reduction systems, which include $LiAlH_4$,[5] $NaBH_4$ / $BF_3{\cdot}Et_2O$,[2,6] and $NaBH_4$ / I_2.[1,7] Among these methods, the $NaBH_4$ / I_2 system has been reported to be effective in the reduction of amides, nitriles, carboxylic esters and acids.[7] Therefore, this reduction system was adopted for reduction of compound **3.3** to the target diol **3.4**.

3.2.2.1 Reduction of compound 3.3 using the $NaBH_4$ / I_2 system

Borane-tetrahydrofuran complex ($BH_3{\cdot}THF$) has been suggested to be the reductant which was generated *in situ* from the reaction of $NaBH_4$ with I_2 (Scheme 3.4, eq. 1).



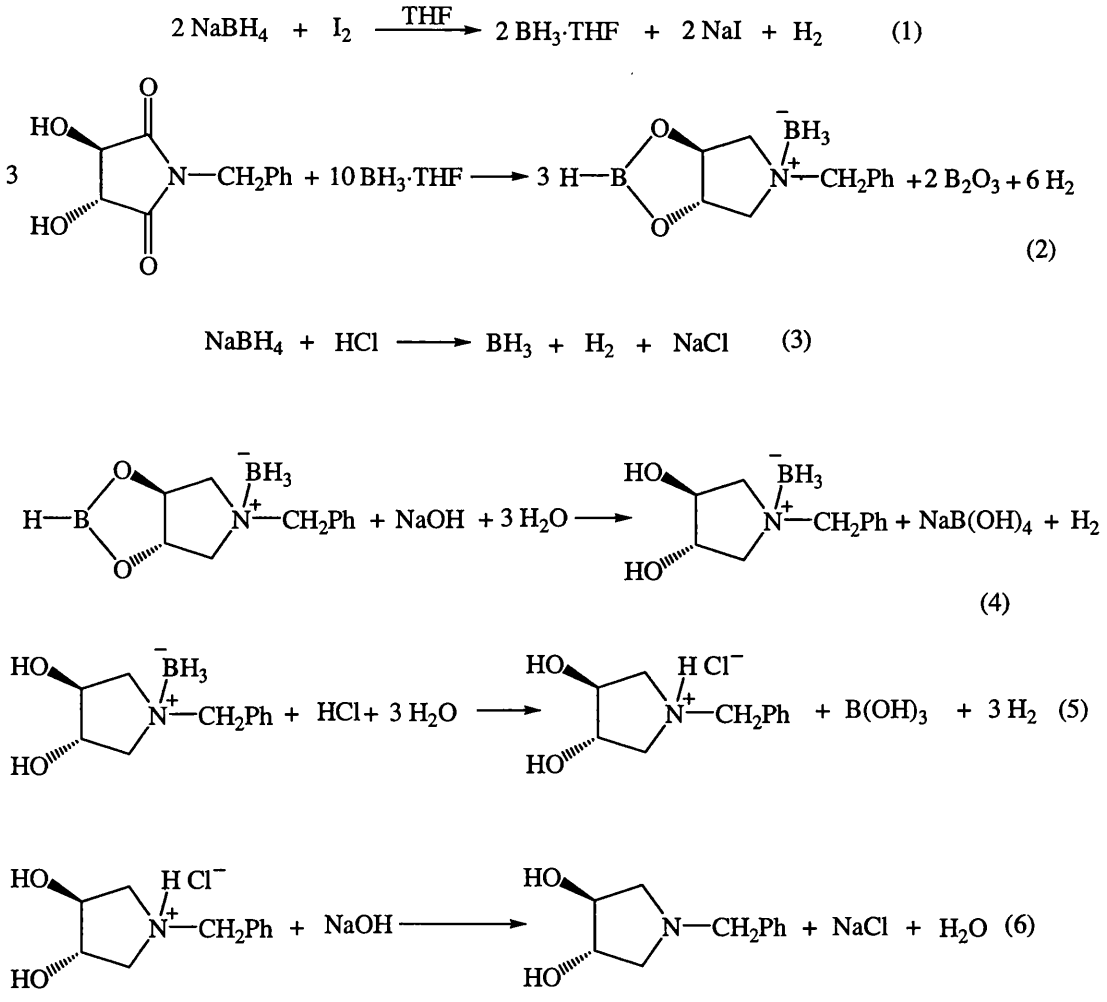
3.3 **3.4**

Scheme 3.3

In the present work, four experiments were carried out using this reduction system (Scheme 3.3). In all cases, the amount of 'BH_3' complex, which was generated *in situ*, was more than required by the stoichiometry. $NaBH_4$ was also used in excess (the molar ratio of $NaBH_4$ to compound **3.3** was 5.4), since it is known that 'BH_3' complexes also react with iodine to give $\rangle B-I$ species, which are known to cleave ethers.[8] The solution of I_2 in THF was added dropwise to $NaBH_4$ in THF at 0 °C in order to avoid possible cleavage of THF. After the addition, the reaction mixture was heated under reflux for the reduction to take place.

The first experiment was carried out following the literature procedure[1] on a 20 mmol scale of compound **3.3**. The solution of I_2 (the molar ratio to compound **3.3** was 2.4) in THF was added dropwise to other reactants at 0 °C over 2.75 h and the reaction mixture was heated under reflux for 6 h. The reaction was worked up and the

product was isolated following the reported procedure. However, the product **3.4** was obtained in a low yield (11%) after recrystallization from EtOAc (lit.[1] 70% isolated yield). The low yield might be attributed to the incomplete reaction and material losses during the work-up procedure. Actually, the work-up procedure was very complicated, which included: decomposition of excess $NaBH_4$ with a 3M HCl solution; neutralization of the reaction mixture with a 3M NaOH solution; decomposition of the borane-amine complex with conc. HCl; removal of the resulting borate compound by distillation off the azeotrope formed between methylborate and methanol; and liberation of the free product with a NaOH solution. The whole procedure, we assumed, could be summarized as in the following equations (Scheme 3.4):



Scheme 3.4

Since material losses during the work-up procedure might account for the low yield in the first experiment, some modifications were therefore made to try to minimize these possibilities during the second experiment. The second experiment was carried out on a smaller scale (10 mmol compound **3.3**) and the reaction mixture was heated under reflux for 6 h, as that used in the first experiment. However, the quantity of 3 M HCl solution, which was used to decompose the excess $NaBH_4$, was adjusted. Also, the quantity of 3 M NaOH solution, which was used to neutralize the reaction mixture following the addition of the 3 M HCl solution, was adjusted to make sure that the product mixture maintained in a neutral state (the pH of the mixture was about 7 - 8) rather than a strongly basic condition, as occurred in the first experiment (the pH was 12). Furthermore, solid K_2CO_3, which was used in the literature to saturate the product mixture after the free product was liberated, was not employed. These modifications had the desirable effect – the yield of the product was increased to 58% after recrystallization from EtOAc.

As described above, in addition to material losses during the work-up procedure, the incompletion of the reaction was also considered to account for the low yield. In the third experiment, which was carried out on a 25 mmol scale of compound **3.3**, tlc was used to monitor the progress of the reaction. Starting material **3.3** was found to be present after being refluxed for 10 h (the reaction time used in the literature[1] was 6 h). In an attempt to drive the reaction to completion, commercial BH_3·THF complex (18 mmol) was added to the reaction mixture. After being refluxed for another 4 h, a second batch commercial BH_3·THF complex (32 mmol) was added. However, the starting material **3.3** was found to be present even after the reaction mixture was heated under reflux for a further 3 h and stirred at r.t. overnight (14 h). The results showed that the reaction somehow could not be driven to completion. The product was isolated in the same way as that used in the second experiment and recrystallized from EtOAc. The low yield (12%) was due to material losses during a hot filtration procedure, which was employed to remove charcoal in a decolourization procedure.

In order to produce enough product to continue with the future synthesis, a fourth experiment was carried out on a 30 mmol scale of compound **3.3** under the optimized conditions. The reaction was reasonably successful; the product was

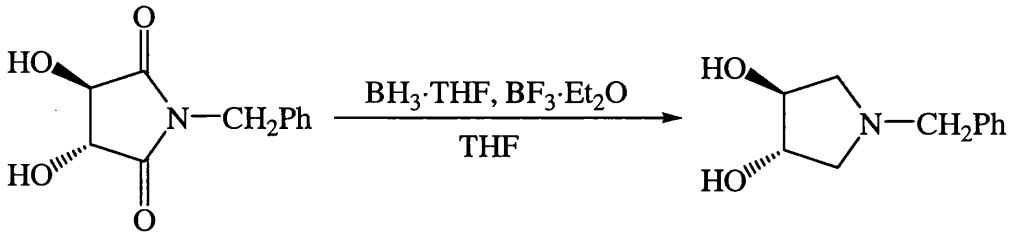
obtained in a 64% yield after recrystallization from EtOAc. The detailed experimental procedure and characterization of the product are reported in the *Experimental Section* of this chapter.

This reduction system possesses several drawbacks which limit its use: a) the relatively small scale of the reaction. The reaction cannot easily be scaled up due to the large amount of solvent used; b) complicated and tedious work-up procedure, especially the procedure used to remove the borate compounds by treating the product mixture with 12 M HCl in a methanolic solution and distilling off the azeotrope formed by methylborate and methanol (1:1).

Since the real reductant was thought to be BH_3·THF complex in the $NaBH_4$ / I_2 reduction system, and, as described above, BH_3·THF complex has been extensively used for reduction of amides into the corresponding amines, the commercial BH_3·THF complex should be expected to effect the reduction of compound **3.3** to compound **3.4**. However, to our knowledge, there is no report to date regarding the reduction of compound **3.3** using BH_3·THF complex. It was therefore considered worthwhile to explore the feasibility and efficiency of reduction of compound **3.3** using BH_3·THF complex directly.

3.2.2.2 Reduction of compound 3.3 using BH_3·THF complex

In the present work, two experiments were conducted using this methodology (Scheme 3.5). In both cases, BH_3·THF complex was used in excess (the molar ratio of BH_3·THF complex to compound **3.3** was 8.7) and added slowly to a solution of compound **3.3** in dry THF at 0 °C. After addition, the reaction mixture was heated under reflux for the reduction to take place. However, different work-up procedure was used for these two experiments. The reaction conditions and the results are listed in Table 3.2.



3.3 **3.4**

Scheme 3.5

Table 3.2 Reduction of compound 3.3 using BH_3·THF complex according to Scheme 3.5

Entry	Quantities (mmol)			Temp. (Reaction time)	Yield (%)[a]
	3.3	BH_3·THF	BF_3·Et_2O		
1	5	43.6	20	0 °C (53 min) / reflux (18 h)	4
2[b]	30	261	120	0 °C (3.3 h) / reflux (36 h)	51

a: Isolated yield after recrystallization from EtOAc.
b. A different work-up procedure was employed.

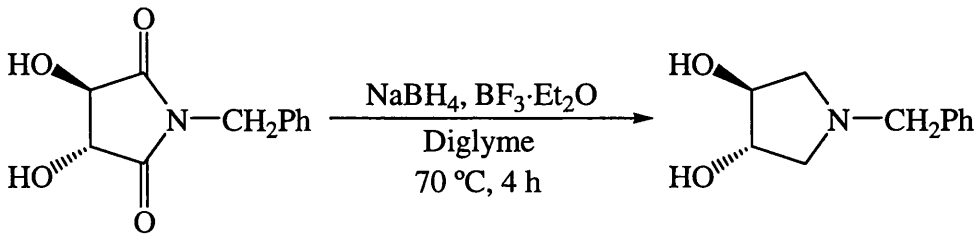
The first experiment was carried out on a small scale (Entry 1). The reaction was found to be complete after being refluxed for 18 h. The solvent was removed and DCM was used as the organic solvent in the following manipulation. The work-up procedure was similar to that used in the above-mentioned $NaBH_4$ / I_2 system. However, the product was obtained in a very low yield (4%). The low yield might be due to material losses during the work-up procedure, especially during separation of the hydrochloride salt of the product between the organic (DCM) and the aqueous phases even though efforts had been made to recover the material from the aqueous phases. It seemed that a water-free work-up procedure might work better. The detailed experimental procedure (denoted as ***Method 1***) and is reported in the *Experimental Section* of this chapter.

Bearing this principle in mind, some modifications were made in the second experiment, which included: a) using a methanolic HCl solution to remove the excess BH_3·THF complex and to decompose the amine-boron trifluoride complex instead of concentrated HCl; b) using a methanolic KOH solution to liberate the product instead of aqueous NaOH solution. The reaction was found to be complete after being heated

for 36 h. And, the product was obtained in 51% yield after recrystallization from EtOAc (Entry 2). The detailed experimental procedure (denoted as ***Method 2***) is reported in the *Experimental Section* of this chapter.

In contrast to the $NaBH_4$ / I_2 reduction system, in which BH_3·THF complex was generated *in situ* in the presence of reactive compounds, the current system had the advantage that higher purity BH_3·THF was used, which, at least in principle, would exclude the possibilities of formation of by-product(s) resulting from the reaction of starting material with alkali metal borohydride and would result in fewer side reactions and a higher purity product. Although the reaction could be driven to completion and a moderate yield had been achieved, the reduction system still had several drawbacks, such as relatively low yield and scale limitation. Therefore, another reduction system, in which $NaBH_4$ / BF_3·Et_2O was used, was also explored.

3.2.2.3 Reduction of compound 3.3 using $NaBH_4$ / BF_3·Et_2O / diglyme system



3.3 **3.4**

Scheme 3.6

The $NaBH_4$ / BF_3·Et_2O system has also been used to reduce amides into the corresponding amines.[2,6] Diborane was thought to be generated *in situ* by reaction of $NaBH_4$ with BF_3·Et_2O (Scheme 3.7).[9]

$$3\ NaBH_4 + 4\ Et_2O{\cdot}BF_3 \xrightarrow{\text{Diglyme}} 2\ B_2H_6 + 3\ NaBF_4 + 4\ Et_2O$$

Scheme 3.7

The reaction was carried out on a lager scale (300 mmol of compound **3.3**) according to a literature procedure (Scheme 3.6).[2] The molar ratios of $NaBH_4$ and $BF_3{\cdot}Et_2O$ to compound **3.3** were 2.6 and 3.9, respectively. The reaction mixture was heated at 70 °C for 4 h and worked up according to the reported procedure. Using diglyme as solvent instead of THF has several advantages: a) diglyme is a particularly useful solvent for reactions involving the *in situ* generation of diborane;[10] b) using diglyme enables the reaction to be carried out at higher temperature, and to prevent material losses during phase separation. At the final stage of the work-up procedure, a liquid-liquid extractor was used to extract the product from the aqueous phase instead of using a simple separatory funnel. This increased the efficiency of the extraction and prevented material losses. The reaction worked well; the product was obtained in 71% isolated yield. This method has several advantages over the above-mentioned two methods: a) higher yield; b) applicability to a larger reaction scale (It was possible to obtain 41 g of product **3.4** in one experiment); and c) a simpler work-up procedure. The detailed experimental procedure is reported in the *Experimental Section* of this chapter.

In conclusion, the reduction of compound **3.3** to compound **3.4** with 'borane' was carried out using three reduction systems. The most simple, practical and efficient one was found to be the system using $NaBH_4$ / $BF_3{\cdot}Et_2O$ / diglyme. This is consistent with the observation that, among the four different 'borane' reducing agents, the most reactive one is the *in situ* generated reagent (actually a number of reagents are possible depending upon the solvent and the order of addition and whether $NaBH_4$ or BF_3 is used in excess).

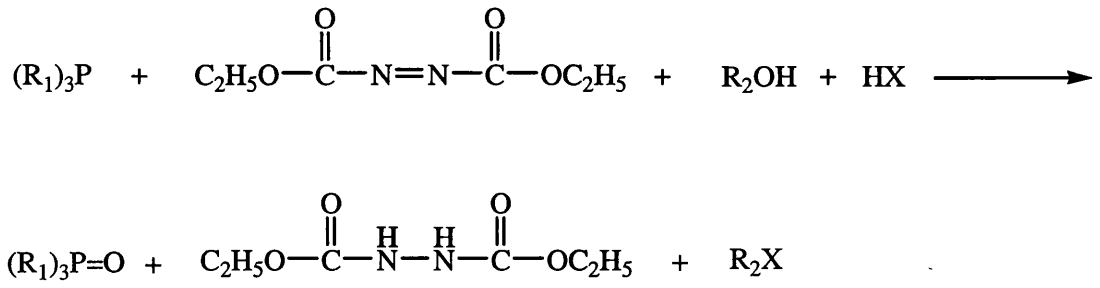
Having successfully reduced compound **3.3** to compound **3.4**, the next step would be conversion of compound **3.4** into the corresponding diazide **3.5**.

3.2.3 Synthesis of (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (3.5) from compound 3.4

In general, there are two main methodologies to replace hydroxyl groups (-OH) by azido groups ($-N_3$). One methodology involves a direct conversion using the Mitsunobu reaction.[1,6a,6c,11] The other involves conversion of the hydroxyl group (-OH) to another functional group such as a mesyl, tosyl or triflyl group first, then displacement of the intermediate functional group by the azido group.[12] Of these two methodologies, the one which involves the use of the Mitsunobu reaction appeared to be attractive since it is a straightforward, one-step reaction. Therefore, this methodology was tried first.

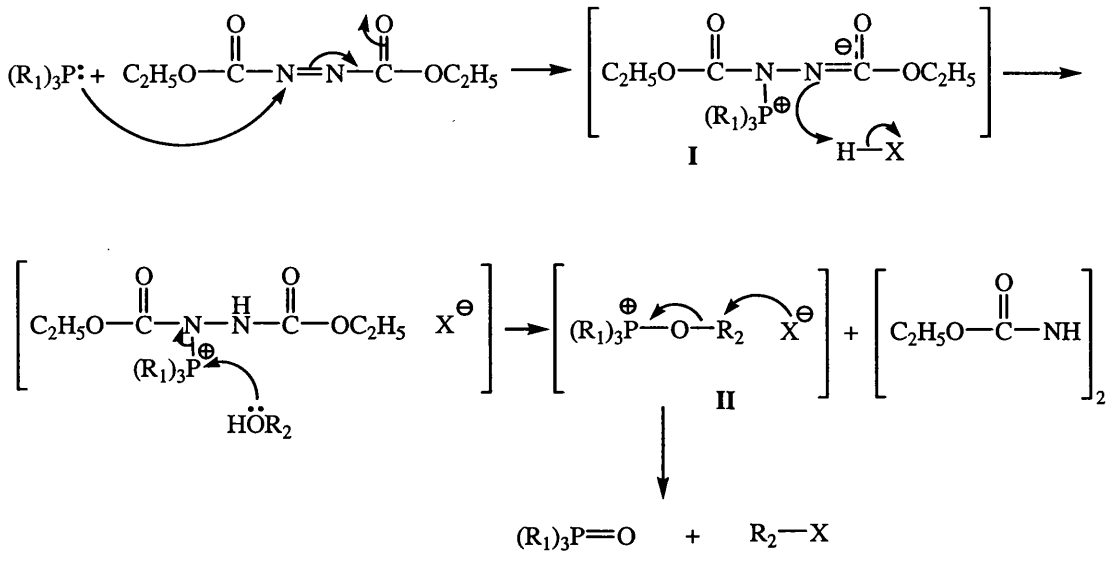
3.2.3.1 Attempt to synthesize (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (3.5) using the Mitsunobu reaction

The Mitsunobu reaction involves the intermolecular or intramolecular dehydration between alcohols and acidic components on treatment with diethyl azodicarboxylate (DEAD) and triphenylphosphine (Scheme 3.8).[13] Acidic components that have been alkylated by this method include phosphoric mono- and di-esters, carboxylic acids, phenols, imides, *N*-hydroxyimides, oximes, and active methylene compounds. The reaction usually proceeds under mild neutral conditions and exhibits stereospecificity, chemoselectivity, and regioselectivity.[11]



Scheme 3.8

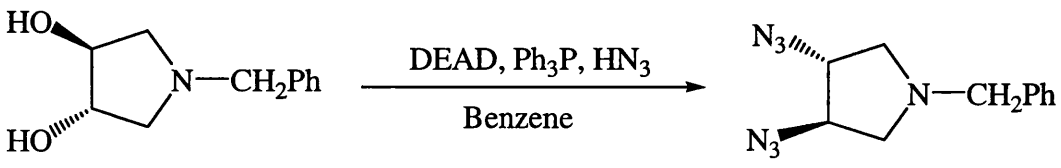
The reaction is believed to proceed through: a) addition of DEAD to triphenylphosphine to give a quaternary phosphonium salt **I**; b) protonation of **I**; c) addition of alcohol to form an alkoxyphosphonium salt **II**; d) S_N2 type displacement of the resulting species **II** to give the product (Scheme 3.9).[11,13]



Scheme 3.9

When the Mitsunobu reaction is used to synthesize azides from the corresponding alcohols, a variety of azide sources has been used, e.g. azidoic acid, zinc diazide bis-pyridine complex[14] or diphenylphosphorylazide.[15]

In the present work, two experiments were carried out using azidoic acid as the azide source (Scheme 3.10). The azidoic acid solution was prepared by reaction of NaN_3 with conc. H_2SO_4 (Scheme 3.11).[16] The reaction conditions and the results are listed in Table 3.3.



3.4 **3.5**

Scheme 3.10

$$2\,NaN_3 + H_2SO_4 \xrightarrow{H_2O,\ C_6H_6} 2\,HN_3 + Na_2SO_4$$

Scheme 3.11

Table 3.3 Synthesis of (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (3.5) using the Mitsunobu reaction according to Scheme 3.10

Entry	Quantities (mmol)				Temp. (Reaction time)	Result
	3.4	DEAD	Ph_3P	HN_3		
1	1.04	2.28	2.38	2.28	0 °C / r.t. (3 h)	failed
2	1.04	2.28	2.38	2.28	0 °C (63 min) / r.t. (16 h)	failed

The first experiment (Entry 1) was carried out following a literature procedure.[1] However, no desired product was obtained after work-up and purification by the procedure reported. By contrast, the starting material (compound **3.4**) was recovered.

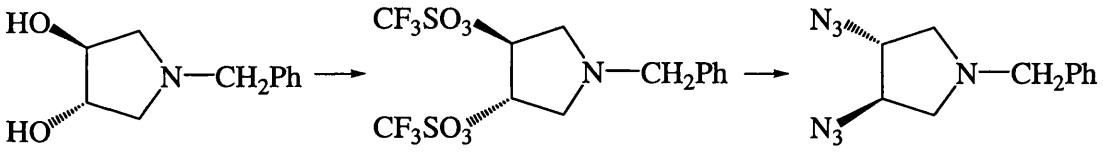
Some modifications were made when the second experiment (Entry 2) was conducted. These included: a) modifying the procedure which was used to prepare the azidoic acid solution to make sure the solution was dry and free from H_2SO_4; b) using tlc to monitor the progress of the reaction; c) the addition of DEAD to triphenylphosphine solution and the addition of azidoic acid solution were carried out slowly, and, after each addition, the mixture was stirred for a period of time to make sure, at least in principle, of the formation of the betaine-type adduct of triphenylphosphine-DEAD-azidoic acid (see Scheme 3.9). According to the literature,[1] the formation of such an adduct is vital to the outcome of the reaction; d) the reaction time was extended to 16 h. However, again no desired product was obtained, and this time no starting material (compound **3.4**) was present after the reaction either. The detailed experimental procedure is reported in the *Experimental Section* of this chapter.

Since the Mitsunobu reaction failed to provide the desired product **3.5**, we decided to turn to the other methodology for diazide synthesis.

3.2.3.2 Attempt to synthesize (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (3.5) *via* (3S,4S)-1-benzyl-3,4-bis(trifluoromethylsulfonyloxy)pyrrolidine (3.6)

Due to the excellent leaving group properties of sulfonate groups and fluorosulfonate groups, alkanesulfonic esters, arenesulfonic esters and perfluoroalkanesulfonic esters are important reagents in modern synthetic chemistry as well as mechanistic organic chemistry. Of these esters, the combination of ready availability and experimental convenience has made triflates the most investigated reagents of the perfluoroalkanesulfonates.[17]

Conversion of triflates into the corresponding azides by treatment with azide sources such as NaN_3 has been reported.[18] Therefore, the first methodology we decided to adopt was to convert the compound **3.4** into the corresponding bistriflate **3.6** [(3S,4S)-1-benzyl-3,4-bis(trifluoromethylsulfonyloxy)pyrrolidine], then convert the bistriflate into diazide **3.5** (Scheme 3.12).



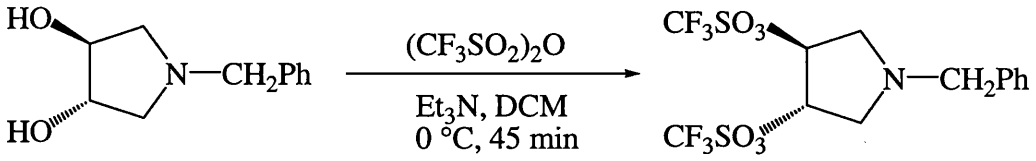
3.4 **3.6** **3.5**

Scheme 3.12

Alkyl triflates can be prepared by reaction of the appropriate alcohols with acid anhydrides or acid halides. The most convenient and widely used procedure is the one involving the use of alcohol and triflic anhydride. The reaction is usually carried out in the presence of a base in an inert solvent. Common solvents include dry DCM or carbon tetrachloride. The base is usually an amine such as pyridine, triethylamine, or lutidine, and occasionally sodium hydrogen carbonate or sodium carbonate.[17,19]

The first experiment was carried out on a 5 mmol scale of compound **3.4.** It had several significant features (Scheme 3.13): a) the reaction was conducted at 0 °C under anhydrous conditions; b) Et_3N was used as catalyst; c) the molar ratio of triflic

anhydride to compound **3.4** was 2; d) the work-up procedure involved operations with aqueous solutions.

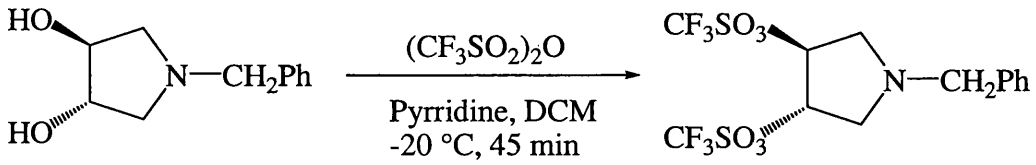


3.4 **3.6**

Scheme 3.13

Although tlc reaction monitoring results showed the complete consumption of compound **3.4**, the desired product was obtained in a low yield (9%) after work-up and purification. The low yield might be due to the following factors: a) side reactions occurred at the relatively high temperature; b) the product might not be stable enough to withstand the work-up procedure, which involved the use of aqueous solutions. It was also observed that the pure product was unstable and would decompose rapidly at r.t. upon exposure to air. The product was initially a white solid after removing solvent from the effluent under vacuum; it turned into viscous oil immediately upon exposure to air. The complexity of the NMR spectra showed the presence of impurities. The detailed experimental procedure is denoted as ***Method 1*** for preparation of bistriflate **3.6** in *Experimental Section* of this chapter.

Another experiment was carried out on a 5.3 mmol scale of compound **3.4** by modifying a literature procedure (Scheme 3.14).[20] It had several significant features: a) pyridine was used as catalyst instead of triethylamine; b) the molar ratio of triflic anhydride to compound **3.4** was increased to 2.3; c) the reaction temperature was lowered to -20 °C in the hope that this would suppress the occurrence of the side reactions; d) the work-up procedure was operated under anhydrous conditions in the hope that this would minimize the possibilities of decomposition of the product.



3.4 **3.6**

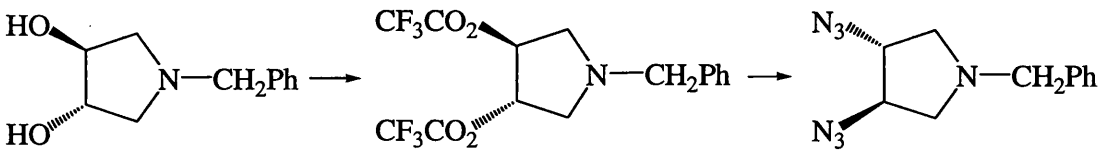
Scheme 3.14

Although the above-mentioned modifications were made, and tlc reaction monitoring results showed the complete consumption of compound **3.4**, the desired product was still obtained in a low yield (7%). It was also observed that the pure product was unstable and would decompose rapidly at r.t. upon exposure to air. The complexity of the NMR spectra showed again the presence of impurities. The detailed experimental procedure is denoted as ***Method 2*** for preparation of bistriflate **3.6** in the *Experimental Section* of this chapter.

The attempts to convert compound **3.4** into its corresponding bistriflate **3.6** gave only unsatisfactory results. Therefore it was decided to attempt an alternative approach, in which the hydroxyl groups (-OH) were expected to be transformed into less reactive functional groups.

3.2.3.3 Attempt to synthesize (3R,4R)-1-benzyl-3,4-diazidopyrrolidine(3.5) *via* (3S,4S)-1-benzyl-3,4-bis(trifluoroacetoxy)pyrrolidine (3.7)

Since bistriflate **3.6** is unstable and difficult to handle, another approach we decided to adopt was to transform diol **3.4** into a less reactive, in principle more stable, compound **3.7**, then to transform it into the target compound **3.5** (Scheme 3.15).

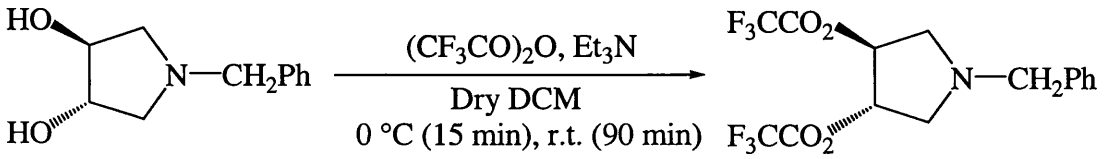


3.4 **3.7** **3.5**

Scheme 3.15

In the present work, two experiments were carried out. In both cases, trifluoroacetic anhydride (TFAA) was used as the trifluoroacetylating agent.

The first experiment was carried out on a 10 mmol scale of compound **3.4**. The molar ratios of TFAA and triethylamime to compound 3.4 were 2, respectively (scheme 3.16).

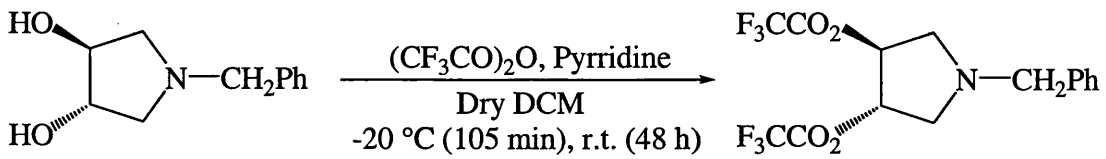


3.4 **3.7**

Scheme 3.16

Monitoring the reaction by tlc showed the presence of a spot with R_f 0.7, which, presumably, corresponded to the expected product based on the chemical information about the different polarity between diol **3.4** and the expected product **3.7**. It was also showed that the spot became fainter under the UV light when the reaction time was extended from 60 min to 90 min at r.t. However, only the starting material (diol **3.4**) was obtained after the work-up and purification procedure. This might suggest that the reaction did not proceed well under such conditions and the expected product was also not stable enough to withstand the work-up procedure and decomposed to the starting material. The detailed experimental procedure is reported in the *Experimental Section* of this chapter.

Another experiment was carried out on a 2.6 mmol scale of compound **3.4**, in which pyridine was used as catalyst instead of triethylamine and the molar ratio of TFAA to diol **3.4** was increased to 2.3 (Scheme 3.17).



3.4 **3.7**

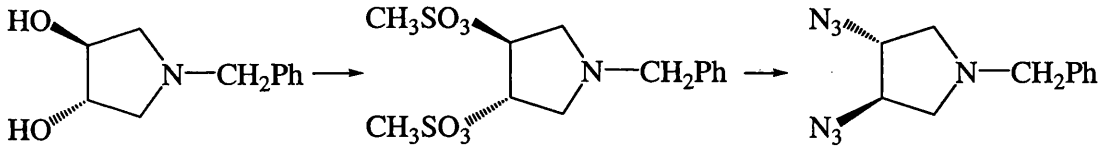
Scheme 3.17

The reaction was initially carried out at -20 °C. No spot likely to correspond to the expected product was observed by tlc. After 105 min, the reaction temperature was raised to r.t. However, still no spot corresponding to the expected product was detected after 48 h. The starting material (diol **3.4**) was recovered after removal of DCM from the reaction mixture.

In view of these results, it was decided to attempt conversion of diol **3.4** into its corresponding dimesylate.

3.2.3.4 Synthesis of (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (3.5) *via* (3S,4S)-1-benzyl-3,4-bis(methylsulfonyloxy)pyrrolidine (3.8)

The third approach we decided to adopt would be to transform compound **3.4** into its dimesylate **3.8**, then to transform it into the target compound **3.5** (Scheme 3.18).



3.4 **3.8** **3.5**

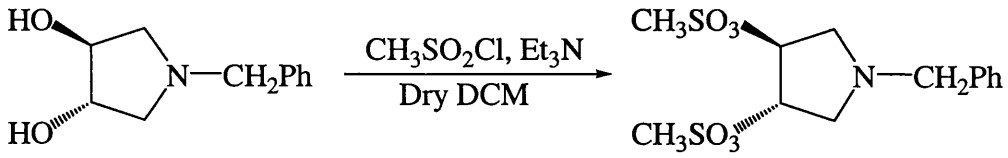
Scheme 3.18

3.2.3.4.1 Synthesis of (3S,4S)-1-benzyl-3,4-bis(methylsulfonyloxy)pyrrolidine (3.8)

Sulfonic esters are usually prepared by treatment of the corresponding acid halides with alcohols in the presence of a base like pyridine. Primary alcohols react the most rapidly.[21]

The reaction was carried out following a literature procedure.[2] Methanesulfonyl chloride was employed as the mesylating agent. Triethylamine was used as catalyst (Scheme 3.19). This method has also been reported as a facile

procedure for the synthesis of methanesulfonate esters, especially for reactive sulfonate esters.[22]



3.4 **3.8**

Scheme 3.19

In the present work, two experiments were carried out. In both cases, the molar ratios of methanesulfonyl chloride and triethylamine to compound **3.4** were 2, respectively. The reaction conditions and the results are listed in Table 3.4.

Table 3.4 Synthesis of (3S,4S)-1-benzyl-3,4-bis(methylsulfonyloxy)pyrrolidine (3.8) according to Scheme 3.19

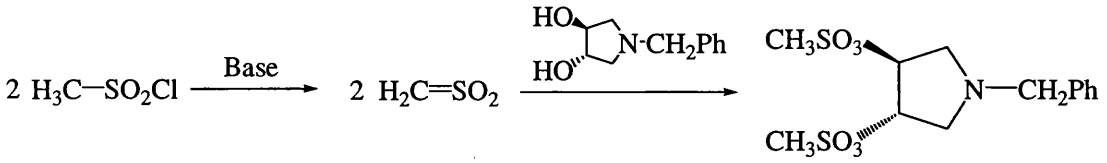
Entry	Quantities (mmol)			Temp. (Reaction time)	Yield (%)
	3.4	CH_3SO_2Cl	Et_3N		
1[a]	10	20	20	0 °C (15 min) / 21 °C (45 min)	80
2[b]	83	166	166	0 °C (25min) / 23 °C (40 min)	93

a. The concentration of compound **3.4** in DCM was 1.42 M.
b. The concentration of compound **3.4** in DCM was 1.66 M.

The first experiment was carried out on a small scale (Entry 1). The reaction proceeded well, and the target compound was obtained in good yield (80 %). The reaction was next applied to a larger scale synthesis. An excellent yield (93 %) was obtained by increasing the concentration of the reactants and slightly increasing the reaction temperature (Entry 2). No significant decomposition of product was observed at r.t. The detailed experimental procedure and characterization of the product are reported in the *Experimental Section* of this chapter.

The mechanism of the reactions between mesyl chloride and alcohols in the presence of a base has been proposed as the addition of alcohol to the sulfene derived

from mesyl chloride by E2 elimination of hydrogen chloride.[21-23] The mechanism of this reaction can therefore be summarized as in Scheme 3.20.



Sulfene **3.8**

Scheme 3.20

It is also important to note that the work-up procedure used in this reaction was the same as that used in the attempted synthesis of (3S,4S)-1-benzyl-3,4-bis(trifluoromethylsulfonyloxy)pyrrolidine (compound **3.6**; Section 3.2.3.2; ***Method 1***). No decomposition of compound **3.8** was observed during the work-up procedure whereas the bistriflate **3.6** was found to decompose. This phenomenon might be explained by the reactivity difference between these two functional groups. Triflates are more reactive than comparable mesylates: the relative leaving ability of triflate has been found to be 5.6×10^4 times greater than that of a comparable mesylate.[17]

The dimesylate **3.8** was synthesized in excellent yield from the corresponding diol. The next step would be to transform it into the corresponding diazide **3.5**.

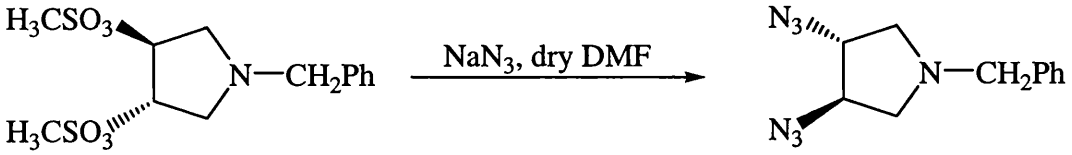
3.2.3.4.2 Synthesis of (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (3.5)

The reaction of sulfonates with azide ion is an important method to synthesize organic azides, especially alkyl examples. The overall process can be used as an indirect conversion of an alcohol to an azide. Choice of conditions for reaction with azide ion is dictated by the same factors as for halide leaving groups. The S_N2 nature of the substitution has been proven from a number of examples.[24] The commonly used azide sources are sodium azide and lithium azide. The most widely used solvents are dipolar aprotic solvents such as DMF, HMPA, DMSO, and acetonitrile. In some

cases, phase transfer catalysts such as 15-crown-5[25] and Bu_4NCl[12b] have been used to facilitate the transformation.

3.2.3.4.2.1 Synthesis of (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (3.5) using sodium azide as the azide source

The transformation of dimesylate **3.8** to diazide **3.5** using sodium azide has been reported (Scheme 3.21).[26] However, the researchers did not isolate and purify the diazide; the crude product was directly used for further treatment without purification.



3.8 **3.5**

Scheme 3.21

In the present work, the reaction was carried out under various conditions in order to work out the optimal reaction conditions. In each case, the reaction mixture was worked up and the product was isolated by chromatography. The results are listed in Table 3.5.

Table 3.5 Synthesis of (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (3.5) using sodium azide as the azide source according to Scheme 3.21.

Entry	Quantities (mmol)		Solvent	Temp. (Reaction time)	Yield [a] (%)
	3.8	NaN_3			
1	12.2	72.9	Dry DMF	100 °C (8 h)	56
2	12.2	72.9	Dry DMF	Reflux (1h)	45
3	3.09	14.7	CH_3CN	reflux (13 h) / r.t. (67.5 h)	0
4[b]	12.2	72.9	Dry DMF	100 °C (4 h) / r.t. (14 h)	44

a. Isolated yield after purification by column chromatography.

b. Phase transfer catalyst 15-crown-5 was used in this experiment.

The first experiment (Entry 1) was carried out by modifying the literature procedure.[26] The molar ratio of sodium azide to dimesylate was increased to 6 (it was 2.34 in the literature) and the reaction time was extended to 8 h (4 h in the literature) based on tlc reaction monitoring results. The reaction was very clean; no spots corresponding to by-product(s) were detected by tlc. The product **3.5** was obtained with a moderate yield (56%) after purification by silica column chromatography. The detailed experimental procedure and characterization of the product are reported in the *Experimental Section* of this chapter.

In an attempt to enhance the yield, a reaction was carried out at higher temperature (reflux, 152 °C). As can be seen from Table 3.6 (Entry 2), the reaction did proceed faster. However, the product **3.5** was obtained with a lower yield (45%). The main possible reason might be attributed to the higher reaction temperature, at which competitive side reactions, such as elimination reactions, might occur. This assumption was supported by tlc reaction monitoring results, which showed the presence of spots corresponding to by product(s).

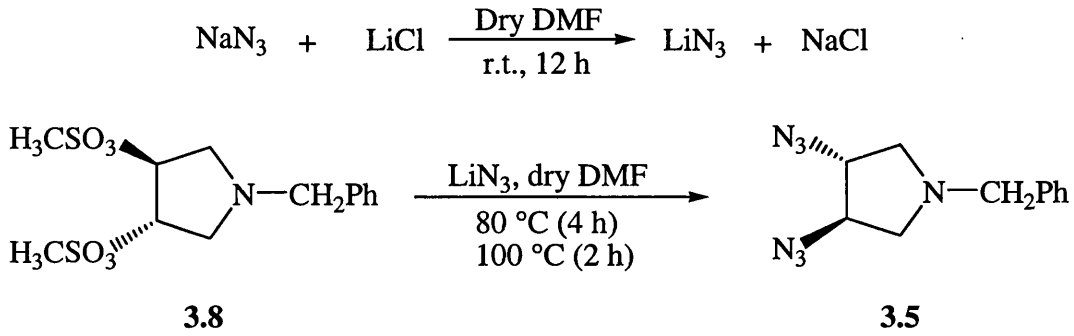
Solvent effects on the yield of the reaction were also studied. Dry acetonitrile was used as solvent instead of DMF (Entry 3). Surprisingly, the reaction did not proceed at all, even though it was subjected to a much longer reaction time. Only a spot corresponding to the starting material (**3.8**) was detected by tlc and the starting material was totally recovered after removal of solvent from the reaction mixture. Considering the fact that the two solvent systems have similar polarity (ε: DMF 36.7; CH_3CN 36.2)[27], the reaction temperature, 100 °C or more for the DMF system but only 82 °C for the acetonitrile system, was thought to play a very important role.

A phase transfer catalyst, 15-crown-5, was also used to try to improve the yield of the reaction. However, after 4 h at 100 °C, the yield (44%; Entry 4) was lower than that obtained after 8 h at 100 °C in the absence of the phase transfer catalyst. It appeared that the phase transfer catalyst had little effect on this occasion.

During the course of these studies, it was observed that the diazide **3.5** appeared to decompose slightly on the silica column.

3.2.3.4.2.2 Synthesis of (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (3.5) using lithium azide as the azide source

Since the reactions using sodium azide as the azide source gave only moderate yields for the synthesis of diazide **3.5**. Lithium azide, which might be more soluble in the reaction system, was used to synthesize diazide **3.5**. In the present work, two experiments were carried out using this methodology. Lithium azide was prepared by treatment of sodium azide with lithium chloride in dry DMF (Scheme 3.22).



3.8 **3.5**

Scheme 3.22

The first experiment was also carried out on a 12.2 mmol scale of compound **3.8**. The molar ratios of the reactants, the work-up and purification procedures remained the same as those in the reactions using sodium azide. The reaction was not very clean; spots corresponding to by-products were detected by tlc. However, a similar yield of the product (55%) was obtained after purification by column chromatography. The detailed experimental procedure is reported in the *Experimental Section* of this chapter.

Since lithium chloride is very hygroscopic, it is reasonable to assume that traces of water would be introduced into the reaction system while handling and transferring the reagent and which might have an adverse effect on the reaction. One solution to this problem might be to add some materials which could adsorb water.[27]

Activated 3 A molecular sieves were therefore added to the reaction mixture for this purpose in the second experiment. Disappointingly, abnormal phenomena, such as the colour of the reaction mixture and the formation of a black solid after addition of water to the reaction mixture, which was absent in the previous experiments, were observed throughout the reaction process. And, the product was obtained in a very low yield (28%) after purification by column chromatography. It appeared that 3 A molecular sieves had an adverse effect on the reaction rather than a beneficial one.

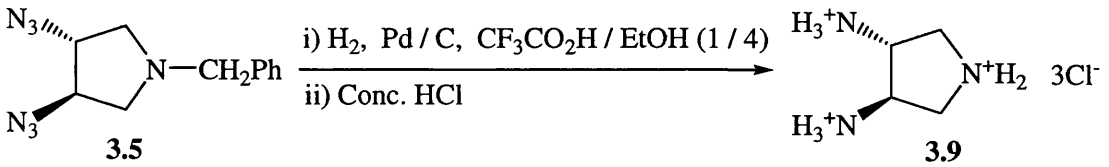
3.2.4 Synthesis of *trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt (3.9)

Reduction of azides to their corresponding amines is an important transformation in synthetic organic chemistry. The reduction permits a controlled introduction of the amine function because many azides can be prepared with regio- and stereo-control. The reaction has wide applicability and has been effected with a wide range of reagents, such as $LiAlH_4$, catalytic hydrogenation, Ph_3P, diborane, H_2S, Zn / HCl, Mg or Ca in MeOH, baker's yeast, and Sm / I_2.[21,24,28]

Hydrogenation methods have been commonly applied to the reduction of azides. The yields are generally good and selective hydrogenation can be achieved if other reducible groups are present.[24] Since our aim was to synthesis *trans*-(3R,4R)-diaminopyrrolidine and *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine from the same diazide **3.5**, in which the benzyl group was required to be cleaved in the former case but was required to be unaffected in the latter case, the hydrogenation method appeared to be a promising option.

3.2.4.1 Synthesis of *trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt (3.9) by hydrogenation of (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (3.5)

Since most polyamines are unstable[29] and difficult to handle and store, the target compound *trans*-(3R,4R)-diaminopyrrolidine was therefore transformed to its hydrochloride salt (**3.9**) after the hydrogenation procedure (Scheme 3.23).



3.5 **3.9**

Scheme 3.23

In the present work, three experiments were carried out under various conditions. The reaction conditions and the results are listed in Table 3.6.

Table 3.6 Synthesis of *trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt (3.9) by hydrogenation of (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (3.5) according to Scheme 3.23[a]

Entry	Quantities				Time (h)	Yield (%)
	3.5 (mmol)	Conc. (**3.5**)[b]	Molar ratio (Pd / **3.5**)	Molar ratio (conc.HCl / **3.5**)		
1	2.48	0.1	0.093	9.7	30	74
2	4.86	0.2	0.095	4.9	27	76
3	3.55	0.2	0.095	3.3	28	82

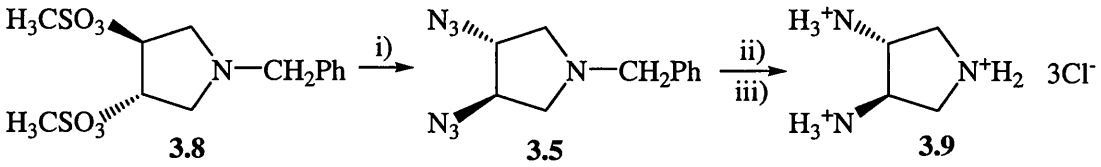
a. All hydrogenation experiments were carried out on a *Parr 3911 Hydrogenation Apparatus* at 4.3 atm at r.t..
b. The unit of the concentration is M (Molarity).

All hydrogenation experiments were conducted at 4.3 atm and at r.t. with mechanical shaking to facilitate contact between the catalyst and the substrate. In all cases, the hydrogenation reactions were very clean, with complete reduction of the azido groups and cleavage of the benzyl group. Conc. HCl was used to convert the trifluoroacetate salt of the product into the trihydrochloride salt, which has advantages of easy handling and storage. A sufficient amount of conc. HCl was needed to ensure complete conversion. However, the use of excess amount of HCl might result in loss of product because the product is soluble in water. The best yield (82%, Entry 3) was obtained using a small excess of HCl over what the stoichiometry required. The detailed experimental procedure and characterization of the product are reported in the *Experimental Section* of this chapter.

In comparison with a procedure reported by Jacobsen and co-workers,[30] in which the resulting *trans*-(3R,4R)-diaminopyrrolidine was not isolated, the hydrogenation procedure developed here has the advantages of: a) a low hydrogenation pressure, which significantly increases the operational safety and convenience; b) complete and clean reduction of the azido and benzyl groups.

3.2.4.2 Synthesis of *trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt (3.9) from (3S,4S)-1-benzyl-3,4-bis(methylsulfonyloxy)pyrrolidine (3.8)

As mentioned in *Section 3.2.3.4.2.1*, the diazide **3.5** appeared to decompose slightly on silica column chromatography. The best yield obtained for synthesis of the diazide from dimesylate **3.8** was 56%. And, the best overall yield for synthesis of target compound **3.9** [*trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt] from dimesylate **3.8** was therefore 46%. In an attempt to overcome the problem that the diazide **3.5** decomposed on the silica column, we also explored the feasibility and efficiency to synthesize target compound **3.9** from dimesylate **3.8** without purification of the intermediate diazide **3.5** (Scheme 3.24).



3.8 **3.5** **3.9**

i) NaN_3, dry DMF; ii) H_2, Pd / C, CF_3CO_2H / EtOH (1 / 4); iii) Conc. HCl

Scheme 3.24

The reaction for diazide synthesis was worked up as that used for previous syntheses (see *Section 3.2.3.4.2.1* and *Section 3.2.3.4.2.2*). The crude product was diluted with a mixture of CF_3CO_2H / EtOH (1 / 4) and then transferred to a reaction bottle for hydrogenation. The reaction conditions and the results are summarized in Table 3.7.

Table 3.7 Synthesis of *trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt (3.9) from (3S,4S)-1-benzyl-3,4-bis(methylsulfonyloxy)pyrrolidine (3.5) according to Scheme 3.24[a]

For preparation of diazide	For hydrogenation				Yield (%)
Temp. (Reaction time)	Molar ratio (Pd/ **3.8**)	Molar ratio (conc.HCl/**3.8**)	Pressure (atm)	Temp. (time)	
100 °C (6 h) / r.t. (14 h)	0.09	3.3	4.3	r.t. (30 h)	47

a. The reaction was carried out on a 10.9 mmol scale of compound 3.8. The molar ratio of NaN_3 to compound 3.8 was 5.5.

The reaction worked reasonably well. Although the diazide was not purified, pure product **3.9** was still obtained with an overall yield of 47%. Any impurities were removed during the work-up procedure after the hydrogenation. The detailed experimental procedure is reported in the *Experimental Section* of this chapter.

This procedure combines the synthesis of diazide **3.5** and the hydrogenation procedure thereafter; it provides a simple, clean and efficient method to synthesize the target compound **3.9** from dimesylate **3.8**.

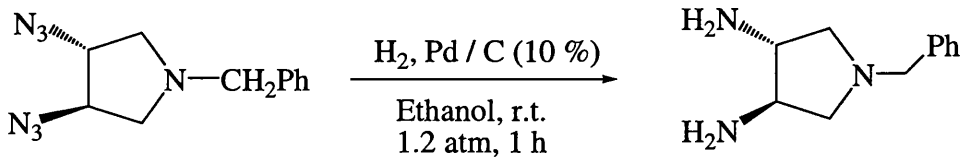
Upon successful synthesis of *trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt (**3.9**), the next compound we decided to synthesize was its analogue *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine.

3.2.5 Synthesis of *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine (3.10) and its trihydrochloride salt 3.11

As mentioned above, selective hydrogenation is possible when other reducible groups are present. In order to reduce azido groups without interfering with a benzyl group, milder hydrogenation conditions should be employed.

3.2.5.1 Synthesis of *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine (3.10) by hydrogenation of the corresponding diazide 3.5

In contrast with the hydrogenation procedure used to synthesize *trans*-(3R,4R)-diaminopyrrolidine, the hydrogenation procedure employed here (Scheme 3.25) had several features: a) lower hydrogenation pressure; b) much shorter reaction time; c) different solvent (ethanol was used as solvent instead of the mixed solvent system, CF_3CO_2H / EtOH, used above); d) lower quantity of catalyst (the molar ratio of Pd to substrate was reduced to 0.03).



3.5 **3.10**

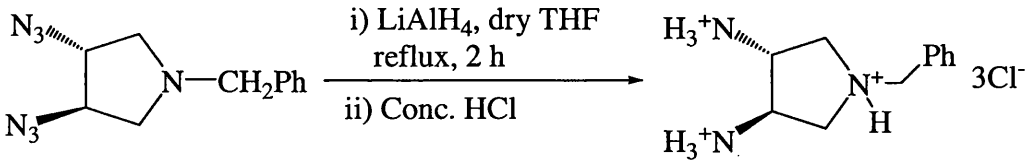
Scheme 3.25

The reaction worked very well; the diazide **3.5** was reduced to the target compound **3.10** quantitatively and cleanly. The detailed experimental procedure and characterization of the product are reported in the *Experimental Section* of this chapter.

3.2.5.2 Synthesis of *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine trihydrochloride salt (3.11) by reduction of diazide 3.5 using $LiAlH_4$

Lithium aluminum hydride ($LiAlH_4$) has also been widely used for the reduction of azides to the corresponding amines. The main advantages of using $LiAlH_4$ over catalytic hydrogenation are the greater safety of the procedure and operational convenience.

$LiAlH_4$ was also used to reduce the diazide **3.5** to the corresponding 1-benzyl-3,4-diaminopyrrolidine (**3.10**). In this case, the diamine was not separated; it was converted into its trihydrochloride salt instead (Scheme 3.26).



3.5 **3.11**

Scheme 3.26

The reduction was carried out on a 2.45 mmol scale of diazide **3.5**. The molar ratio of $LiAlH_4$ to diazide **3.5** was 2.7. The reaction was found to be incomplete by tlc after the reaction mixture was heated under reflux for 2 h. However, the tlc results remained almost the same for a sample taken at 30 min as for one taken at 2 h. Therefore the reaction was worked up. The target compound **3.11** was obtained in a 66 % isolated yield. The detailed experimental procedure and characterization of the product are reported in the *Experimental Section* of this chapter

3.3 Conclusions

- The target compound *trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt (**3.9**) was synthesized by a five-step reaction from (2R,3R)-(+)-tartaric acid with an overall yield of 22%.
- The target compound *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine (**3.10**) was synthesized by a five-step reaction from (2R,3R)-(+)-tartaric acid with an overall yield of 26%.
- (3R,4R)-1-Benzyl-3,4-dihydroxy-2,5-pyrrolidinedione (**3.3**) was synthesized from (2R,3R)-(+)-tartaric acid in a 71% isolated yield.
- The reduction of (3R,4R)-1-benzyl-3,4-dihydroxy-2,5-pyrrolidinedione (**3.3**) to diol (3S,4S)-1-benzyl-3,4-dihydroxypyrrolidine (**3.4**) was intensively investigated using three reduction systems: $NaBH_4$ / I_2 / THF system, BH_3·THF complex and $NaBH_4$ / BF_3·Et_2O / diglyme system. The best result was obtained using the $NaBH_4$ / BF_3·Et_2O / diglyme reduction system, which produced a 71% isolated yield. A new method was tried in which BH_3·THF complex was used as the reductant, and this resulted in a 51% isolated yield.

- Diol (3S,4S)-1-benzyl-3,4-dihydroxypyrrolidine (**3.4**) was successfully transformed into dimesylate (3S,4S)-1-benzyl-3,4-bis(methylsulfonyloxy)pyrrolidine (**3.8**) in a 93% isolated yield.
- Dimesylate (3S,4S)-1-benzyl-3,4-bis(methylsulfonyloxy)pyrrolidine (**3.8**) was successfully transformed into diazide (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (**3.5**) by reaction with sodium azide or lithium azide. The influences of reaction parameters, such as reaction temperature, solvent, and catalyst, on the efficiency of the reaction were investigated. The best isolated yield obtained was 56% using sodium azide as the azide source.
- Diazide (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (**3.5**) was successfully reduced to the target compound *trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt **(3.9)** by a simple hydrogenation procedure. The reaction was complete and clean. The best isolated yield obtained was 82%.
- A simple, clean and efficient method has been developed to synthesize the target compound *trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt **(3.9)** directly from dimesylate **3.8** in a 47% isolated yield.
- Diazide (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (**3.5**) was reduced to the target compound *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine **(3.10)** quantitatively and cleanly by a hydrogenation method.
- Diazide (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (**3.5**) was also reduced to trans-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine trihydrochloride salt (**3.11**) in a 66% isolated yield using $LiAlH_4$ as the reductant.

3.4 Experimental section

Chemicals were obtained from Aldrich Chemical Company or Lancaster Synthesis Limited.

Thin layer chromatography (tlc) analyses were carried out on silica plates (Alugram® Sil G / UV254) from Macherey-Nagel and visualised under ultraviolet light.

Separations of products by column chromatography were performed on columns packed with Matrex Silica 60 (35 - 70 mesh) from Fisher Scientific. Eluting solvents were distilled prior to use.

Melting points (m. p.) were measured on a Sanyo Gallenkamp capillary melting point apparatus and are reported uncorrected.

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC 400 spectrometer. The internal reference used in all spectra was tetramethylsilane (Me_4Si). Chemical shifts δ are reported in parts per million (ppm) and coupling constants J are in Hz. Abbreviations: br. = broad, s = singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet.

IR spectra were recorded on a PerkinElmer Spectrum One FT-IR spectrometer with PerkinElmer Universal ATR Sampling Accessory.

Low resolution electron impact (EI), chemical ionisation (CI) and electrospray (ES) mass spectra were recorded on a Micromass Quattro II low resolution triple quadrupole mass spectrometer. High resolution mass data (HRMS) were obtained on a Finnigan MAT 900 XLT high resolution double focussing mass spectrometer by manual peak matching.

Specific rotations were measured on a PerkinElmer 141 polarimeter using the Na D line (589 nm) as the light source.

Drying of glassware

Wherever anhydrous operation was needed, the glassware was heated in the oven (120 °C) overnight. The apparatus was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t.

Drying of solvents [27,31]

Refluxing of a solvent over drying agent and the following distillation were carried out under an Ar atmosphere. The molecular sieves were activated in oven and cooled to r.t. under an Ar atmosphere.

Drying of THF

THF was dried over sodium-benzophenone in a solvent still.

Drying of methanol

Clean and dry magnesium turnings (9 g), iodine (0.9 g) and methanol (112 ml) were placed in a dry 3-L flask fitted with a magnetic follower and a condenser under an Ar atmosphere. The mixture was heated until all magnesium had been consumed (converted into methanolate). Methanol (1680 ml) was then added. The mixture was heated under reflux for 3 h, then distilled onto 3Å molecular sieves (10% w / v) and allowed to stand for 24 h.

Drying of diglyme

Diglyme was dried by stirring over NaOH pellets overnight.

Drying of benzene

Benzene was dried by refluxing over anhydrous CaH_2 (5% w / v) for 3 h, and then distilled onto 4 Å molecular sieves. The fraction of b. p. 79 - 81 °C was collected.

Drying of DCM

DCM was dried by refluxing over anhydrous CaH_2 (5% w / v) for 3 h, and then distilled onto 4 Å molecular sieves. The fraction of b. p. 41 - 43 °C was collected.

Drying of DMF

DMF was sequentially dried over three batches of activated 3 Å molecular sieves (5% w / v, 12 h, respectively).

Drying of acetonitrile

CH_3CN was stirred over P_2O_5 (5% w / v) for 24 h and then distilled. The fraction of b. p. 81 - 82 °C was collected.

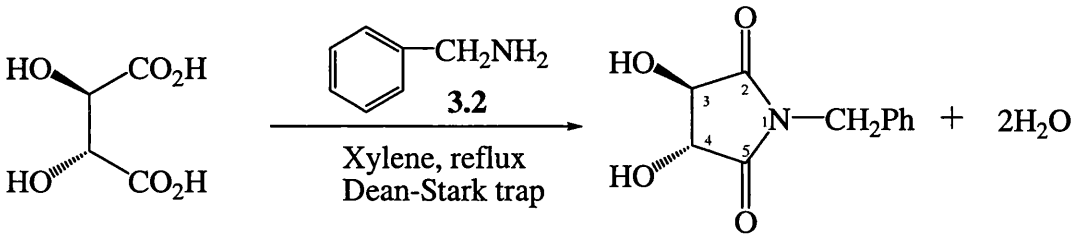
Removal of solvents under the reduced pressure (*in vacuo*)

Removal of solvent from a reaction mixture, a filtrate or an extract was carried out on a rotary evaporator using a water aspirator at r.t. or at specific temperature noted.

Reactions

The reactions were carried out under an Ar atmosphere wherever anhydrous conditions were needed.

Synthesis of (3R,4R)-1-benzyl-3,4-dihydroxy-2,5-pyrrolidinedione (3.3)



3.1 **3.3**

Tartaric acid (**3.1**) (150 g, 1 mol) and xylene (800 ml) were added to a 1-L two-necked round bottomed flask equipped with a magnetic follower and a

Dean-Stark trap connected to a condenser. Benzylamine (**3.2**) (110 ml, 1 mol) was then added. The reaction mixture was heated under reflux until no further H_2O separated from the system (*ca.* 34.7 ml H_2O collected). After cooling to r.t., the crystalline product was collected by suction filtration, washed with a little xylene, then with acetone (380 ml) until the colour changed to white. The crystals obtained (182.87 g, m.p. 172 - 201°C) were recrystallized from ethanol (1.3 L) to give the pure product **3.3** (157.67 g, 71% yield).

Melting point (m.p.): 199 - 202 °C (from ethanol).

TLC (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}):

R_f = 0.78 (developing solvent: CH_3OH / EtOAc = 1 / 3).

R_f = 0.66 (developing solvent: CH_3OH / CH_3Cl = 1 / 3).

NMR

δ_H (400MHz, DMSO-d^6): 4.19 (d, 2H, **H**-3, **H**-4, J = 4 Hz); 4.32 (d, 1H, $\mathbf{H^a}$ of PhC$\mathbf{H^aH^b}$-, ^2J = 15 Hz); 4.38 (d, 1H, $\mathbf{H^b}$ of PhC$\mathbf{H^aH^b}$-, ^2J = 15 Hz); 6.10 (br., 2H, -O**H**); 7.03 - 7.15 (m, 5H, Ar**H**).

δ_C (400MHz, DMSO-d^6): 41.5 (**C**H_2Ph); 74 .8 (**C**-3 and **C**-4); 127.8 / 127.9 / 128.9 / 136.3 (carbons on the benzene ring); 174.9 (**C**-2 and **C**-5).

IR

ν_{max} (cm^{-1}): 3190(br. HO-, H-bonded); 3025 (Ar-H); 2881(-CH_2-); 1782 / 1704 (-**CO**-N-**CO**-); 1605; 1495; 1454; 1435; 1393; 1350; 1340; 1215; 1157; 1097; 1075; 1002; 746; 690; 662.

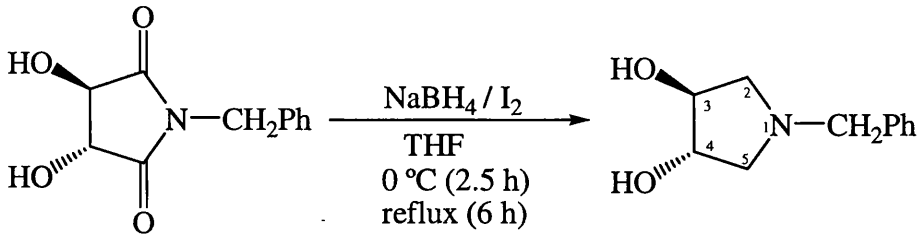
MS

m /z (EI): 221 (M^+, 15%); 91 ($C_7H_7^+$, 100%); 60 (72%).

HRMS

Found $[M+H]^+$: 222.0763; $C_{11}H_{12}O_4N$ requires: 222.0761.

Synthesis of (3S,4S)-1-benzyl-3,4-dihydroxypyrrolidine (3.4) by reduction of compound 3.3 using a $NaBH_4$ / I_2 / THF system



3.3 **3.4**

The reaction set-up consisted of a three-necked round bottomed flask equipped with a magnetic follower, a condenser, a pressure equalizing addition funnel and a stopcock capped with a septum. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. Compound **3.3** (6.64 g, 30 mmol) and dry THF (180 ml) were added to the flask. The solution was cooled to 0 °C in an ice-water bath. $NaBH_4$ (6.14 g, 162 mmol) was added to the flask. Then a solution of iodine (18.3 g, 72 mmol) in THF (180 ml) was added dropwise from the pressure equalizing addition funnel over 2.5 h. After addition, the reaction mixture was brought to r.t. and then heated under reflux for 6 h.

The reaction mixture was cooled to 0 °C. 3M HCl was added carefully to the reaction mixture until no further gas evolved (28 ml of HCl was required). Then 3 M NaOH was added to neutralize the mixture (*ca.* 35 ml; pH of the mixture was 7 - 8). The solid was filtered off. Solid NaCl was added to the filtrate and the aqueous layer was separated off. The THF layer was washed with brine (2 × 60 ml), dried over anhydrous $MgSO_4$ and filtered. The filtrate was evaporated to dryness *in vacuo.* Methanol (90 ml) was added to the residue to dissolve it. Then 12 M HCl (7.5 ml) was added. The azeotrope, which was formed between methanol and methylborate, was distilled off. Another batch of methanol (90 ml) was added to the residue, and again the azeotrope was distilled off. The addition and distillation process was repeated until no borate ester was present in the distillate (detected by burning a small amount of distillate on copper wire in the flame of a microburner until no green flame was observed). A methanolic KOH solution (1.5 g, in 75 ml methanol) was added to the residue. Then anhydrous K_2CO_3 (105 g) was added. The mixture was evaporated to

dryness *in vacuo*. The remaining solid was extracted continuously with Et_2O in a Soxhlet extractor for 32 h. Removal of solvent from the extract *in vacuo* and recrystallization of the residual crystals from EtOAc gave the product (3.71 g, 64% yield).

Melting point (m.p.): 101 - 102 °C (from EtOAc).

TLC (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}):

$R_f = 0.28$ (developing solvent: CH_3OH / EtOAc = 1 / 3).

$R_f = 0.38$ (developing solvent: CH_3OH / CH_3Cl = 1 / 3).

NMR

δ_H (400MHz, $CDCl_3$): 2.33 (dd, 2H, **H**-2^a, **H**-5^a, ^2J = 11 Hz, ^3J = 4 Hz); 2.80 (dd, 2H, **H**-2^b, **H**-5^b, ^2J = 11 Hz, ^3J = 4 Hz); 3.45 (d, 1H, **H**^{a} of PhC**H**^{a}**H**^{b}-, ^2J = 13 Hz); 3.52 (d, 1H, **H**^{b} of PhC**H**^{a}**H**^{b}-, ^2J = 13 Hz); 3.95 (apparent triplet, 2H, **H**-3, **H**-4, ^3J = 4 Hz); 4.10 (s, 2H, O**H**-); 7.15 - 7.23 (m, 5H, Ar**H**).

δ_C (400MHz, $CDCl_3$): 60.5 (**C**-2 and **C**-5); 60.6 (**C**H_2Ph); 78 .8 (**C**-3 and **C**-4); 127.8 / 128.7 / 129.6 / 137.9 (carbons on the benzene ring).

IR

ν_{max} (cm^{-1}): 3432 (–OH); 3137 (br. HO-, H-bonded); 3019 (Ph-H); 2970 / 2931 / 2808 / 2772 (CH); 1602; 1583; 1496; 1473; 1449; 1436; 1377; 1322; 1294; 1218; 1201; 1142; 1121; 1088; 1050; 1030; 980; 909; 843; 738; 697.

MS

m/z (EI): 193 (M^+, 12%); 91 ($C_7H_7^+$, 100%); 42 (42%).

m/z (CI, NH_3): 194 ($[M+H]^+$, 85%); 158 (100%); 106 (55%).

HRMS

Found $[M+H]^+$: 194.1176; $C_{11}H_{16}O_2N$ requires: 194.1176.

Synthesis of (3S,4S)-1-benzyl-3,4-dihydroxypyrrolidine (3.4) by reduction of compound 3.3 using BH_3·THF complex

Preparation of HCl / MeOH solution [31]

The reaction set-up consisted of a three-necked round bottomed flask equipped with a magnetic follower, a pressure equalizing addition funnel, a stopper

and a glass gas outlet tube. The gas outlet was connected to a Dreschel bottle containing conc. H_2SO_4, and then on to another empty reversed Dreschel bottle which was used as a suck-back trap. The dry gas would then pass into a two-necked round bottomed flask containing dry methanol and equipped with a calcium chloride guard tube. PVC tubing was used and all joints were wrapped with Teflon® tape and wired with copper wire.

Calcium chloride was added to the reaction flask. conc. H_2SO_4 was added through the pressure equalizing addition funnel cautiously and the rate of addition was adjusted so that no gas escaped from the methanol container.

The molarity of the HCl / MeOH solution generated was estimated by adding an excess amount of standard NaOH solution (0.2030 M), and then back titrating it with a standard HCl solution (1.025 M).

The molarities of the three batches of HCl / MeOH solution prepared were: 1st 800 ml, 0.94 M; 2nd 200 ml, 3.28 M; 3rd 800 ml, 1.54 M, respectively.

Quantitative analysis of BH_3·THF solution using a gas burette [27]

The procedure for analysis of BH_3·THF solution was as follows.

a. A 1:1 mixture of glycerol and water (50 ml) and a magnetic follower were placed in a two-necked round bottomed flask equipped with a septum and a gas outlet tube.

b. The burette was opened to the flask and a few milliliters of BH_3·THF solution was added to the flask in order to saturate the atmosphere with hydrogen.

c. The burette was opened to the atmosphere and the levelling bulb was raised to give a reading of zero.

d. The three-way tap was turned so that the burette was connected only to the flask. An accurately measured volume of BH_3·THF solution was added to the flask with rapid stirring. When hydrogen evolution had ceased, the leveling bulb was lowered so that the liquid levels in the burette and the reservoir were equal, and the volume was read.

e. The molarity of the BH_3·THF solution was calculated using the following equation.

$$\text{Molarity} = \frac{(P_a - P_s)\,(273)(V_h - V_a)}{(760)(T)(22.4)(V_a)}$$

Where,

P_a = atmospheric pressure (mmHg)

P_s = vapor pressure of the solvent (mmHg) in the reservoir at temperature T

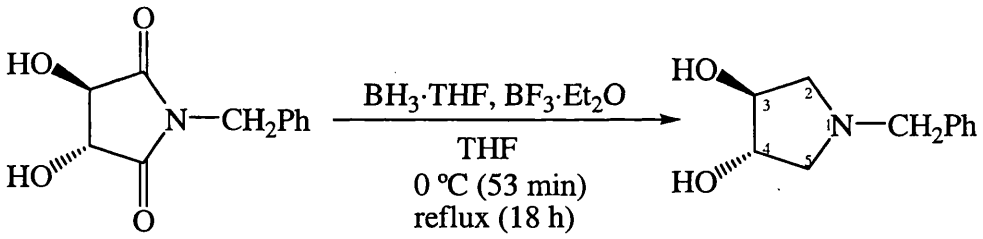
V_h = volume of hydrogen evolved (ml)

V_a = volume of BH_3·THF solution added (ml)

T = temperature (K)

The molarity of the BH_3·THF solution used was calculated as 1.09 M.

Reduction of (3R,4R)-1-benzyl-3,4-dihydroxy-2,5-pyrrolidinedione(3.3) using BH_3·THF complex (Method 1)



3.3 **3.4**

The reaction set-up consisted of a three-necked round bottomed flask equipped with a magnetic follower, a pressure equalizing addition funnel, a condenser and a stopcock capped with a septum. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. Compound **3.3** (1.108 g, 5 mmol) and dry THF (25 ml) were added to the flask and the solution was cooled to 0 °C in an ice-water bath. BH_3·THF (40 ml, 43.6 mmol) was added to the solution dropwise through the funnel over 48 min with good stirring. Then BF_3·Et_2O solution (2.53 ml, 20 mmol) was added dropwise over 5 min. After addition, the reaction mixture was brought to r.t. and then heated under reflux for 18 h.

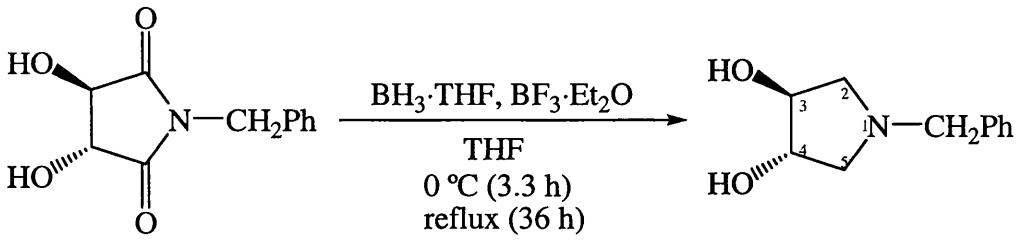
The solvent was removed *in vacuo*. DCM (50 ml) was added to the residue and the resulting solution was cooled to 0 °C. Conc. HCl was added dropwise to the solution with good stirring until the gas evolution ceased (*ca.* 11 ml HCl used). The solid that precipitated from the mixture was filtered off (1.180 g; borate compounds). The filtrate was composed of a DCM layer and an aqueous layer. The aqueous layer was separated (named as aqueous layer 1). The DCM layer was dried over anhydrous $MgSO_4$ and filtered. Removal of DCM from the filtrate *in vacuo* gave some yellow oil (1.31g). DCM was added to make a solution. Then 6M NaOH solution was added until the pH reached 14. The aqueous layer (named as aqueous layer 2) was separated. The DCM layer was washed with brine and again the aqueous layer (named as aqueous layer 3) was separated. The DCM layer was dried over anhydrous $MgSO_4$ and filtered. Removal of DCM from the filtrate *in vacuo* gave a little yellow oil (0.016 g; this meant that the product was present in the aqueous layers separated earlier).

Solid KOH was added carefully to aqueous layer 1 until the pH reached 14. The solid was filtered off (0.828 g, inorganic compound). Then solid KCl was added to saturate the filtrate. The filtrate was extracted with DCM (3 × 50 ml) and the aqueous layer was separated (named as aqueous layer 4). Removal of DCM from the extract *in vacuo* gave the crude product (0.125 g, m.p. 94 - 96 °C, 13% yield).

Aqueous layers 2, 3, and 4 were extracted with Et_2O (3 × 25 ml), respectively. The resulting aqueous phases were combined and water was removed *in vacuo*. The residue was extracted continuously with Et_2O in a Soxhlet extractor overnight. The ethereal extract was combined with the ether layer separated earlier, then dried over anhydrous $MgSO_4$ and filtered. Removal of Et_2O from the filtrate *in vacuo* gave the crude product (0.016 g, m.p. 94 - 97 °C, 2% yield). Combination of the two batches of crude product and recrystallization it from EtOAc gave the pure product (0.041 g, 4% yield).

***The product** was identical with the previously synthesized product using the $NaBH_4$ / I_2 / THF reduction system.*

Reduction of (3R,4R)-1-benzyl-3,4-dihydroxy-2,5-pyrrolidinedione (3.3) by BH_3·THF complex (Method 2)



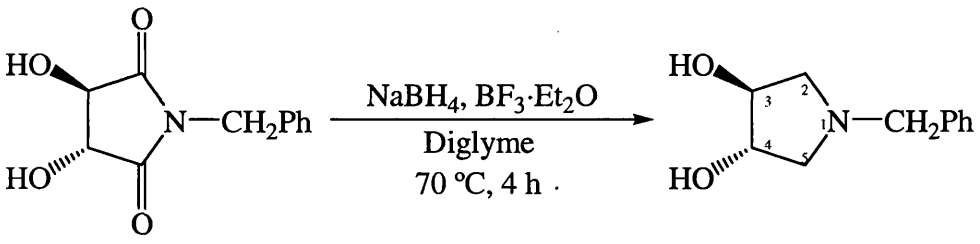
3.3 **3.4**

The reaction set-up was similar to that used in *Method 1*, but larger sized glassware was used. Compound **3.3** (6.64 g, 30 mmol) and dry THF (100 ml) were added to the flask and the solution was cooled to 0 °C in an ice-water bath. BH_3·THF solution (240 ml, 261 mmol) was added dropwise from the pressure equalizing addition funnel over 3 h with good stirring. Then BF_3·Et_2O solution (15.2 ml, 120 mmol) was added dropwise through the funnel over 20 min. After addition, the reaction mixture was brought to r.t. and then heated under reflux for 36 h.

The reaction mixture was cooled to r.t. and the solid was filtered off. THF was removed *in vacuo* and the resulting residue was dissolved in methanol (12 ml). A methanolic HCl solution (0.94 M; 30 ml) was added dropwise to the solution and the mixture was heated under reflux for 30 min. The azeotrope formed by methylborate and methanol (1:1) was distilled off under Ar atmosphere while the methanolic HCl solution was being added to the mixture. The addition rate was adjusted so that it was equal to the distillation rate. The process was continued until no borate ester existed in the distillate. Methanol was removed from the residue *in vacuo*. Then a methanolic KOH solution was added to the residue until the pH reached 14 (3.93 g KOH in 32 ml methanol). Methanol was again removed *in vacuo*. Anhydrous K_2CO_3 (20 g) was added to the residue and the resulting solid was extracted continuously with Et_2O in a Soxhlet extractor for 40 h. Removal of Et_2O from the extract gave the crude product (3.47 g, m.p. 89 - 99 °C). It was recrystallized from EtOAc (13 ml) to give the pure product (2.75 g, 47% yield). A second crop was also obtained by evaporating off 1 / 3 volume of the mother liquor and set it aside for crystallization (0.20 g, 4% yield). A 51% yield was obtained altogether.

***The product** was identical with the product obtained by Method 1.*

Synthesis of (3S,4S)-1-benzyl-3,4-dihydroxypyrrolidine (3.4) by reduction of compound 3.3 using a $NaBH_4$ / $BF_3{\cdot}Et_2O$ / diglyme system



3.3 **3.4**

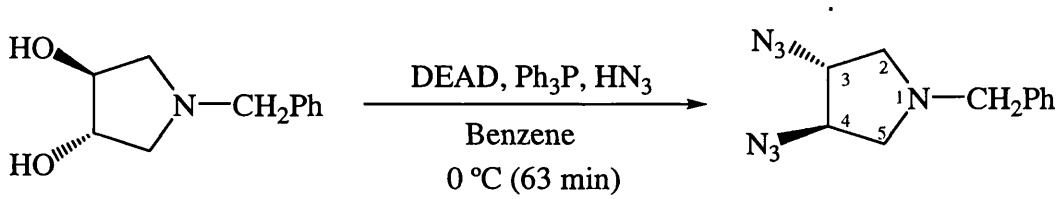
The reaction set-up consisted of a 2-L two-necked round bottomed flask equipped with a magnetic follower and a three-necked Claisen adapter to which a pressure equalizing addition funnel, a condenser, and a glass stopper were connected. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. Compound **3.3** (66 g, 0.3 mol), diglyme (600 ml) and $BF_3{\cdot}Et_2O$ (148 ml, 1.18 mol) were added to the flask and the resulting solution was cooled to 0 °C in an ice-water bath. $NaBH_4$ (30 g, 0.79 mol) was added in four equal portions with good stirring. The reaction mixture was brought to r.t. and then heated at 70 °C for 4 h.

The reaction mixture was cooled to r.t. 6 M HCl (400 ml) was added and the mixture was heated at 70 °C for 15 min. NaF (184 g, 4.38 mol) was added immediately with good stirring and the mixture was heated under reflux for 45 min. After cooling to r.t., NaOH solution (20%; 380 ml, 2.33 mol) was added. The solid and the aqueous phase were separated off. Removal of diglyme from the organic phase *in vacuo* gave a white solid (198.76 g). The solid was divided into two parts. One part was extracted continuously with Et_2O in a Soxhlet extractor for 45 h. The crystals which precipitated from the extract were collected by filtration (6.84 g, m.p. 100 - 101 °C. 12% yield). Removal of Et_2O from the filtrate *in vacuo* gave another batch of product (5.57 g, m.p. 98 - 100 °C).

The other part of the solid was dissolved in H_2O (240 ml). The aqueous solution was extracted continuously with Et_2O in a liquid-liquid extractor for 43 h. The crystals which precipitated from the ethereal extract were collected by filtration (23.67 g, m.p. 100 - 101 °C, 41% yield). Removal of Et_2O from the filtrate *in vacuo* gave some yellow solid (8.73 g). It was combined with the white solid from Soxhlet extraction (5.57 g, m.p. 98 - 100 °C) and recrystallized from EtOAc (15.5 ml) to give another batch pure product (10.46 g, m.p. 99 - 101 °C. 18% yield). A 71% yield was obtained altogether.

***The product** was identical with that prepared by the other methods.*

Attempt to synthesize (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (3.5) by use of the Mitsunobu reaction



3.4 **3.5**

Preparation of azidoic acid solution in benzene

(**Hazard note**: since azidoic acid is very poisonous, all reactions involving it should be carried out under a good hood)

Sodium azide (3.25 g, 50 mmol) and warm water (3.25 g, 180 mmol, 80 °C) were added to a three-necked round bottomed flask equipped with a magnetic stirrer, an addition funnel, a thermometer and a condenser. The mixture was stirred to form a paste, to which benzene (20 ml) was added. The mixture was cooled to 0 °C in an ice-water bath. Conc. H_2SO_4 (1.36 ml, 25mmol) was added dropwise with good stirring so that the reaction temperature was kept under 10 °C. After addition of the acid, the mixture was cooled to 0 °C. The solid was filtered off. The organic layer was

separated from the filtrate and dried over anhydrous Na_2SO_4 to provide a solution of azidoic acid in benzene.

The strength of the azidoic acid solution was determined by pipetting a small volume of the solution into a glass-stoppered bottle, shaking it with distilled water (40 ml), and titrating with a standard NaOH solution (0.2030 M) using phenolphthalein as indicator.

- Result:

  The volume of azidoic acid solution pipetted: a) 0.70 ml; b) 0.47 ml.

  The volume of the standard NaOH solution used: a) 5.50 ml; b) 4.00 ml.

  The average strength of the azidoic acid solution was determined as: 1.6 M.

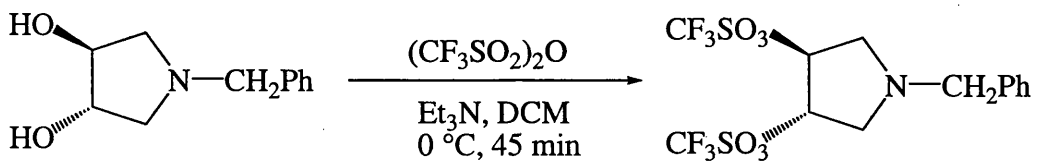
Attempt to Synthesize (3R,4R)-1-benzyl-3 4-diazidopyrrolidine (3.5)

The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower, an addition funnel and a glass stopper. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. Triphenylphosphine (0.624 g, 2.38 mmol) and dry benzene (7 ml) were added to the flask and the solution was cooled to 0 °C in an ice-water bath. A solution of DEAD (0.396 g, 2.28 mmol) in dry benzene (2 ml) was added dropwise over 18 min with good stirring. After the addition, the mixture was stirred for a further 25 min. A solution of azidoic acid in benzene (1.6 M; 1.43 ml, 2.29 mmol) was added dropwise over 10 min and the mixture was stirred for another 10 min. Compound **3.4** (0.204 g, 1.04 mmol) was added in one portion. The reaction mixture was brought to r.t. and stirred for 16 h.

The solid was filtered off and the solvent was removed from the filtrate *in vacuo*. The residue was separated by column chromatography [silica gel: 15g; eluting solvent: hexane / diisopropyl ether / chloroform (100 : 2.5 : 2.5 ~ chloroform / methanol (2 : 1)]. After combination of the fractions with the same R_f and removal of the solvent *in vacuo*, four separate components were obtained, but none of them showed NMR spectra corresponding to the desired product (compound **3.5**).

Synthesis of (3S,4S)-1-benzyl-3,4-bis(trifluoromethylsulfonyloxy)pyrrolidine (3.6)

(Method 1)



3.4 **3.6**

Drying and purification of triethylamine

Triethylamine (40 ml) and CaH_2 (2 g) were added to a two-necked round bottomed flask equipped with a magnetic follower, a condenser and a glass stopper. The mixture was heated under reflux for 3 h, and then distilled under an Ar atmosphere. The fraction of b. p. 89 - 91 °C was collected.

Method

The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower and capped with two septa. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. Compound **3.4** (0.97 g, 5 mmol), dry DCM (30 ml) and triethylamine (1.4 ml, 10 mmol) were added to the flask and the solution was cooled to 0 °C in an ice-water bath. Triflic anhydride (1.6 ml, 10 mmol) was added slowly by syringe. The reaction mixture was stirred at 0 °C for 45 min.

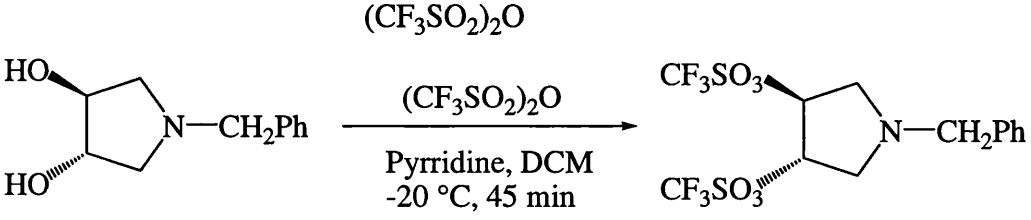
H_2O (2 ml) was added to the reaction mixture, which was then stirred for 10 min. The mixture was brought to r.t. and separated into two layers. The DCM layer was extracted with H_2O (2 ×10 ml) and then stirred vigorously with 1 M HCl (18 ml, 18 mmol) at 0 °C for 1 min. The acidic aqueous layer was separated off (it did not contain the desired product). The DCM layer was dried over anhydrous $MgSO_4$ and filtered. Removal of DCM from the filtrate *in vacuo* gave some dark red viscous oil (1.92 g) which was then dissolved in DCM (30 ml). The resulting DCM solution was divided into two equal parts: Part 1 and Part 2. Part 1 was shaken with 1M HCl (12 ml,

12 mmol) for 4 min in a separatory funnel. The aqueous layer was separated off (it did not contain the desired product). The DCM layer was dried over anhydrous $MgSO_4$ and filtered. Removal of DCM from the filtrate *in vacuo* gave some dark red viscous oil (0.77 g). It was purified by column chromatography (adsorbent: silica 60, 12 g; a gradient elution method was applied, eluting solvent: hexane / ethyl acetate = 100 / 0 ~ 1 / 4) to give the product (0.1 g, 4 % isolated yield). The product was found to be unstable and decompose rapidly upon exposure to air at r.t.

DCM was removed from Part 2 *in vacuo*. The residue was purified by column chromatography (adsorbent: silica 60, 12 g; a gradient elution method was applied, eluting solvent: hexane / ethyl acetate = 100 / 0 ~ 1 / 4) to give the product (0.12 g, 5 % isolated yield). The product was found to be unstable and decompose rapidly upon exposure to air at r.t.

TLC (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}):
$R_f = 0.69$ (developing solvent: hexane / ethyl acetate = 3 / 2).
NMR (The NMR spectra were very complicated. They showed the presence of impurities which might be due to decomposition of the product).
IR
ν_{max} (cm^{-1}): 3036 (Ph-H); 2917 / 2849 (CH); 1422 / 1191 (-SO_2-O); 1394; 1138; 1085; 1028; 961; 907; 738; 699; 639; 611; 583.
MS
m/z (EI): 457 (M^+, 3%); 91 ($C_7H_7^+$, 100%).
m/z (CI, NH_3): 458 ($[M+H]^+$, 10%); 158 (100%); 108 (62%).

Synthesis of (3S,4S)-1-benzyl-3,4-bis(trifluoromethylsulfonyloxy)pyrrolidine (3.6) (*Method 2*)



3.4 **3.6**

Drying and purification of pyridine

Pyridine (100 ml) and CaH_2 (5 g) were added to a 250-ml round bottomed flask. The mixture was heated under reflux over 3 h, and then distilled onto 4 A molecular sieves under an Ar atmosphere. The fraction of b. p. 114 - 115 °C was collected.

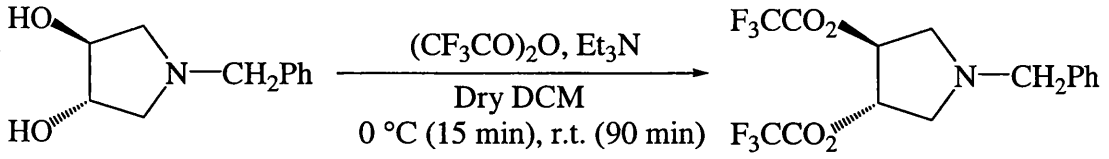
Method

The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower and capped with two septa. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. Compound **3.4** (1.03 g, 5.3 mmol), dry pyridine (1.2 ml, 14 mmol) and dry DCM (37 ml) were added to the flask and the solution was cooled to -20 °C in a solid CO_2 - acetone cooling bath. Triflic anhydride (2.0 ml, 12.2 mmol) was added slowly by syringe. After addition, the reaction mixture was stirred for 45 min at -20 °C.

The reaction mixture was brought to r.t. The solid was filtered off and the solvent was removed from the filtrate *in vacuo*. The resulting residue was purified by column chromatography (adsorbent: silica 60, 12 g; eluting solvent: hexane / ethyl acetate = 100 / 0 ~ 3 / 2) to give the product (0.16 g, 7% yield). The product was found to be unstable and decompose rapidly upon exposure to air at r.t.

TLC (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}):
$R_f = 0.70$ (developing solvent: hexane / ethyl acetate = 3 / 2).
NMR (The NMR spectra were very complicated. They showed the presence of impurities which might be due to decomposition of the product).
IR
ν_{max} (cm^{-1}): 3036 (Ph-H); 2749 (CH); 1426 / 1210 (-SO_2-O); 1278; 1169; 1135; 1026; 963; 895; 839; 758; 701; 637; 607; 575.
MS
m/z (EI): 457 (M^+, 1%); 91 ($C_7H_7^+$, 100%); 69 (65%).
m/z (CI, NH_3): 458 ($[M+H]^+$, 50%); 340 (100%); 158 (85%).

Attempt to synthesize (3S,4S)-1-benzyl-3,4-bis(trifluoroacetoxy)pyrrolidine (3.7)

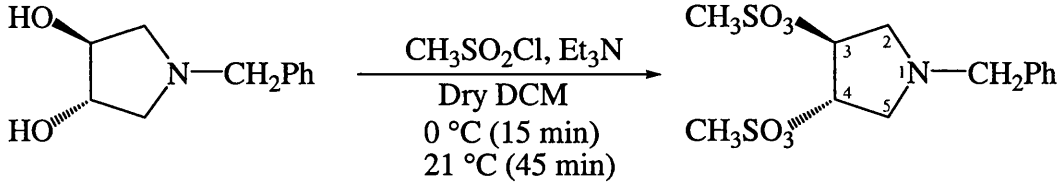


3.4 **3.7**

The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower and capped with a septum and a glass stopper. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. Compound **3.4** (1.93 g, 10 mmol), dry DCM (7 ml) and Et_3N (2.8 ml, 20 mmol) were added to the flask and the mixture was cooled to 0 °C in an ice-water bath. TFAA (2.8 ml, 20 mmol) was added slowly by syringe. The reaction mixture was stirred at 0 °C for 15 min, then brought to r.t. and stirred for a further 90 min.

The reaction mixture was extracted with water (2 × 3.6 ml). The aqueous extracts were separated off (it did not contain the desired product). The DCM layer was shaken with 1 M HCl (36.2 ml, 36.2 mmol) vigorously for 1 min in a separatory funnel. The DCM layer was separated off (it did not contain the desired product). The aqueous layer was made strongly alkaline by adding a 20% NaOH solution (9 ml, 56.3 mmol) and then extracted with DCM (3 × 7 ml). The DCM extract was dried over anhydrous $MgSO_4$ and filtered. Removal of DCM from the filtrate *in vacuo* gave a little yellow solid (0.1 g; confirmed to be the starting material **3.4** by tlc, IR, NMR and MS).

Synthesis of (3S,4S)-1-benzyl-3,4-bis(methylsulfonyloxy)pyrrolidine (3.8)



3.4 **3.8**

The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower, a septum and a glass stopper. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. Compound **3.4** (1.95 g, 10 mmol), dry DCM (7 ml) and Et_3N (2.8 ml, 10 mmol) were added to the flask and the mixture was cooled to 0 °C in an ice-water bath. Mesyl chloride (1.55 ml, 20 mmol) was added slowly by syringe. The reaction mixture was stirred at 0 °C for 15 min and then stirred for another 45 min at r.t.

The reaction mixture was extracted with water (2 × 3.6 ml). The DCM phase was then shaken with 1 M HCl (36.2 ml, 36.2 mmol) vigorously in a separatory funnel for 1 min. The DCM layer was separated off. The aqueous layer was made strongly alkaline (pH: 12 - 14) by adding a 20% NaOH solution (7 ml, 43.8 mmol) and then extracted with DCM (3 × 7 ml). The DCM extract was dried over anhydrous $MgSO_4$ and filtered. Removal of DCM from the filtrate *in vacuo* gave some yellow viscous oil (3.14 g), which solidified on standing. It was recrystallized from ethanol (4.8 ml) to give the product (2.78 g, 80% yield).

TLC (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}):
R_f = 0.19 (developing solvent: hexane / ethyl acetate = 3 / 2).

NMR

δ_H (400MHz, $CDCl_3$): 2.77 (dd, 2H, **H**-2^a, **H**-5^a, ^2J = 11 Hz, ^3J = 4 Hz); 3.08 (s, 6H, CH_3-); 3.11 (dd, 2H, **H**-2^b, **H**-5^b, ^2J = 11 Hz, ^3J = 4 Hz); 3.63 (d, 1H, **H**^{a} of PhC**H**^{a}**H**^{b}, ^2J = 13 Hz); 3.67 (d, 1H, **H**^{b} of PhC**H**^{a}**H**^{b}, ^2J = 13 Hz); 5.14 (apparent triplet, 2H, **H**-3, **H**-4, ^3J = 4 Hz); 7.26 - 7.36 (m, 5H, Ar**H**).

δ_C (400MHz, $CDCl_3$): 38.7 (CH_3); 58.2 (**C**-2 and **C**-5); 59.5 (CH_2Ph); 83.0 (**C**-3 and **C**-4); 128.0 / 128.8 / 128.9 / 137.4 (carbons on the benzene ring).

IR

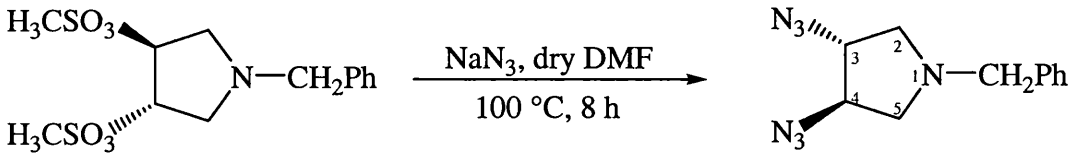
ν_{max} (cm^{-1}): 3029 (Ar-H); 2938 / 2807 (CH); 1601; 1582; 1496; 1454; 1354 / 1333 (-SO_2-); 1170 (-SO_2-O-); 958; 933; 899; 842; 809; 740; 701; 521.

MS

m/z (EI): 349 (M^+, 3%); 270 (24%); 158 (100%).

m/z (CI, NH_3): 350 ($[M+H]^+$, 100%).

Synthesis of (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (3.5) using sodium azide



3.8 **3.5**

The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower, a condenser and a stopcock capped with a septum. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. NaN_3 (4.74 g, 72.9 mmol) was added to the flask. A solution of compound **3.8** (4.25 g, 12.2 mmol) in dry DMF (54 ml) was added by syringe with good stirring. The reaction mixture was stirred at 100 °C for 8 h.

The reaction mixture was cooled to r.t. The solid was filtered off. H_2O (54 ml) was added to the filtrate and the mixture was extracted with Et_2O (5 × 54 ml). The combined ethereal extract was washed with brine (54 ml), dried over anhydrous $MgSO_4$ and filtered. Removal of Et_2O from the filtrate *in vacuo* gave some dark red oil (2.54 g). It was purified by column chromatography (adsorbent: silica 60, 50 g; eluting solvent: hexane / ethyl acetate = 3 / 1 ~ 3 / 2) to give the product (1.65 g; 56% yield).

TLC (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}):
$R_f = 0.71$ (developing solvent: hexane / ethyl acetate = 3 / 2).

NMR

δ_H (400MHz, $CDCl_3$): 2.67 (dd, 2H, **H**-2^a, **H**-5^a, ^2J = 10 Hz, ^3J = 4 Hz); 3.04 (dd, 2H, **H**-2^b, **H**-5^b, ^2J = 10Hz, ^3J = 4 Hz); 3.69 (d, 1H, **H**^{a} of PhC**H**^{a}**H**^{b}, ^2J = 13 Hz); 3.74 (d, 1H, **H**^{b} of PhC**H**^{a}**H**^{b}, ^2J = 13 Hz); 3.93 (apparent triplet, 2H, **H**-3, **H**-4, ^3J = 4 Hz); 7.34 - 7.45 (m, 5H, Ar**H**).

δ_C (400MHz, $CDCl_3$): 58.1 (**C**-2 and **C**-5); 59.8 (CH_2Ph); 66.2 (**C**-3 and **C**-4); 127.8 / 128.9 / 129.1 / 138.3 (carbons on the benzene ring).

IR

ν_{max} (cm^{-1}): 3029 (Ar-H); 2919 / 2800 (CH); 2089 ($-N_3$); 1604; 1582; 1496; 1474; 1454; 1381; 1328; 1243; 1133; 1071; 1028; 958; 910; 738; 698; 554.

MS

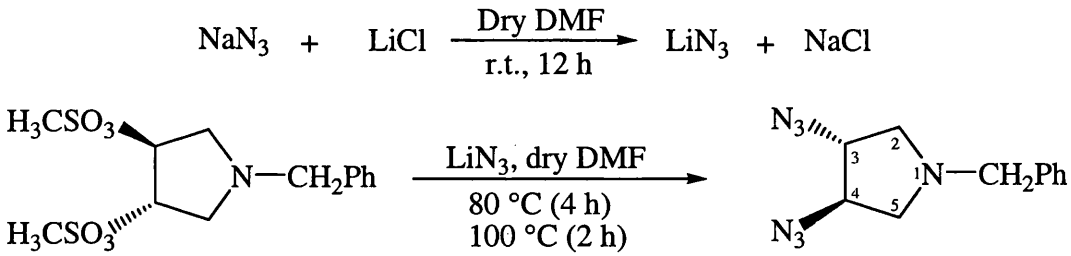
m/z (EI): 244 ($[M+H]^+$, 3%); 91 ($C_7H_7^+$, 45%); 42 (100%).

m/z (CI, NH_3): 244 ($[M+H]^+$, 100%); 158 (37%); 91 ($C_7H_7^+$, 26%).

Specific rotation

$[\alpha]_D^{27}$ = -90.7 (c 1.45, MeOH).

Synthesis of (3R,4R)-1-benzyl-3,4-diazidopyrrolidine (3.5) using lithium azide



3.8 **3.5**

The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower, a condenser and a stopcock capped with a septum. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. NaN_3 (4.74 g, 72.9 mmol), LiCl (3.09 g, 72.9 mmol) and dry DMF (44 ml) were added to the flask and the mixture was stirred at r.t. for 12 h. A solution of compound **3.8** (4.25 g, 12.2 mmol) in dry DMF (10 ml) was added to the mixture with good stirring. The reaction mixture was stirred at 80 °C for 4 h and then at 100 °C for 2 h.

The reaction mixture was cooled to r.t. The solid was filtered off. The filtrate was cooled to 0 °C, to which H_2O (54 ml) was added. The mixture was extracted with Et_2O (4 × 54 ml). The combined ethereal extract was washed with brine (54 ml), dried over anhydrous $MgSO_4$ and filtered. Removal of Et_2O from the filtrate *in vacuo* gave some dark red oil (2.39 g). It was purified by column chromatography (adsorbent:

silica 60, 40 g; eluting solvent: hexane / ethyl acetate = 6 / 1 ~ 3 / 1) to give the product (1.63 g; 55% yield).

***The product** was identical with the previously synthesized one using sodium azide except for a slightly higher measured specific rotation.*

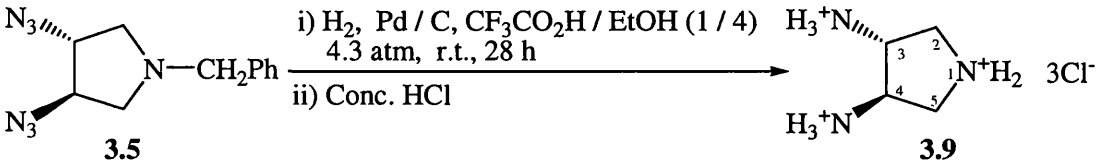
Specific rotation

$[\alpha]_D^{24}$ = -91.4 (c 1.17, MeOH).

HRMS

Found $[M+H]^+$: 244.1307; $C_{11}H_{14}N_7$ requires: 244.1305.

Synthesis of *trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt (3.9) by hydrogenation of the corresponding diazide 3.5



3.5 **3.9**

Pd / C (10%, 0.36 g, 0.34 mmol) was added to a hydrogenation reaction bottle. Then a solution of compound **3.5** (0.864 g, 3.55 mmol) in EtOH / CF_3CO_2H (4 / 1, 20 ml) was added. The mixture was hydrogenated on a *Parr 3911 Hydrogenation Apparatus* at 4.3 atm with vigorous shaking for 28 h at r.t.

The catalyst was removed by suction filtration through a pad of Celite® on a sintered glass funnel. Removal of solvent from the filtrate *in vacuo* gave some yellow solid (1.769 g), to which ethanol (4 ml) was added. Conc. HCl (1 ml, 12 mmol) was added to the solution and the mixture was stirred for a few minutes, then kept in a refrigerator for 1 h. The product was collected by suction filtration, washed with a little EtOH then a little Et_2O, and dried in a drying pistol overnight (0.613 g, 82% yield).

NMR

δ_H (400MHz, D_2O): 3.41 (dd, 2H, **H**-2^a, **H**-5^a, ^2J = 13 Hz, ^3J = 6 Hz); 3.84 (dd, 2H, **H**-2^b, **H**-5^b, ^2J = 13 Hz, ^3J = 6 Hz); 4.14 (m, 2H, **H**-3, **H**-4).

δ_C (400MHz, D_2O): 47.4 (**C**-2, **C**-5); 52.1 (**C**-3, **C**-4).

IR

ν_{max} (cm^{-1}): 2848 / 2781 (br., $=N^+H_2$, $-NH_3^+$); 1588 / 1561 / 1472 ($-NH_3^+$, $=N^+H_2$); 1397; 1356; 1190; 1060; 1017; 939; 859; 639; 572.

MS

m/z (CI, NH_3): 102 ([M - 3 HCl + H]$^+$, 100%).

m/z (ES^+): 102 ([M - 3 HCl + H]$^+$, 100%).

m/z (ES^-): 37 (37%) / 35 (Cl^-, 100%).

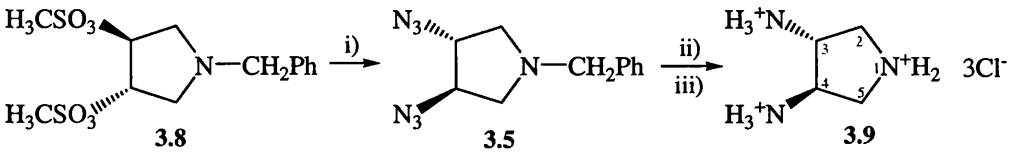
HRMS

Found [M - 3 HCl + H]$^+$: 102.1026; $C_4H_{12}N_3$ requires: 102.1026.

Specific rotation

$[\alpha]_D^{26}$ = -15.0 (c 1.33, H_2O).

Synthesis of *trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt (3.9) from (3S,4S)-1-benzyl-3,4-bis(methylsulfonyloxy)pyrrolidine (3.8)



i) NaN_3, dry DMF, 100 °C (6 h), r.t. (14 h); ii) H_2, Pd / C, CF_3CO_2H / EtOH (1 / 4), 4.3 atm, r.t., 30 h; iii) Conc. HCl.

The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower, a condenser and a stopcock capped with a septum. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. NaN_3 (3.556 g, 54.7 mmol) was added to the flask. A solution of compound **3.8** (3.823 g, 10.9 mmol) in dry DMF (48 ml) was added by syringe with good stirring. The mixture was stirred at 100 °C for 6 h then at r.t. for 14 h.

The solid was filtered off. H_2O (48 ml) was added to the filtrate and the mixture was extracted with Et_2O (5 × 48 ml). The combined ethereal extract was washed with brine (48 ml), dried over anhydrous $MgSO_4$ and filtered. A small portion of ethereal solution (1.5 ml) was taken and set aside until the solvent evaporated. The residue was characterized by ^{1}HNMR and IR to analyses the efficiency of the diazide formation.

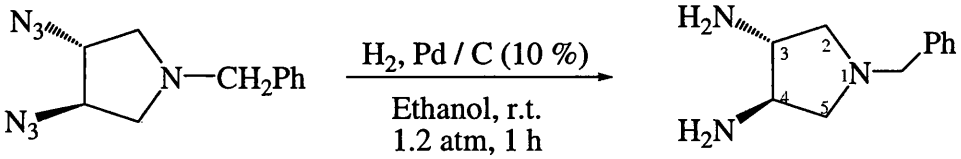
The main portion of the ethereal solution was concentrated *in vacuo* to a volume of about 50 ml. It was then diluted with EtOH / CF_3CO_2H (4 / 1, 40 ml). The solution was transferred to a hydrogenation reaction bottle which contained Pd / C (10%, 1.003 g) as the catalyst. The mixture was hydrogenated on a *Parr 3911 Hydrogenation Apparatus* at 4.3 atm with vigorous shaking for 30 h at r.t. The catalyst was removed by suction filtration through a pad of Celite® on a sintered glass funnel. Removal of solvent from the filtrate *in vacuo* gave some viscous oil (9.07g). Conc. HCl (3 ml) was added to the residue and the mixture was stirred for a few minutes. The product was collected by suction filtration, washed with a little EtOH then a little Et_2O, and dried in a drying pistol overnight (white solid; 1.09 g; 47% yield).

***The product** was identical to that produced previously except for a slightly higher measured specific rotation.*

Specific rotation

$[\alpha]_D^{26} = -16.8$ (c 1.34, H_2O).

Synthesis of *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine (3.10) by hydrogenation of the corresponding diazide 3.5 in ethanol



3.5 **3.10**

Pd / C (10%, 75 mg) was added to a hydrogenation reaction bottle. Then a solution of compound **3.5** (0.562 g, 2.31mmol) in EtOH (20 ml) was added. The mixture was hydrogenated on a *Parr 3911 Hydrogenation Apparatus* at 1.2 atm for 1 h at r.t. with vigorous shaking. The catalyst was removed by suction filtration through a pad of Celite® on a sintered glass funnel. Removal of solvent from the filtrate *in vacuo* and drying of the resulting residue in a vacuum desiccator gave the product (0.445 g, 100% yield).

NMR

δ_H (400MHz, $CDCl_3$): 1.55 (br, 4H, -NH_2); 2.23 (dd, 2H, **H**-2^a, **H**-5^a, ^2J = 9 Hz, ^3J = 4 Hz); 2.87 (dd, 2H, **H**-2^b, **H**-5^b, ^2J = 9 Hz, ^3J = 4 Hz); 2.96 (m, 2H, **H**-3, **H**-4); 3.50 (d, 1H, **H**^{a} of PhC**H**^{a}**H**^{b}, ^2J = 13 Hz); 3.57 (d, 1H, **H**^{b} of PhC**H**^{a}**H**^{b}, ^2J = 13 Hz); 7.11 - 7.32 (m, 5H, Ar**H**).

δ_C (400MHz, $CDCl_3$): 60.7 (**C**-2 and **C**-5); 61.4 (**C**-3 and **C**-4); 62.5 (CH_2Ph); 127.3 / 128.6 / 129.1 / 139.2 (carbons on the benzene ring).

IR

ν_{max} (cm^{-1}): 3348 / 3277 (-NH_2); 3027 (Ar-H); 2912 / 2791 (CH); 1601 (-NH_2); 1587; 1495; 1453; 1373; 1337; 1143; 1072; 1028; 871; 818; 738; 698.

MS

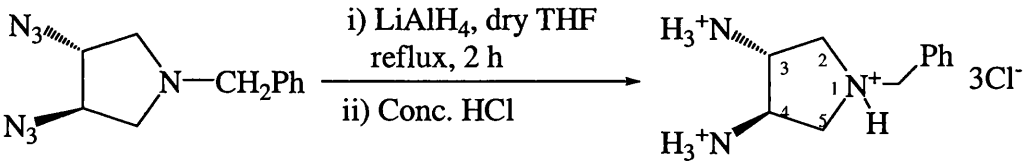
m/z (EI): 191 (M^+, 1%); 91 ($C_7H_7^+$, 100%); 42 (35%).

m/z (CI, NH_3): 192 ($[M+H]^+$, 100%); 106 (20%).

Specific rotation

$[\alpha]_D^{27}$ = -47.9 (c 1.28, MeOH).

Synthesis of *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine trihydrochloride salt (3.11) by reduction of the corresponding diazide (3.5) using $LiAlH_4$



3.5 **3.11**

The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower, a condenser and a stopcock capped with a septum. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. $LiAlH_4$ (0.250 g, 6.59 mmol) and dry THF (2.5 ml) were added to the flask. A solution of compound **3.5** (0.597 g, 2.45 mmol) in dry THF (7.5 ml) was added to the flask slowly by syringe with good stirring. After addition, the mixture was heated under reflux for 2 h.

The reaction mixture was cooled to 0°C in an ice-water bath and 1 M NaOH solution (2 ml) was added dropwise until the pH reached 12. H_2O (2 ml) was then added. The solid formed was filtered off. Removal of solvent from the filtrate *in vacuo* gave some oil (0.674 g). EtOH (10 ml) was added to the oil and the suspension was stirred for 10 min. The solid was filtered off. The filtrate was concentrated *in vacuo* to a volume of about 2 ml, to which conc. HCl (1 ml) was added. The product was collected by suction filtration, washed with a little EtOH then a little Et_2O, and dried in a drying pistol overnight (0.422 g, 58% yield). A second crop was also obtained from the mother liquor (0.049 g, 8% yield). A yield of 66% was obtained altogether.

NMR

δ_H (400MHz, D_2O): 3.58 (m, 2H, **H**-2^a, **H**-5^a); 3.96 (m, 2H, **H**-2^b, **H**-5^b); 4.30 (m, 2H, PhC**H**$_2$-); 4.45 (m, 2H, **H**-3, **H**-4); 7.38 - 7.49 (m, 5H, Ar**H**).

δ_C (400MHz, D_2O): 51.6 (**C**-3 and **C**-4); 54.6 (**C**-2 and **C**-5); 59.5 (**C**H_2Ph); 129.9 / 130.8 (carbons on the benzene ring; due to poor resolution, only two peaks were observed).

IR

ν_{max} (cm^{-1}): 2989 / 2887 / 2630 / 2543 (br. $\equiv N^+H$, $-NH_3^+$, CH); 1595; 1488; 1423; 1330; 1214; 1176; 1101; 1075; 1056; 1029; 952; 753; 699; 635.

MS

m/z (EI): 192 ([M - 3 HCl + H]$^+$, 1%); 91 ($C_7H_7^+$, 100%); 42 (78%).

m/z (CI, NH_3): 192 ([M - 3 HCl + H]$^+$, 100%).

HRMS

Found [M - 3 HCl + H]$^+$: 192.1496; $C_{11}H_{18}N_3$ requires: 192.1495.

Specific rotation

$[\alpha]_D^{24} = -6.77$ (c 0.99, H_2O).

3.5 References for *Chapter 3*

1. J. Skarzewski and A. Gupta. *Tetrahedron: Asymmetry*, 1997, 8, 1861.
2. U. Nagel, E. Kinzel, J. Andrade and G. Prescher. *Chem. Ber.*, 1986, 119, 3326.
3. U. Nagel. *Angew. Chem. Int. Ed. Engl.*, 1984, 23, 435.
4. a) C. F. Lane. *Chem. Rev.,* 1976, 76, 773; b) H. C. Brown, Y. M. Choi and S. Narasimhan. *J. Org. Chem.,* 1982, 47, 3153. And references cited therein.
5. a) U. Nagel. *Angew. Chem.,* 1984, 96, 425; b) S. Takano, Y. Sugihara and K. Ogasawara. Heterocycles, 1992, 34, 1519; c) Y. Arakawa and S. Yoshifuji. *Chem. Pharm. Bull.,* 1991, 39, 2219;
6. a) D. W. P. M. Loewik, D. M. Weingarten, M. Broekema, A. J. Brouwer, C. W. Still and R. M. J. Liskamp. *Angew. Chem. Int. Ed. Engl.*, 1998, 37, 1846; b) Y. K. Kang, J. K. Shin, K. H. Yoo, K. J. Seo and S. Y. Park. *Bioorg. Med. Chem. Lett.*, 1999, 9, 2385; c) A. J. Brouwer, H. J. Linden and R. M. J. Liskamp. *J. Org. Chem.,* 2000, 65, 1750.
7. A. S. B. Prasad, J. V. B. Kanth and M. Periasamy. *Tetrahedron,* 1992, 48, 4623.
8. C. Narayana and G. W. Kabalka. *Tetrahedron Lett.,* 1990, 31, 6977.
9. H. C. Brown. *Organic Synthesis via Boranes*. Wiley-Interscience: New York, 1975.
10. H. C. Brown and B. C. Subba. Rao. *J. Am. Chem. Soc.,* 1960, 82, 681.
11. O. Mitsunobu. *Synthesis,* 1981, 1.
12. a) D. R. Reddy and E. R. Thornton. *J. Chem. Soc., Chem. Commun.,* 1992, 172; b) J. Skarzewski and E. Daniluk. *Monatsh. Chem.,* 1983, 114, 1071; c) H. Ohrui, T. Misawa and H. Meguro. *J. Org. Chem.,* 1985, 50, 3007; d) R. K. Olsen, K. L. Bhat and R. B. Wardle. *J. Org. Chem.,* 1985, 50, 896.
13. H. Loibner and E. Zbiral. *Helv. Chim. Acta.*, 1976, 59, 2100.
14. M. C. Viaud and P. Rollin. *Synthesis, 1990, 130.*
15. B. Lal, B. N. Pramanik, M. S. Manhas and A. K. Bose. *Tetrahedron Lett.,* 1997, 1977.
16. H. Wolff. *Organic Reactions*, Ed. R. Adams. John & Sons: New York, 1947, 3,

327.

17. P. J. Stang, M. Hanack and L. R. Subramanian. *Synthesis*, 1982, 85.
18. a) R. W. Binkley, M. G. Ambrose and D. G. Hehemann. *J. Org. Chem.*, 1980, 45, 4387; b) R. Ranganathan. *Tetrahedron Lett.*, 1977, 1291; c) S. Knapp, A. B. J. Naughton, C. Jaramilo and B. Pipik. *J. Org. Chem.*, 1992, 57, 7328; d) T. G. Hansson and J. O. Kihlberg. *J. Org. Chem.*, 1986, 51. 4490; e) J. C. Dho, G. W. J. Fleet, J. M. Peach, K. Prout and P. W. Smith. *Tetrahedron Lett.*, 1986, 27, 3203.
19. I. L. Baraznenok, V. G. Nenajdenko and E. S. Balenkova. *Tetrahedron,* 2000, 56, 3077.
20. Diéguez, A. Ruiz, C. Claver, M. M. Pereira and A. M. d'A. R. Gonsalves. *J. Chem. Soc., Dalton Trans.,* 1998, 3517.
21. M. B. Smith and J. March. *Advanced Organic Chemistry: Reactions, Mechanisms and Structure,* 5th Edn. Wiley & Sons: New York, 2001, 2000.
22. R. K. Crossland and K. L. Servis. *J. Org. Chem.*, 1970, 35, 3195.
23. J. F. King and T. W. S. Lee. *J. Am. Chem. Soc.,* 1969, 91, 6524.
24. E. F. V. Scriven and K. Turnbull. *Chem. Rev.*, 1988, 88, 297.
25. T. Sasaki, S. Eguchi, N. Toi, T. Okano and Y. Furukawa. *J. Chem. Soc., Perkin Trans.,* 1983, 1, 2529.
26. D. Kuppert, J. Sander, C. Roth, M. Wörle, T. Weyhermüller, G. J. Reiss, U. Schilde, I. Müller and K. Hegetschweiler. *Eur. J. Inorg. Chem.,* 2001, 2525.
27. J. Leonard, B. Lygo and G. Procter. *Advanced practical organic chemistry*, 2nd Edn. Chapman &Hall, 1995.
28. C. G. Dubois and M. Hesse. *Tetrahedron Lett.,* 1995, 36, 7427.
29. H. Sasaki and T. Katsuki. *Tetrahedron,* 1994, 50, 11835.
30. R. G. Konsler, J. Karl and E. N. Jacobsen. *J. Am. Chem. Soc.,* 1998, 120, 10780.
31. B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tactchell. *Vogel's Textbook of Practical Organic Chemistry,* 5th Edn. Longman: Harlow, 1989.

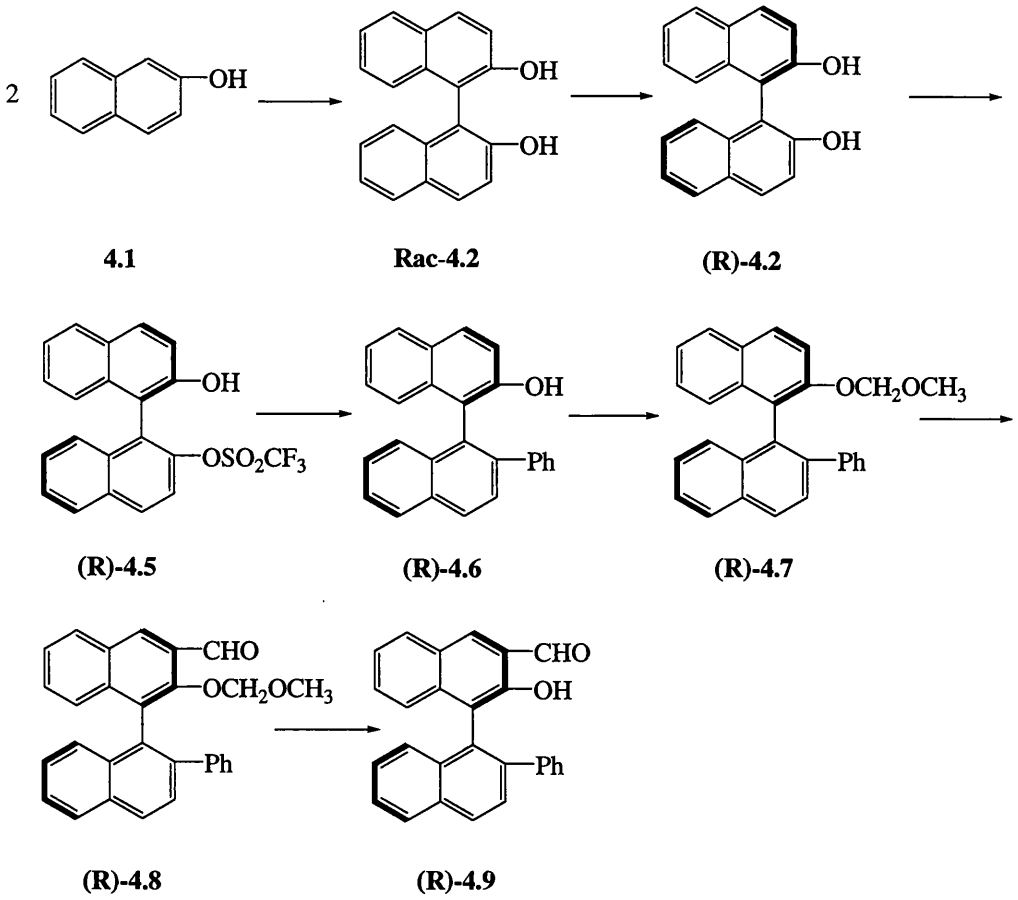
CHAPTER FOUR

SYNTHESIS OF (R)-3-FORMYL-2-HYDROXY-2'-PHENYL-1,1'-BINAPHTHALENE

4.1 Introduction

As described in *Chapter 2*, optically pure (R)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene (named as **2.8** in *Chapter 2*) would be used as the chiral salicylaldehyde derivative for construction of the target salen ligands and the corresponding (salen)Mn(III) complexes.

(R)-3-Formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene is not commercially available. The proposed synthetic route involved a multi-step synthesis (Scheme 4.1).



Scheme 4.1

Racemic 2,2'-dihydroxy-1,1'-binaphthalene (Rac-**4.2**) would be synthesized from 2-naphthol (**4.1**) by an oxidative coupling reaction. Rac-**4.2** would then be resolved into both of its enantiomers. In this project, compound (R)-**4.2** would be used for further transformations. Compound (R)-**4.5** would be synthesized from compound (R)-**4.2** by conversion of one of its hydroxyl groups to a triflate functional group.

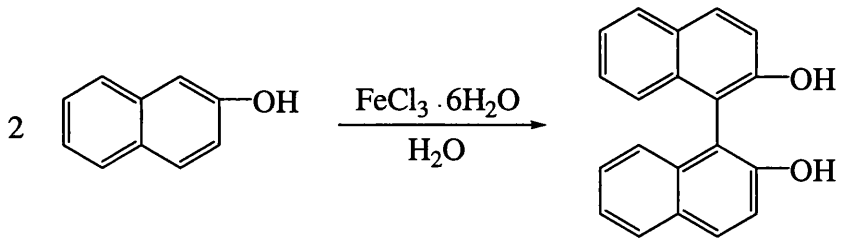
Compound (R)-**4.6** would be synthesized by treatment of compound (R)-**4.5** with a Grignard reagent. Then, the hydroxyl group of compound (R)-**4.6** would be protected by conversion to a methoxymethoxyl group (MOM) to give compound (R)-**4.7**. Formylation at the position *ortho-* to the MOM ether group would give compound (R)-**4.8**. Finally, regeneration of the hydroxyl group from compound (R)-**4.8** would give the target compound (R)-**4.9**.

4.2 Discussion and results

4.2.1 Synthesis of racemic 2,2'-dihydroxy-1,1'-binaphthalene (Rac-4.2)

Oxidative coupling of 2-naphthols represents a well established method for the preparation of binaphthols. The couplings are usually carried out by treatment of naphthols with excess of a metal, such as Fe(III), Mn(III) or Cu(II), in organic media[1] or in the solid state.[2] Catalytic processes have also been developed by the use of a $CuCl_2$-amine / AgCl system,[3] $FeCl_3$ in the solid state,[2] or CuCl(OH)·TMEDA complex.[4] The reactions in organic media were sometimes found to give quinones as by-products, and have other disadvantages, such as waste disposal problems and difficulties in isolation of the coupling product.[2,4]

K. Ding and co-workers reported an interesting method to prepare 2,2'-dihydroxy-1,1'-binaphthalene (Rac-**4.2**) by oxidative coupling of 2-naphthol (**4.1**), in which 2-naphthol was suspended in an aqueous $FeCl_3$ solution.[5] It was reported that the reaction proceeded much faster and more efficiently than those carried out in homogeneous solution. Therefore we decided to adopt such a method to prepare 2,2'-dihydroxy-1,1'-binaphthalene (Rac-**4.2**) (Scheme 4.2).



4.1 **Rac-4.2**

Scheme 4.2

4.2.1.1 Initial attempts

The first reaction was carried out following the literature procedure.[5] The molar ratio of Fe^{3+} to compound **4.1** was 2. The reaction conditions and the results are summarized in Table 4.1 (Entry 1).

Table 4.1 Initial attempts to synthesize Rac-4.2 by oxidative coupling of 2-naphthol (4.1) according to Scheme 4.2[a,b]

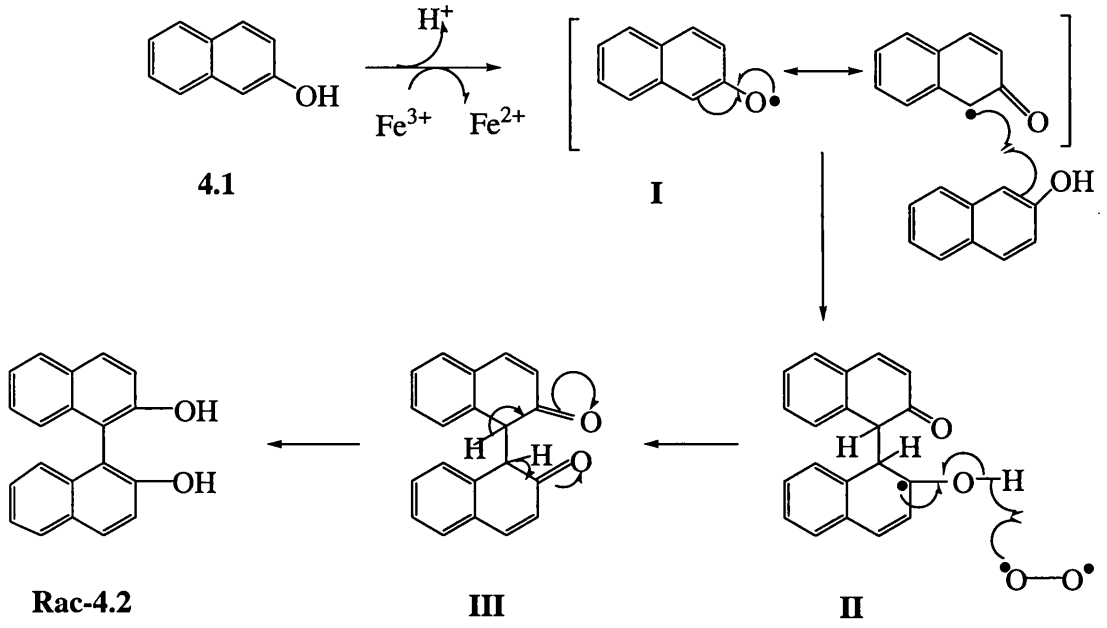
Entry	Temp. (°C)	Reaction Time (h)	Yield [c] (%)
1	50 (heating bath)	1	58
2	50 (internal)	3	56

a. The reactions were carried out on a 7 mmol scale of compound **4.1** in a two-necked round bottomed flask equipped with a condenser and a glass stopper. A magnetic stirrer was employed.
b. The isolated yield reported the in literature was 95%.
c. Isolated yield after recrystallization from toluene.

As can be seen from Table 4.1 (Entry 1), the yield obtained was much lower than that the literature claimed. Extending the reaction time to 3 h and changing the reaction temperature (the temperature of the reaction mixture should be lower than the temperature of the heating bath) did not lead to any increase in the yield of the product (Entry 2). In order to establish a highly practical and efficient procedure, it was decided that investigations must be made to find out which factor(s) influence the yield of the reaction.

4.2.1.2 Mechanistic considerations

The mechanism of the oxidative coupling of 2-naphthol has been proposed[2,5] as below (Scheme 4.3).



Scheme 4.3

The radical species **I** is formed from a one electron oxidation of 2-naphthol (**4.1**) with Fe^{3+}. It couples with another neutral 2-naphthol molecule to form a new C-C bond and generate radical species **II.** Radical **II** reacts with O_2, which abstracts a hydrogen atom, to give the intermediate **III.** The intermediate **III** tautomerizes to give the product (Rac-**4.2**).

Considering the heterogeneous nature of the reaction, it has been suggested that the reaction occurs at the surface of the crystalline 2-naphthol particles.[5] Therefore, the more easily Fe^{3+}, which is homogeneously dispersed in the aqueous solution, can contact with the surface of the crystalline 2-naphthol particles, the more efficiently the one electron oxidation procedure will occur. Also, the more easily the radical **II** can contact with oxygen, the more easily the hydrogen atom will be abstracted. As a result, factors, such as the molar ratio of oxidant (Fe^{3+}) to 2-naphthol, the surface area of the 2-naphthol particles, the reaction temperature, and the type of the reaction vessel, were anticipated to play important roles in determining the yield of the reaction.

Several experiments were carried out to try to work out the optimal conditions for the oxidative coupling reaction.

4.2.1.3 The influences of the surface area of 2-naphthol (4.1) particles and type of the reaction vessel on the yield of the product Rac-4.2

Two experiments were carried out to explore the influences of the surface area of starting material (2-naphthol) particles and type of the reaction vessel on the yield of the desired product.

The first experiment was carried out in a standard round-bottomed flask using untreated 2-naphthol. The molar ratio of Fe^{3+} to the starting material **4.1** was 2. The reaction mixture was stirred at 50 °C (internal temperature) for 3 h and was followed by hplc [column: APEX II, 5μ, ODS; solvent: MeOH / H_2O = 80 / 20; flow rate: 1 ml / min; UV (nm): 254; internal standard: naphthalene]. The yield of the product Rac-**4.2** was calculated as 44% from hplc results.

In the second experiment, an open beaker was used as the reaction vessel to provide a greater surface area of contact with air. The starting material (2-naphthol; 21 mmol) was pre-ground in a mortar prior to use. Furthermore, the reaction mixture was sonicated for 10 min at r.t. prior to being heated to 50 °C for 3 h. The hope was that these measures would break up the particles to provide greater surface area of contact with the Fe^{3+} solution and with O_2 in the air. The molar ratio of Fe^{3+} to 2-naphthol was also 2. These measures had a desirable effect; the yield of the product Rac-**4.2** was increased to 70% (calculated from hplc results).

Clearly, the surface area of the starting material (2-naphthol) particles and the type of the reaction vessel did have a significant influence on the yield of the product. Grinding the insoluble starting material (2-naphthol) into fine particles and using ultrasonic waves to further break up the particles increased their surface area and facilitated their contact with the oxidant (Fe^{3+}) solution, therefore facilitated the one electron oxidation procedure. Also, using a beaker as the reaction vessel to provide maximum contact between the reaction mixture and O_2 in the air favoured abstraction of a hydrogen atom from radical **II.** All these modifications led to an increase in the product yield.

Since it was clear that the use of pre-ground and sonicated 2-naphthol improved the yield of the desired product (Rac-**4.2**), it was possible that the reaction might proceed well even at r.t. Therefore, a controlled experiment was carried out to test this possibility.

4.2.1.4 The influence of the reaction temperature on the yield of the product Rac-4.2

One experiment was carried out to explore the influence of the reaction temperature on the yield of the product. The results are summarized in Table 4.2.

Table 4.2 Influence of reaction temperature on the yield of the product Rac-4.2[a]

Temp. (°C)	Reaction time (h)	Yield [b] (%)
r.t. [c]	2	47
r.t. [c]	3	47
50	2 [d]	79
50	3 [d]	82

a. Fe^{3+} / **4.1** (mol / mol) = 2. 2-Naphthol was finely powdered prior to use.
b. Calculated from hplc results using naphthalene as the internal standard.
c. Reaction was carried out in an ultrasonic bath at r.t.
d. The reaction vessel was moved out of the ultrasonic bath and heated to 50 °C. The reaction times refer to the time after being heated to 50 °C.

The reaction was carried out in a beaker. 2-Naphthol was finely powdered and the molar ratio of Fe^{3+} to 2-naphthol was 2. The reaction was first carried out at r.t. for 3 h in an ultrasonic bath with continuous sonication. However, it was found that the reaction proceeded slowly (Entry 1 and 2). So the reaction vessel was moved out of the ultrasonic bath and heated to 50 °C for a further 3 h.

It was likely that the ultrasonic waves would break up the solid into very fine particles, facilitating the contact between Fe^{3+} solution and the insoluble 2-naphthol particles. However, it was also probable that sonication would help to remove dissolved O_2 from the aqueous media, which might disfavour the abstraction of a hydrogen atom from radical **II** (see Scheme 4.3). The best option, it seemed, was to

sonicate the reaction mixture for a period of time, then heat it to 50 °C for reaction without sonication.

The yield was still not as high as hoped. Therefore, a series of experiments was carried out to see whether the amount of oxidant would affect the yield of the product.

4.2.1.5 The influence of the molar ratio of oxidant (Fe^{3+}) to 2-naphthol on the yield of the product Rac-4.2

The influence of the molar ratio of oxidant (Fe^{3+}) to 2-naphthol on the yield of the desired product Rac-**4.2** was also examined. The reactions were carried out on a 21 mmol scale of compound **4.1**. The results are summarized in Table 4.3.

Table 4.3 Influence of the amount of oxidant on the yield of the product Rac-4.2[a]

Entry	Fe^{3+} / **4.1** (mol / mol)	Reaction time (h)	Yield [b] (%)
1	2	5	81
2	3	5	89
3	4	4.5	95

a. The reactions were carried out in a beaker, which was sonicated in an ultrasonic bath for 30 min. Then it was moved out of the ultrasonic bath and heated to 50 °C for reaction. 2-Naphthol was finely powdered prior to use.
b. Calculated from hplc results using naphthalene as the internal standard.

As can be seen from Table 4.3, the yield of the product increased when the molar ratio of oxidant (Fe^{3+}) to 2-naphthol was increased, and was almost quantitative when the ratio was 4:1. The reaction was now sufficiently successful to be applied on a large scale for production of a stock of Rac-**4.2**.

4.2.1.6 A large scale synthesis of racemic 2,2'-dihydroxy-1,1'-binaphthalene (Rac-4.2) by oxidative coupling of 2-naphthol (4.1)

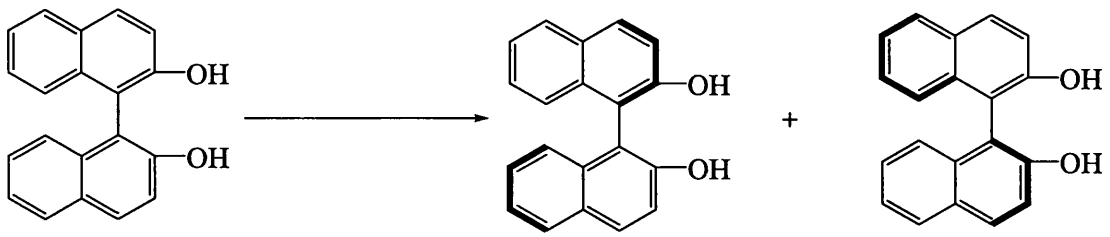
A larger scale experiment (200 mmol of 2-naphthol) was carried out under the optimised reaction conditions discussed above. The reaction was carried out in a 1-L beaker using a mechanical stirrer. The starting material 2-naphthol was finely powdered. The reaction mixture was sonicated in an ultrasonic bath for 30 min then moved out of the ultrasonic bath and heated at 50 °C for 9 h. The reaction was successful; the product was obtained in 82% yield after recrystallization from toluene. The detailed experimental procedure and characterization of the product are reported in the *Experimental Section* of this chapter.

In conclusion, racemic 2,2'-dihydroxy-1,1'-binaphthalene (Rac-**4.2**) was synthesized by the oxidative coupling of 2-naphthol (**4.1**) in an aqueous Fe^{3+} solution. Several factors that influence the yield of the reaction were investigated. The reaction was effectively applied to a larger scale synthesis and gave a yield of 82%.

Having successfully prepared Rac-**4.2**, the next step would be resolution of it into both of its enantiomers. This is reported in the next section.

4.2.2 Resolution of racemic 2,2'-dihydroxy-1,1'-binaphthalene (Rac-4.2)

A wide variety of methods has been reported for resolution of Rac-**4.2** into its enantiomers (Scheme 4.4). These include: a) enzymatic resolution;[6] b) separation of diastereomers using cinchonidinium derivatives,[7] a tartaric acid amide,[8] binaphthyl phosphoric acid,[9] boric acid derivatives;[10] or a copper complexes of chiral amines.[11] Among these methods, the most convenient method appeared to be the one introduced by Periasamy and co-workers, in which boric acid and (R)-(+)-α-methylbenzylamine were used as the resolving reagents.[12] One of the main advantages of this method is that the resolving reagents, both boric acid and optically pure α-methylbenzylamine, are commercially available. It was therefore decided to attempt the resolution using this method.

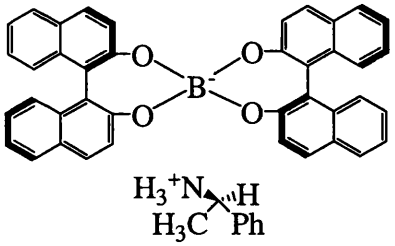


Rac-**4.2** (R)-**4.2** (S)-**4.2**

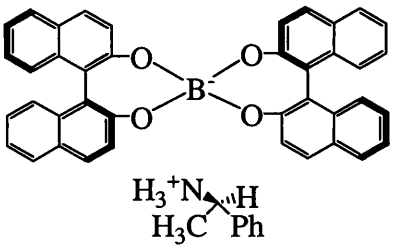
Scheme 4.4

4.2.2.1 Resolution of racemic 2,2'-dihydroxy-1,1'-binaphthalene (Rac-4.2) using boric acid and (R)-(+)-α-methylbenzylamine

The Periasamy method involves formation of diastereomeric complexes **4.2a** and **4.2b**. According to Periasamy, these two diastereomeric complexes have different solubility in THF and CH_3CN. Complex **4.2a** is insoluble in THF and complex **4.2b** is insoluble in CH_3CN.[12]



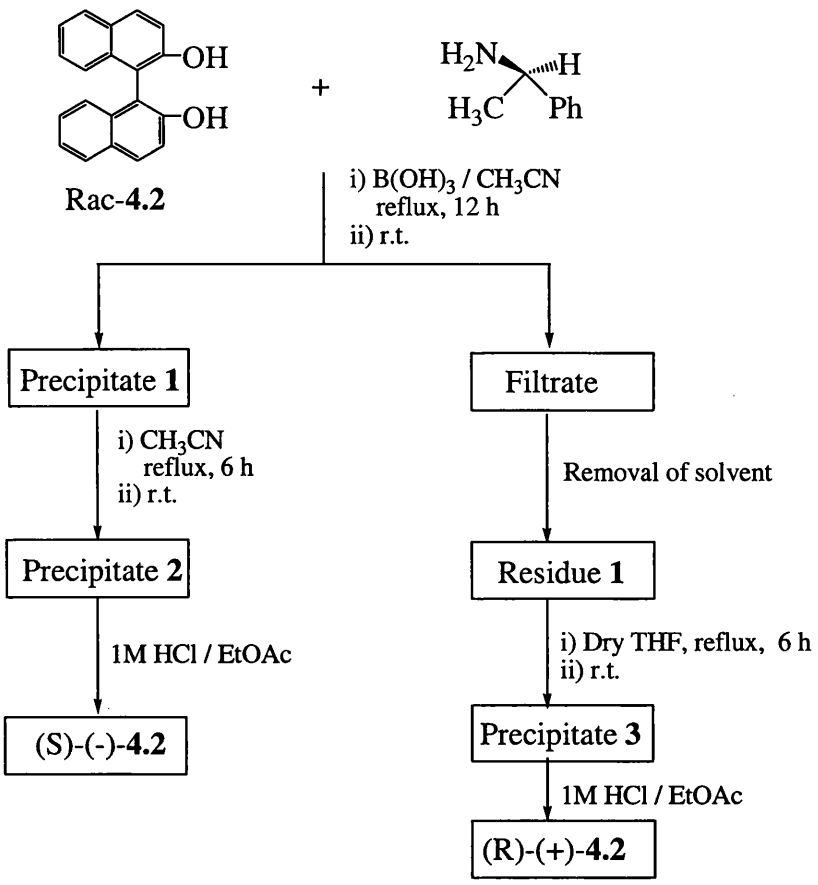
4.2a



4.2b

In Periasamy's work, these solubility differences were utilized to resolve the racemic **4.2**. It was claimed that both the (S) and (R) enantiomers of Rac-**4.2** could be obtained in optically pure form in good yields [for (R)-**4.2**: 26% yield, > 99% ee; for (S)-**4.2**: 35% yield, > 99% ee].[12]

In the present work, three experiments were carried out using this method. The experimental procedure is illustrated in Scheme 4.5.



Scheme 4.5

The first experiment was carried out following the literature procedure.[12] The reaction was carried out under an Ar atmosphere. The molar ratio of boric acid and (R)-(+)-α-methylbenzylamine to Rac-**4.2** (2.863 g; 10 mmol) were 0.5 and 1.5, respectively. However, the result was far from satisfactory. Only the (R) enantiomer was obtained in optically pure form, but in a low yield [11% yield; 22% of the theoretical yield of compound (R)-**4.2**; 98% ee; The ee value was based on $[\alpha]_D^{25}$ = -34.5 (c 1, THF)[12]]. During the experiment, it was found that Precipitate 1 (see Scheme 4.5) was obtained in more than the theoretical weight [3.81 g was obtained; 152% of the theoretical weight. The theoretical weight should be, in principle, half of the overall weight of all the reagents (2.50 g)]. This indicated that some of the complex **4.2a**, which was formed between (R)-**4.2** and boric acid and (R)-(+)-α-methylbenzylamine, had precipitated along with the complex **4.2b**. Also, the subsequent treatment of Precipitate 1 with refluxing CH_3CN failed to remove the co-precipitated complex **4.2a**. As a result, only partially resolved (S)-**4.2** was obtained (61% yield; 122% of the theoretical yield of compound (S)-**4.2**; 46% ee).

A second experiment was carried out on the same scale. But several modifications were made to try to improve the efficiency of the resolution. These included: a) the solvent was dried and freshly distilled prior to use; b) the temperature, at which Precipitate 1 precipitated from the reaction mixture, was increased to 28 °C from r.t. in the hope that the diastereomeric complex **4.2a** would remain in the solution instead of precipitating along with complex **4.2b**. Indeed, this time Precipitate 1 was obtained less than the theoretical weight (2.36 g, 95% of the theoretical weight). However, the resolution result was still unsatisfactory. The yield of the (R) enantiomer was only slightly increased (16% yield; 32% of the theoretical yield of compound (R)-**4.2**; 98% ee). The optical purity and yield of the (S) enantiomer were decreased (56% yield; 112% of the theoretical yield of compound (S)-**4.2**; 32% ee). The detailed experimental procedure is reported in the *Experimental Section* of this chapter.

The quality of the starting material (Rac-**4.2**) and the resolving reagents, boric acid and (R)-(+)-α-methylbenzylamine, were verified by their spectroscopic data, and in the case of (R)-(+)-α-methylbenzylamine also by its specific rotation. Therefore, the poor resolution results might indicate that the solubility differences of the diastereomeric complexes (**4.2a** and **4.2b**) in THF and CH_3CN might be not big enough for them to be separated from each other.

It was also claimed in the literature that when the experiment was carried out using 50 mmol of Rac-**4.2** and proportional amounts of other reagents, the enantiomers were obtained in > 99% ee without significant change in yields. A third experiment was therefore conducted at three times the scale (8.59 g of Rac-**4.2**; 30 mmol). However, a poorer resolution result was obtained, with comparable yields but very much lower optical purities [for (R)-**4.2**: 17% yield; 22% ee; for (S)-**4.2**: 77% yield; 6% ee].

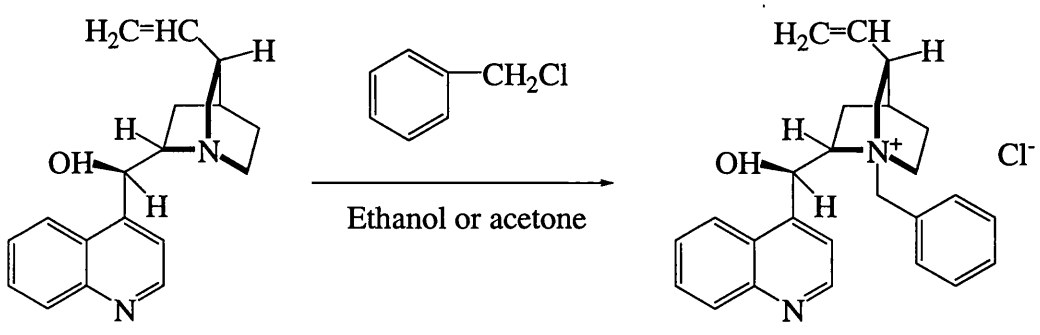
Since this resolution method only produced one optically pure enantimer in low yields, we decided to turn to another resolution method, in which (8S,9R)-(-)-*N*-benzylcinchonidinium chloride would be used as the resolving reagent.

4.2.2.2 Resolution of racemic 2,2'-dihydroxy-1,1'-binaphthalene (Rac-4.2) using (8S,9R)-(-)-*N*-benzylcinchonidinium chloride

As mentioned above, cinchonidinium derivatives have also been used to resolve racemic 2,2'-dihydroxy-1,1'-binaphthalene (**4.2**) with good results.[7] One disadvantage of this method is that the resolving reagent [(8S,9R)-(-)-*N*-benzylcinchonidinium chloride] is not commercially available. Fluka Ltd once produced this reagent, but when we were carrying out the research, there was no commercial product available. Fortunately, we had a small amount of this commercial product in hand, which could be used as an authentic sample to evaluate the quality of a synthesised product.

4.2.2.2.1 Synthesis of (8S,9R)-(-)-*N*-benzylcinchonidinium chloride (4.4)

The resolving reagent (8S,9R)-(-)-*N*-benzylcinchonidinium chloride (**4.4**) has been synthesized by reaction of (-)-cinchonidine (**4.3**) with benzyl chloride in two different solvent system, ethanol or acetone (Scheme 4.6).[13,14] Among these two methods, the one reported by Liu[13], in which the reaction was carried out in ethanol on a 100 mmol scale of (-)-cinchonidine (**4.3**) and the product was obtained in 72% yield after recrystallization from H_2O, appeared to be superior. It was therefore decided to use this method to synthesize the resolving reagent **4.4**. Two experiments were carried out using this method. The reaction conditions and the results are summarized in Table 4.4 (Entry 1 and 2).



4.3 **4.4**

Scheme 4.6

Table 4.4 Synthesis of resolving reagent (8S,9R)-(-)-*N*-benzylcinchonidinium chloride (4.4) according to Scheme 4.6 [a]

Entry	**4.3** (mmol)	Solvent [b] Type	Amount (ml)	Reaction time (h)	Yield[c] (%)	Results
1	20	Ethanol	200	20	73	Red-brown solid / [α] could not be measured [d]
2	20	Ethanol	56	7	71	Red-brown solid / [α] could not be measured [d]
3	10	Acetone	100	66	65	$[\alpha]_D^{23}$ = -173.1 (c 0.54, H_2O) [e]
4	50	Acetone	1250	139	48	$[\alpha]_D^{28}$ = -181.8 (c 0.51, H_2O) [e]

a. The reactions were carried out at reflux, i.e. approximately 78 °C in ethanol or 56 °C in acetone.
b. The solvents were dried and distilled prior to use.
c. Isolated yield.
d. The specific rotation could not be measured on a polarimeter due to the dark colour of the sample solution.
e. [Literature]: $[\alpha]_D^{20}$ = -175.4 (c 0.5, H_2O)[14]

The first experiment (Entry 1) was carried out following the literature procedure.[13] The molar ratio of benzyl chloride to compound **4.3** was 1.2. The concentration of compound **4.3** in dry ethanol was 0.1 M. It was observed that the reaction mixture turned to a dark red colour after 20 hours and red brown crystals were obtained after recrystallization twice from H_2O. The colour of the product was so dark that the specific rotation could not be measured on a polarimeter. As a result, the optical purity of the product could not be determined. However, the NMR spectra confirmed that the crystals obtained were mainly the desired product **4.4**. Tlc also showed the presence of the desired product (by co-spotting with the commercial product from Fluka Ltd.) and the presence of impurities corresponding to some compounds of dark colour.

When measuring the melting point of the commercial product (colourless crystals), we observed that the colour of the crystals turned darker and darker before they melted, and black liquid was obtained after the product melted. This

phenomenon indicated that the product might decompose at high temperature. Indeed, it has been reported that the product decomposes when being heated.[14]

It is therefore reasonable to assume that the dark colour of the product and the presence of impurities might be due to decomposition of the product at high reaction temperature (78 °C) and / or after prolonged reaction time (20 h). Lowering the reaction temperature or reducing the reaction time might solve the problem.

A second experiment was carried out in which the concentration of the starting material **4.3** was increased to 0.36 M in the hope that the reaction rate would increase and the reaction time would be reduced. Indeed, tlc reaction monitoring results showed the reaction was complete after 7 h (Entry 2). The product was obtained in a comparable yield (71%) after recrystallization from H_2O and characterised by NMR spectra. Unfortunately, the product was again in dark red colour. The specific rotation could again not be measured and tlc showed the presence of impurities corresponding to compound(s) of dark colour.

Since the reaction temperature seemed to play an important role in determining the quality of the product, we decided to use a low-boiling-point solvent instead of ethanol. Another synthetic method was therefore adopted; in which dry acetone was used as the solvent.[14] The reaction conditions and the results are summarized in Table 4.4 (Entry 3 and 4).

A third experiment (Entry 3) was carried out in which the concentration of starting material **4.3** was 0.1 M and the molar ratio of benzyl chloride to compound **4.3** was 1, as used in the literature procedure.[14] The product was obtained with a yield of 65% after recrystallization from H_2O and comprised colourless crystals. The NMR spectra and tlc (by co-spotting with the commercial product) confirmed that it was identical with the commercial product. The specific rotation of the product was a little lower than that of the commercial product {the specific rotation of the commercial product was measured as: $[\alpha]_D^{26}$ = -178.1 (c 0.52, H_2O)} and that claimed in the literature {$[\alpha]_D^{20}$ = -175.4 (c 0.5, H_2O)}.[14]

The third experiment showed that the reaction temperature and / or the nature of the solvent did have a significant influence on the quality of the product. The lower reaction temperature favoured the formation of the pure product and prevented it from decomposition. During the experiment, it was also observed that the starting material **4.3** did not totally dissolve in the acetone, which suggested that the amount of solvent used was insufficient.

A fourth experiment was designed based on the following criterion: since the starting material **4.3** is soluble in the acetone but the product **4.4** is not, the work-up and purification procedure would be simplified if the volume of the solvent was chosen to such an extent that the starting material would remain in solution throughout the reaction whereas the product would precipitate when it formed. Indeed, the volume of the acetone used in the fourth experiment was 2.5 times larger than that in the literature procedure. The reaction worked well. The work-up procedure was greatly simplified - a simple filtration sufficed. More importantly, the product was pure enough that no further purification procedure was needed. The NMR spectra and tlc (by co-spotting with the commercial product) confirmed that the product was identical with the commercial product. The specific rotation of the product was higher than that of the commercial product and that claimed in the literature (Entry 4). Also, the experiment was carried out on a relatively large scale (50 mmol of the starting material **4.3**). The detailed experimental procedure and characterization of the product **4.4** are reported in the *Experimental Section* of this chapter.

In conclusion, two different solvents were tried for synthesis of the resolving reagent (8S,9R)-(-)-*N*-benzylcinchonidinium chloride (**4.4**). A simple and highly practical method has been developed to prepare the pure product using acetone as the solvent. However, when ethanol was used as the solvent, the product was found to be contaminated with some dark coloured impurities, which were assumed to derive from decomposition of the product at high temperature.

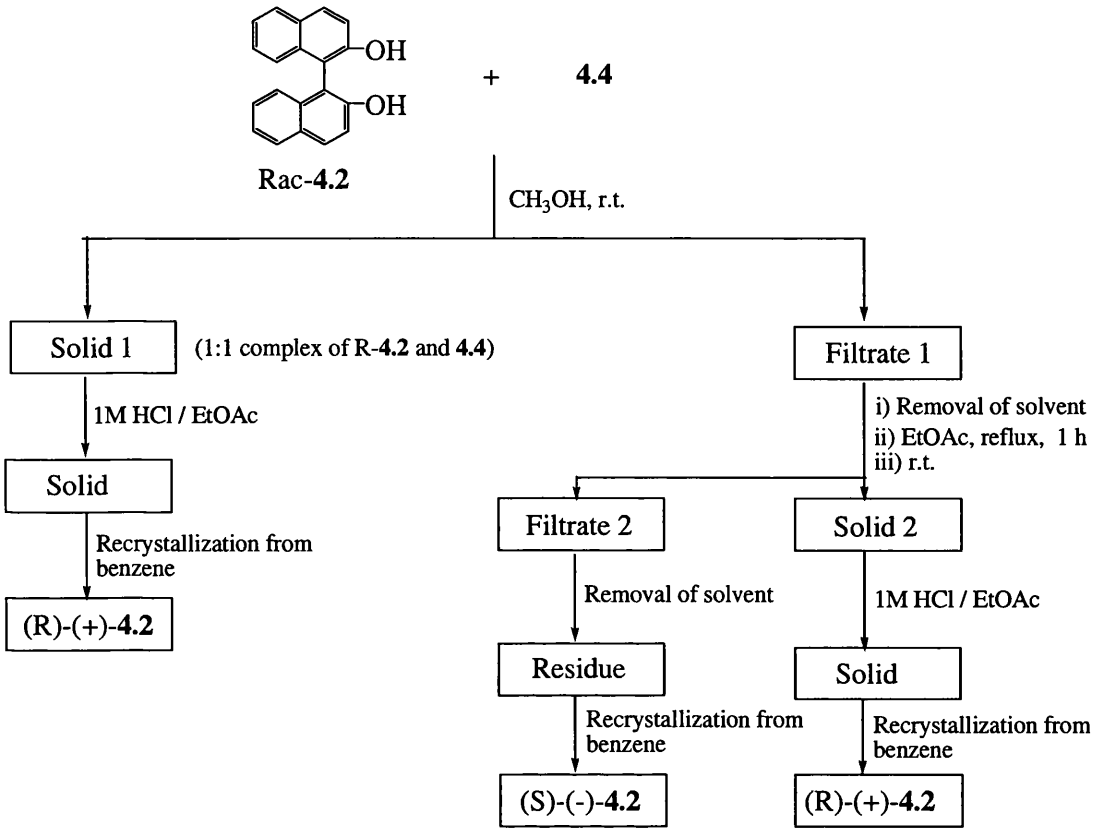
4.2.2.2.2 Resolution of racemic 2,2'-dihydroxy-1,1'-binaphthalene (Rac-4.2) using (8S,9R)-(-)-*N*-benzylcinchonidinium chloride (4.4)

Resolution of Rac-**4.2** using (8S,9R)-(-)-*N*-benzylcinchonidinium chloride (**4.4**) has been reported by Toda and co-workers.[7a,15] Compound (R)-**4.2** was obtained in optically pure form (> 99 % ee) with a yield of 30% [60% of the theoretical yield of compound (R)-**4.2**]. However, compound (S)-**4.2** was only partially resolved [42% ee, 124% of the theoretical yield of compound (S)-**4.2**].[7a]

It has been reported by Toda that a 1:1 complex was formed selectively by complexation of the resolving reagent **4.4** with compound (R)-**4.2**. X-ray crystal structure analysis showed that the complex was mainly constructed *via* formation of an intermolecular hydrogen bond between Cl^- of the resolving reagent **4.4** and the OH groups of compound (R)-**4.2**. It was also found that an intramolecular hydrogen bond between the OH group of resolving reagent **4.4** and Cl^- played an important role in forming the complex.[15]

Pu and co-workers reported a modified procedure, by which compound (R)-**4.2** was obtained in optically pure form [> 99% ee; 75% of the theoretical yield of compound (R)-**4.2**] and compound (S)-**4.2** was also obtained in optically pure form by using a '*kinetic crystallization*' technique [> 99% ee; 70% of the theoretical yield of compound (S)-**4.2**].[7b]

In the present work, the resolution experiments were carried out by modifying Pu's procedure. The experimental procedure is illustrated in Scheme 4.7 and the results are summarized in Table 4.5.



Scheme 4.7

Table 4.5 Resolution of racemic 2,2'-dihydroxy-1,1'-binaphthalene (Rac-4.2) using (8S,9R)-*N*-benzylcinchonidinium chloride (4.4) according to Scheme 4.7 [a]

Entry	Rac-**4.2** (g)	(R)-(+)- **4.2** Yield (%)	ee (%)[d]	(S)-(-)- **4.2**[e] Yield (%)	ee (%)[d]
1[b]	4.29	20 7	98 97	32	> 99
2[c]	12.6	28 8	98 95	35	> 99

a. The molar ratio of the resolving reagent **4.4** to Rac-**4.2** was 0.5. The reactions were carried out by adding the resolving reagent **4.4** to a solution of Rac-**4.2** in methanol. The mixture was stirred at r.t. for 18 h for the 1:1 complex formation.
b. The resolving reagent used was the commercial product (from Fluka Ltd).
c. The synthesized resolving reagent (see Section **4.2.2.2.1**) was used.
d. The ee values are based on: $[\alpha]_D^{25}$ = -34.5 (c 1, THF).[12]
e. In the literature, a '*kinetic crystallization*' technique was used to get the enantiometrically pure (S)-**4.2**.[7b]

Since the resolving reagent **4.4** selectively forms a 1:1 complex with compound (R)-**4.2**, the degree of completion of the complex formation and the degree

of the following separation between the formed complex and the remaining compound (S)-**4.2** would therefore be expected to play important roles in determining the outcome of the resolution. That is, the optical purity of Solid 1 (the 1:1 complex) and Filtrate 2 [containing the remaining (S)-**4.2**] would be crucial for the resolving result (see Scheme 4.7).

In Toda and Pu's work,[7] the complex formation between the resolving reagent **4.4** and compound (R)-**4.2** was carried out for 6 h (the reaction scale: 210 mmol of Rac-**4.2** in Pu's work and 3.5 mmol of Rac-**4.2** in Toda's work). Compound (R)-**4.2** was obtained in optically pure form in both cases. However, only partially resolved compound (S)-**4.2** was obtained. In Pu's work, a second separation was carried out by extraction of the residue after removing the solvent from Filtrate 1 using EtOAc (see Scheme 4.7) and compound (S)-**4.2** was obtained in 84% ee. In Toda's work, no such operation was carried out and compound (S)-**4.2** was obtained in 42% ee. It seemed that the reaction time (6 h) was not sufficient for complete formation of the 1:1 complex in both cases. As a result, some of the remaining compound (R)-**4.2** was present in Filtrate 1 (see Scheme 4.7) and this led to poor optical purity of compound (S)-**4.2**. It has also been reported by Liu,[13] a former researcher in our group, that a higher optical purity of compound (S)-**4.2** (93% ee) was obtained when the reaction time for 1:1 complex formation was extended to 12 h. By taking into account all this information, the reaction time for 1:1 complex formation was further extended to 18 h in our work. This modification had the desired effect - the complexation seemed to be complete. Optically pure compound (S)-**4.2** (> 99% ee) could be obtained simply by separating off the 1:1 complex (Solid 2 in Scheme 4.7) and recrystallizing the resulting residue from benzene (Table 4.5).

In addition to the complete formation of the 1:1 complex, the complete separation between the complex and the remaining compound (S)-**4.2** is crucial for the resolution result. It could be concluded from the literature work that most of the 1:1 complex would precipitate out of the methanolic solution. However, a small amount of complex would still remain in the filtrate (Filtrate 1; Scheme 4.7), and could be separated from the compound (S)-**4.2** by using EtOAc to extract the residual solid after removing the solvent from Filtrate 1 (see Scheme 4.7). There was no detailed experimental procedure available in regard to the extraction. We found that refluxing

the residual solid in EtOAc for 1 h followed by filtration resulted in complete separation and led to good optical purity of the compound (S)-**4.2** and the second batch of compound (R)-**4.2**.

We also found that decomposition of the 1:1 complex could be carried out more easily and efficiently using a mixture of 1 M HCl and EtOAc rather than using 1 M HCl alone, as used in the literature.

The resolution was also carried out on a relatively large scale (44 mmol of Rac-**4.2**) using the synthesized resolving reagent (Entry 2). As can be seen from Table 4.5, better results were obtained for both (R)-**4.2** and (S)-**4.2** enantiomers than the small scale resolution. This not only confirmed the high efficiency and applicability of the resolution method developed, it also confirmed the high optical purity of the resolving reagent **4.4** we synthesized. The detailed experimental procedure is reported in the *Experimental Section* of this chapter

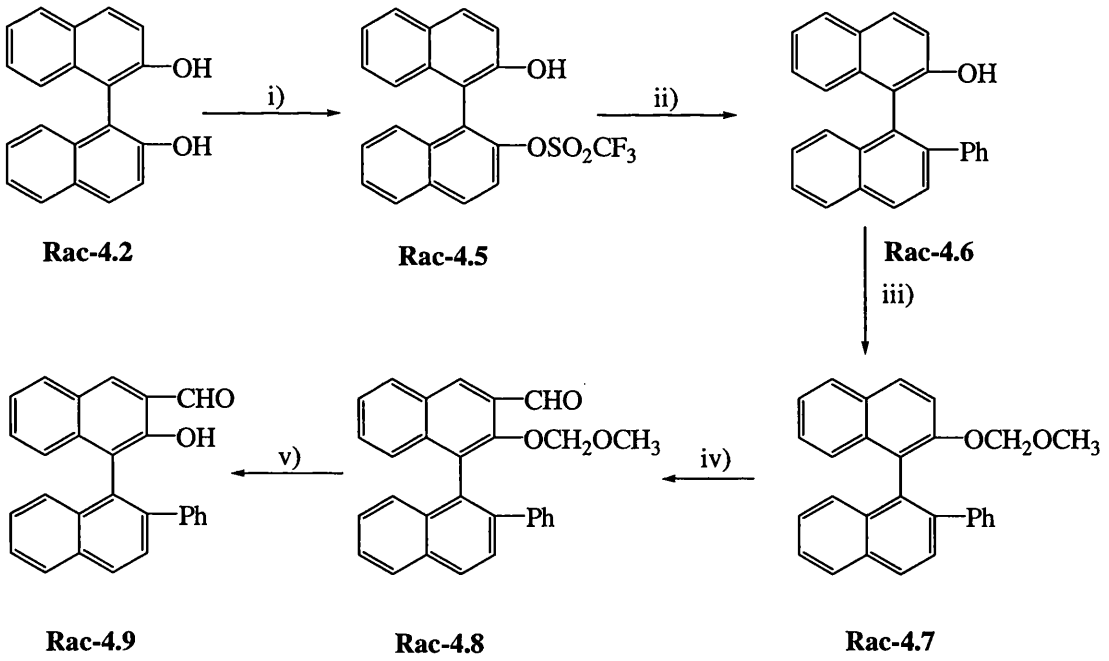
In conclusion, a simple and efficient method has been developed to resolve racemic 2,2'-dihydroxy-1,1'-binaphthalene (Rac-**4.2**) using (8S,9R)-(-)-*N*-benzylcinchonidinium chloride (**4.4**). Both of the enantiomers could be obtained in optically pure form, especially the (S) enantiomer, which was normally partially resolved or was obtained in optically pure form using specialized techniques.

Having successfully obtained the enantiomerically pure compound (R)-**4.2** and compound (S)-**4.2**, the next step would be transformation of one of the enantiomers, (R)-**4.2** in this work, to the target compound (R)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene *via* a muti-step synthesis (Scheme 4.1).

Before using compound (R)-**4.2** as the starting material, it would be better to use Rac-**4.2** as the starting material first to work out the optimal conditions for these transformations.

4.2.3 Synthesis of racemic 3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene (Rac-4.9) from racemic 2,2'-dihydroxy-1,1'-binaphthalene (Rac-4.2)

Preparation of Rac-**4.9** was carried out following an established synthetic route (Scheme 4.8).[13,16] All steps worked well and the product was obtained in 28% overall yield. The synthetic sequence was therefore next applied to the synthesis of compound (R)-**4.9**. Since the reaction conditions for these transformations are similar or identical whether using racemic compounds as reactants or using the corresponding enantiomers as reactants, only the reaction conditions and the results for the synthesis of racemic products are summarized in this section. The detailed experimental procedures, discussion and results for these transformations are reported in the following sections relating to the use of optically pure enantiomers.



Reaction conditions and results

i) Tf_2NPh, 2,4,6-collidine, DMAP, dry DCM, reflux, 18 h, 79% isolated yield.

ii) $PhMgBr{\cdot}Et_2O$, $NiCl_2(dppe)$, dry Et_2O, reflux, 1 h, 61% isolated yield.

iii) $ClCH_2OCH_3$, $(i\text{-}Pr)_2NEt$, DCM, r.t., 24 h, 76% isolated yield.

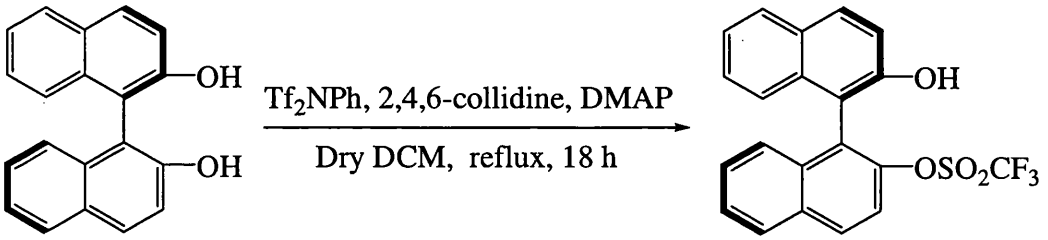
iv) a. *t*-BuLi, THF, -78°C, 3 h; b. DMF, r.t., 1 h, 93% isolated yield.

v) $SiMe_3Br$, dry DCM, r.t., 1 h, 83% isolated yield.

Scheme 4.8

4.2.4 Synthesis of (R)-2-hydroxy-2'-trifluoromethanesulfonyloxy-1,1'-binaphthalene [(R)-4.5]

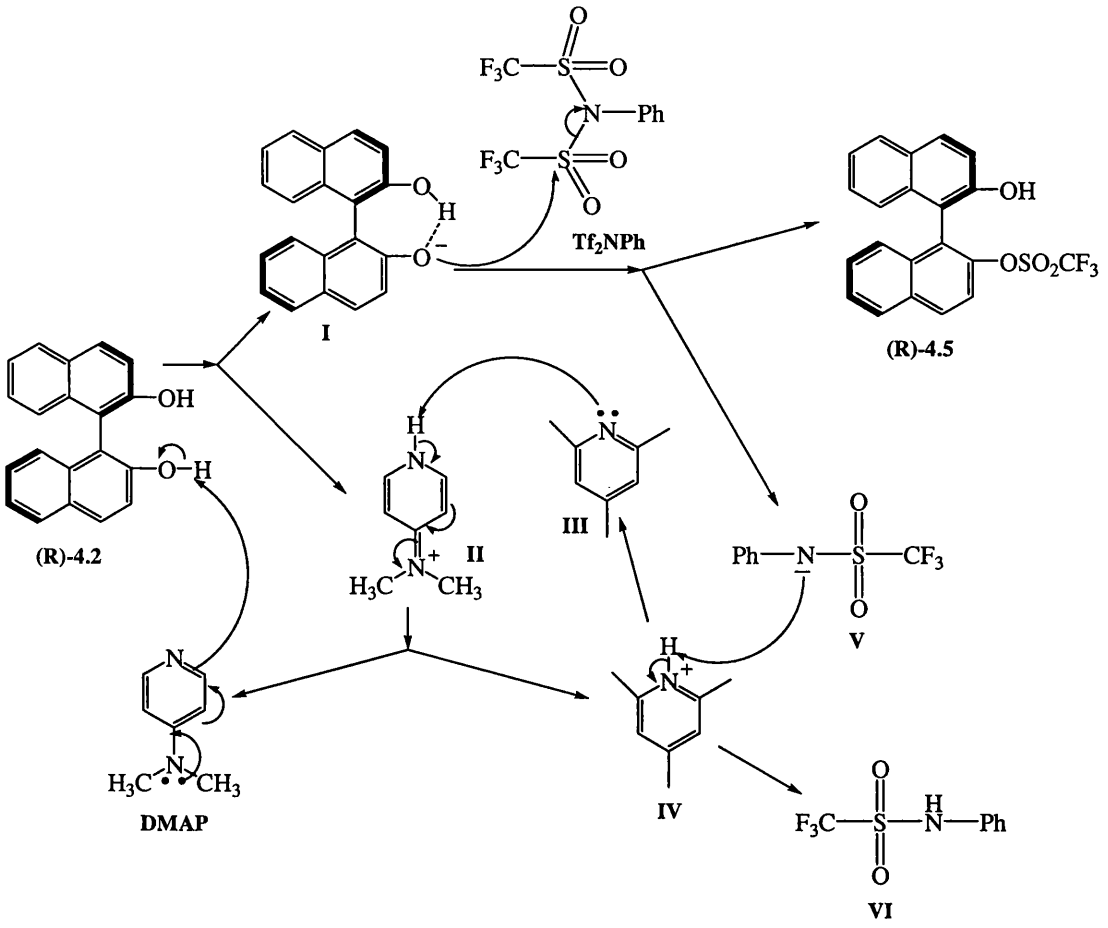
Compound (R)-**4.5** was synthesized from compound (R)-**4.2** following a literature procedure (Scheme 4.9).[13,16] In order to transform just one of the two hydroxyl groups to the triflate group, a mild triflating reagent *N*-phenylbis(trifluoromethanesulfonimide) (Tf_2NPh) was employed and the molar ratio of Tf_2NPh to compound (R)-**4.2** was 1. 4-Dimethylaminopyridine (DMAP) was employed as a hypernucleophilic catalyst [12 mol% relative to compound (R)-**4.2**] which would greatly accelerate the sulfonation of compound (R)-**4.2**.



(R)-4.2 **(R)-4.5**

Scheme 4.9

A possible mechanism for the selective formation of the monotriflate (R)-**4.5** is shown in Scheme 4.10.[13] DMAP reacts with compound (R)-**4.2** to give a monoanion **I** and a protonated DMAP **II**. The monoanion **I**, which is possibly stabilized by formation of an intramolecular hydrogen bond, reacts with Tf_2NPh to give the product (R)-**4.5** and an anion of phenyl trifluoromethanesulfonamide **V**. The protonated DMAP reacts with the hindered base 2,4,6-collidine (**III**) to yield a protonated 2,4,6-collidine **IV** and regenerate the free DMAP. The protonated 2,4,6-collidine **IV** reacts with the anion **V** to give phenyl trifluoromethanesulfonamide (**VI**).



Scheme 4.10

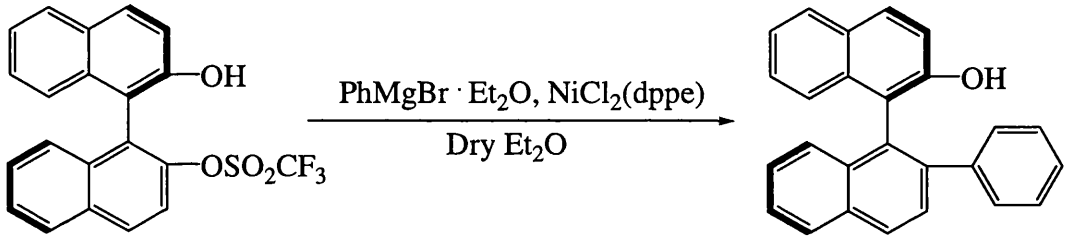
The reaction was carried out under the literature conditions on a 2.22 mmol [compound (R)-**4.2**] scale and monitored by tlc. After 12 h (the reaction time reported in the literature),[16] tlc indicated that the reaction was incomplete, so refluxing was continued for a further 6 h. At that point, although some (R)-**4.2** remained, the reaction appeared to have stopped. It was worked up and the crude product was purified by flash silica chromatography to give the product (R)-**4.5** in 72% yield. The reaction was repeated on a larger scale [12.1 mmol of compound (R)-**4.2**] in order to produce a large quantity of (R)-**4.5**. The isolated yield on this scale was improved to 89%.

The detailed experimental procedure and characterization of the product (R)-**4.5** are reported in the *Experimental Section* of this chapter.

It was noted that compound (R)-**4.2** and Rac-**4.2** showed different solubilities in DCM. The solubility of compound (R)-**4.2** in DCM was nearly twice that of Rac-**4.2**.

4.2.5 Synthesis of (R)-2-hydroxy-2'-phenyl-1,1'-binaphthalene [(R)-4.6]

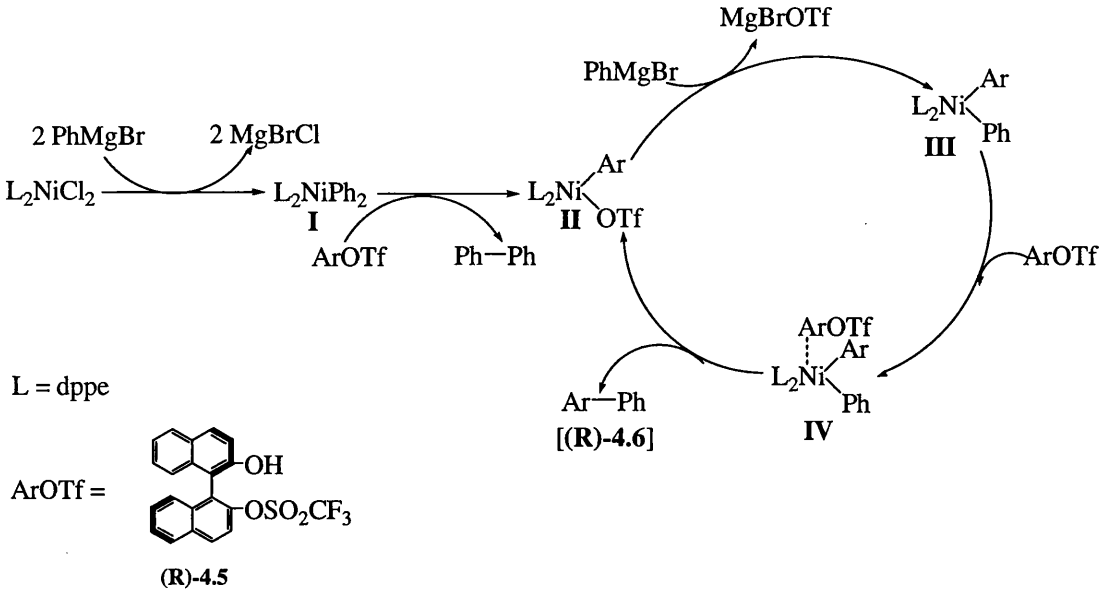
Compound **(R)-4.6** has been synthesized by reaction of compound **(R)-4.5** with a Grignard reagent (PhMgBr) in dry diethyl ether. [1,2-bis(diphenylphosphino)ethane]dichloronickel(II) [$NiCl_2$(dppe)] was used as a catalyst (Scheme 4.11).[13,16]



(R)-4.5 **(R)-4.6**

Scheme 4.11

A possible mechanism for this nickel-catalyzed reaction is shown in Scheme 4.12.[13,17] $NiCl_2$(dppe) reacts with the Grignard reagent to form an intermediate diorganonickel complex **I**, which reacts with one mole of the starting material (R)-**4.5** to yield another organonickel complex **II**. Complex **II** reacts with another mole of Grignard reagent to yield a new diorganonickel complex **III**, which reacts with another mole of the starting material (R)-**4.5** to give the target compound (R)-**4.6** *via* a pentacoordinated intermediate complex **IV** and regenerate the organonickel complex **II**.



Scheme 4.12

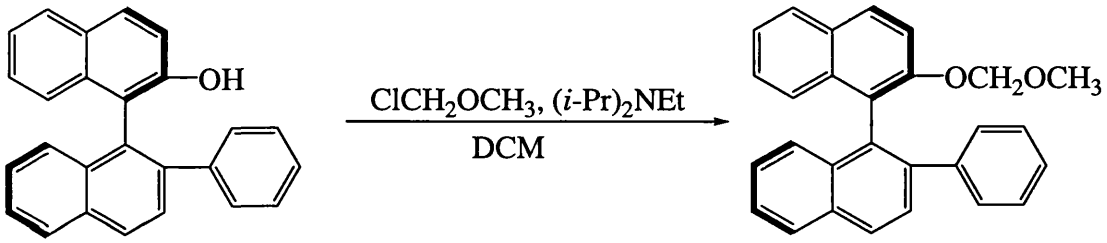
In the present work, two experiments were carried out by modifying the literature procedure.[13,16] The first experiment was carried out on a small scale [0.96 mmol of (R)-**4.5**]. The concentration of compound (R)-**4.5** in dry Et_2O was increased to 0.27 M (it was 0.1 M in the literature[13]) in the hope that the reaction rate would increase. The Grignard reagent was used in excess [the molar ratio of the Grignard reagent to (R)-**4.5** was 4]. It was found by tlc that the reaction was complete after 1 h. It was also found that a by-product having a higher R_f (R_f = 0.81; silica plate, developing solvent: hexane / toluene = 2 / 3) than that of the product (R)-**4.6** (R_f = 0.23) was formed. According to the reaction mechanism (Scheme 4.12), the by-product might correspond to biphenyl. The addition rate of the Grignard reagent to the reaction mixture was found to be important to the outcome of the reaction. A slower addition rate appeared to favour the formation of the product. The product (R)-**4.6** was obtained in 70% yield after purification by flash silica column chromatography.

The reaction was next carried out on a larger scale [10.05 mmol of (R)-**4.5**] under the same conditions in order to produce enough material to continue with the synthesis. Again, the reaction was found to be complete after 1 h by tlc. The target compound (R)-**4.6** was obtained with an isolated yield of 64% after purification by flash silica column chromatography. The detailed experimental procedure and

characterization of the product (R)-**4.6** are reported in the *Experimental Section* of this chapter.

4.2.6 Synthesis of (R)-2-methoxymethoxy-2'-phenyl-1,1'-binaphthalene [(R)-4.7]

Hydroxyl groups can be protected by conversion to *O*-methoxymethyl (*O*-MOM) groups. The transformations have usually been carried out by reaction of the substrates with chloromethyl methyl ether (ClMOM).[18] Compound (R)-**4.7** has been synthesized by reaction of compound (R)-**4.6** with ClMOM in dry DCM. A hindered non-nucleophilic base *N,N*-diisopropylethylamine (DIEA) was used as a catalyst (Scheme 4.13).[13,16]



(R)-4.6 **(R)-4.7**

Scheme 4.13

In the present work, the reaction was carried out according to the literature procedure.[13,16] ClMOM and DIEA were used in excess [the molar ratios of ClMOM and DIEA to compound (R)-**4.6** were each 2.8] and the concentration of (R)-**4.6** in dry DCM was 0.26 M.

The transformation had first been carried out under the same conditions using Rac-**4.6** (0.53mmol) as the starting material (see *Section 4.2.3*; Scheme 4.8). Commercial ClMOM (technical grade) had been used without further purification. The reaction was reasonably successful; Rac-**4.7** was obtained in 76% yield. It was found by tlc that the reaction was incomplete after 24 h at r.t. and the difference of R_f between the product Rac-**4.7** and the unreacted starting material Rac-**4.6** was very marginal in several tlc developing solvent systems (actually, only '8' shaped spots could be observed). As a result, a gradient elution technique had been employed to

purify the crude product on a silica column. The technique worked well; the product could be separated from the unreacted starting material, which could be recovered.

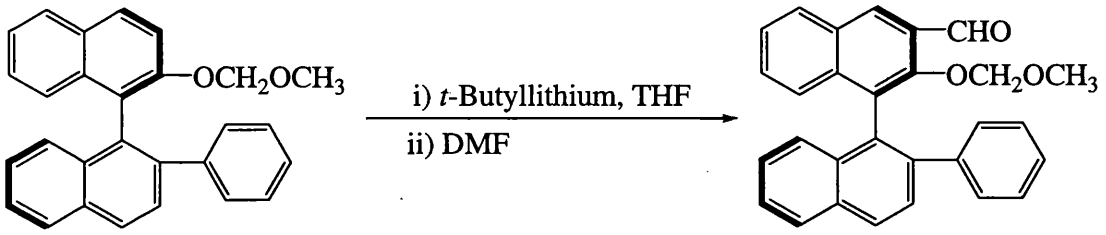
When compound (R)-**4.6** was used as the starting material to carry out the same transformation on a small scale (0.61 mmol), an attempt to further purify ClMOM was carried out (ClMOM was carefully distilled over anhydrous K_2CO_3 under an Ar atmosphere; the fraction of b.p. 58 - 59 °C was collected) and the reaction was conducted at a controlled temperature (22 - 25 °C) instead of r.t. The reaction was again found to be incomplete after 24 h, and surprisingly, the product (R)-**4.7** was obtained with a poor yield (33%) after the same work-up and purification procedure. Tlc analysis of the reaction mixture was similar to that in the experiment using commercial ClMOM and Rac-**4.6**. However, it was found during the work-up procedure that the pHs of the aqueous phases from the two experiments were different: the pH of the aqueous layer after quenching the reaction with H_2O was about 1 - 2 in the experiment using commercial ClMOM, whereas it was about 6 - 7 in the experiment using 'purified' ClMOM. Clearly, less HCl had been generated in the latter reaction, which might have indicated that the supposedly 'purified' ClMOM had in reality been of poor quality, with a reduced Cl content.

Therefore, for another larger scale experiment [6.07 mmol of compound (R)-**4.6**] to produce a stock of (R)-**4.7** for future use, ClMOM was used without purification. The reaction was still found to be incomplete after 24 h at r.t., but the pHs of the aqueous phases were similar to those in the experiment using Rac-**4.6** as the starting material. The target product (R)-**4.7** was obtained with a yield of 73% after purification on a silica column using the gradient elution technique. The detailed experimental procedure and characterization of the product (R)-**4.7** are reported in the *Experimental Section* of this chapter.

4.2.7 Synthesis of (R)-3-formyl-2-methoxymethoxy-2'-phenyl-1,1'-binaphthalene [(R)-4.8]

It has been reported that *N,N*-dimethylamides, such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide and *N,N*-dimethylbenzamide, can be used for formylation and acylation with alkyllithium or Grignard reagents.[19]

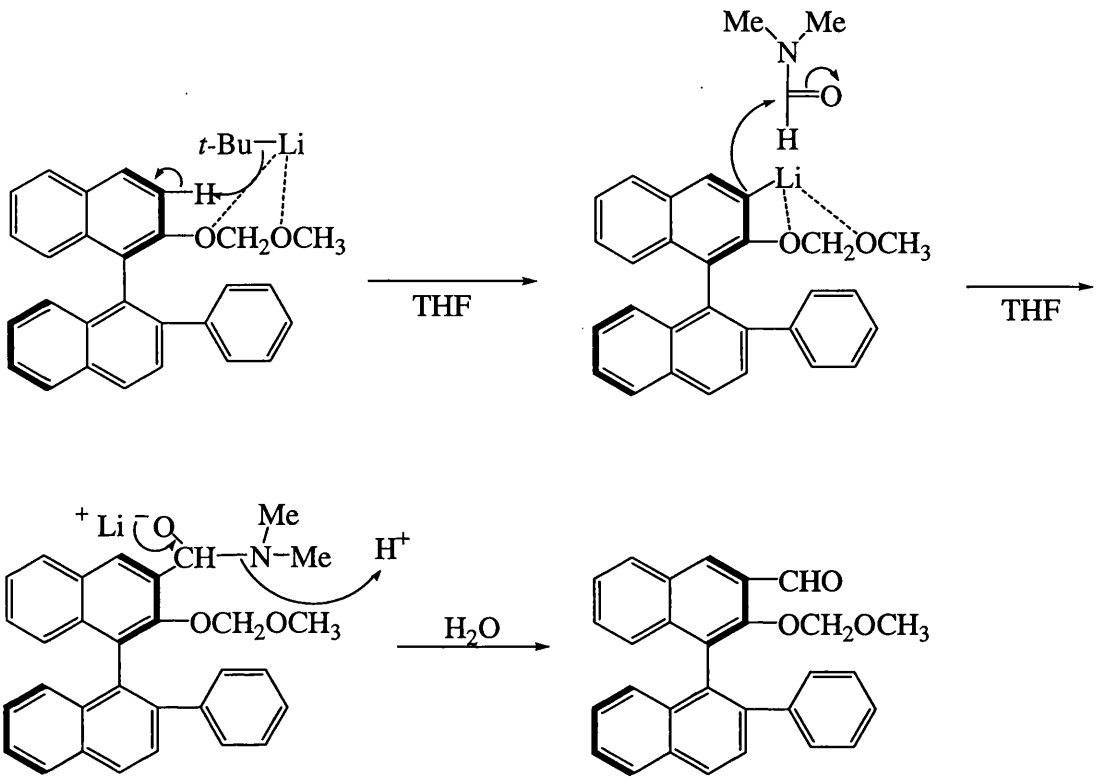
Compound (R)-**4.8** has been synthesized by reaction of compound (R)-**4.7** with *t*-butyllithium and DMF in dry THF (Scheme 4.14).[13,16] The position of substitution is determined by the controlling influence of the OMOM group at the lithiation step, presumably by co-ordinating to the organolithium reagent.



(R)-4.7 **(R)-4.8**

Scheme 4.14

The reaction might proceed as shown in Scheme 4.15.



Scheme 4.15

In the present work, the reaction was carried out according to the literature procedure.[13,16] *t*-Butyllithium and DMF were used in excess [the molar ratios of *t*-butyllithium and DMF to compound (R)-**4.7** were 2.3 and 5, respectively] and the concentration of (R)-**4.7** in dry THF was 0.23 M. The lithiation step was carried out at - 78 °C for 3 h and the following step was carried out at r.t. for 1 h.

The transformation had first been carried out on a small scale using Rac-**4.7** (0.36 mmol) as the starting material (see *Section 4.2.3*). Although *t*-butyllithium had been used in excess, the reaction was found to be quite clean by tlc. No side reactions, such as further reduction of the product, were observed. Rac-**4.8** was obtained with a yield of 93% after purification by flash silica column chromatography. It was also found that slower addition of *t*-butyllithium and DMF to the reaction system favoured formation of the product.

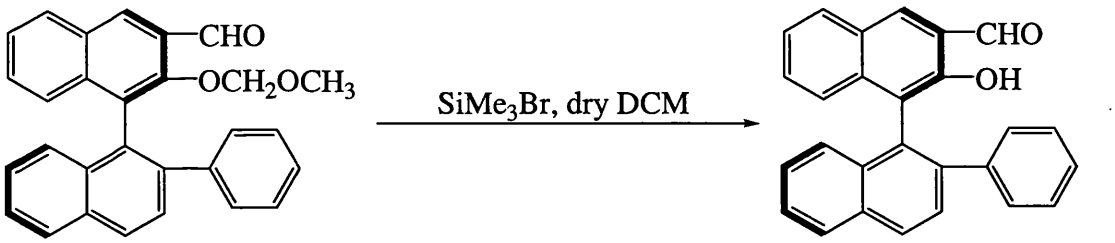
Therefore, the same reaction conditions were applied to compound (R)-**4.7** (3.05 mmol) to carry out the transformation. The reaction was again found to be very clean. The product (R)-**4.8** was obtained with a yield of 92% after purification by

flash silica column chromatography. The detailed experimental procedure and characterization of the product (R)-**4.7** are reported in the *Experimental Section* of this chapter.

4.2.8 Synthesis of (R)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene [(R)-4.9]

A number of procedures has been reported for the regeneration of hydroxyl groups (-OH) from MOM ethers, among which treatment with trimethylsilyl bromide ($SiMe_3Br$) was found to be a mild and effective method. The reactions can be carried out at low temperature (-30 °C to 0 °C) and a variety of functional groups, such as esters, amides etc., were found to be stable under the cleavage conditions. It has also been reported that the cleavage might take place *via* the intermediacy of oxonium ions.[20]

Compound (R)-**4.9** has been synthesized by reaction of compound (R)-**4.8** with $SiMe_3Br$ in dry DCM (Scheme 4.16). Some activated 4 Å molecular sieves were added to the reaction system to facilitate the transformation.[13,16]



(R)-4.8 **(R)-4.9**

Scheme 4.16

In the present work, the experiment was carried out according to the literature procedure.[13,16] $SiMe_3Br$ was used in excess [the molar ratio of $SiMe_3Br$ to compound (R)-**4.8** was 4.1] and the concentration of (R)-**4.8** in dry DCM was 0.22 M.

The transformation had previously been carried out on a small scale using Rac-**4.8** (0.36 mmol) as the starting material (see *Section 4.2.3*). It was found by tlc

that the reaction was complete after 1 h at r.t. Additionally, the fomyl group was found to be stable under the cleavage conditions. Rac-**4.9** was obtained in 83% yield after purification by flash silica column chromatography.

The same reaction conditions were therefore applied to compound (R)-**4.8** (2.68 mmol). The reaction was again found to be complete and clean by tlc after 1 h at r.t. The target compound **(R)-4.9** was obtained in 88% yield after purification by flash silica column chromatography. The detailed experimental procedure and characterization of the product (R)-**4.9** are reported in the *Experimental Section* of this chapter.

4.3 Conclusions

- The target compound (R)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene [(R)-**4.9**] was synthesized from 2-naphthol (**4.1**) *via* a seven-step synthetic procedure with an overall yield of 9%.
- Racemic 3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene (Rac-**4.9**) was synthesized from 2-naphthol (**4.1**) *via* a similar six-step synthetic procedure with an overall yield of 23%.
- 2,2'-Dihydroxy-1,1'-binaphthalene (Rac-**4.2**) was synthesized by oxidative coupling of 2-naphthol in aqueous Fe^{3+} solution. Several factors that influence the yield of the reaction were investigated. These factors include: the particle size of 2-naphthol; the reaction vessel type; the reaction temperature; and the molar ratio of oxidant (Fe^{3+}) to 2-naphthol. The reaction was effectively applied to a large scale synthesis with a yield of 82%.
- Racemic 2,2'-dihydroxy-1,1'-binaphthalene (Rac-**4.2**) was resolved into its enantiomers using two methods. Although quite a lot of efforts had been made to optimize the resolving conditions using boric acid and (R)-(+)-α-methylbenzylamine as the resolving reagent, only one optically pure enantiomer (R)-**4.2** was obtained, and in a low yield (16%). Conversely, a simple, practical and efficient method has been developed using (8S,9R)-(-)-*N*-benzylcinchonidinium chloride as the resolving reagent. Both of

the enantiomers could be obtained in optically pure form. This is especially important for the (S) enantiomer, which has normally been partially resolved or obtained in optically pure form only after using some specialized techniques.

- Two different solvents were used to synthesize the resolving reagent (8S,9R)-(-)-*N*-benzylcinchonidinium chloride (**4.4**). A simple procedure has been developed to prepare the pure product in 48% yield using dry acetone as the solvent. However, when dry ethanol was used as the solvent, the product was found to be contaminated with some dark coloured impurities, which were presumed to derive from decomposition of the product at high temperature.
- (R)-2-Hydroxy-2'-trifluoromethanesulfonyloxy-1,1'-binaphthalene [(R)-**4.5**] was synthesized from compound (R)-**4.2** with a yield of 89%.
- (R)-2-Hydroxy-2'-phenyl-1,1'-binaphthalene [(R)-**4.6**] was synthesized from compound (R)-**4.5** with a yield of 70%.
- (R)-2-Methoxymethoxy-2'-phenyl-1,1'-binaphthalene [(R)-**4.7**] was synthesized from compound (R)-**4.6** with a yield of 73%.
- (R)-3-Formyl-2-methoxymethoxy-2'-phenyl-1,1'-binaphthalene [(R)-**4.8**] was synthesized from compound (R)-**4.7** with a yield of 92%.
- (R)-3-Formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene [(R)-**4.9**] was synthesized from compound (R)-**4.8** with a yield of 88%.

4.4 Experimental section

See also *Experimental Section 3.4* in *Chapter 3* for related experimental details.

Hplc was operated on a Milton Roy® Spectromonitor 3100 system with Milton Roy® Constameric® 3000 solvent delivery system.

Enantiomeric excesses (ee%) were determined by comparing the specific rotation of the product $[\alpha]_{obs}$ with the specific rotation reported in the literature $[\alpha]_{ref}$ and calculated using the following equation:

$$ee\ (\%) = \frac{[\alpha]_{obs}}{[\alpha]_{ref}} \times 100\%$$

Drying of solvents [21]

Drying of acetone

Acetone (analytical grade) was stirred over boron oxide (B_2O_3, 5% w /v) for 24 h. The liquid was filtered and distilled. The fraction of b.p. 55 - 57 °C was collected.

Drying of diethyl ether

Et_2O was pre-dried by standing over anhydrous $CaCl_2$ (5% w /v) for 24 h. After filtration, the filtrate was heated under reflux over sodium-benzophenone until the deep blue colour of the ketyl radical anion persisted. It was then distilled. The fraction of b.p. 32 - 33 °C was collected.

Synthesis of racemic 2,2'-dihydroxy-1,1'-binaphthlene (Rac-4.2) by oxidative coupling of 2-naphthol (4.1)

***Hplc analysis of* 2,2'-dihydroxy-1,1'-binaphthlene (Rac-4.2)**

- Hplc conditions
  Column: APEX II, 5μ, ODS, 4.6 × 250 mm; Solvent: MeOH / H_2O = 80 / 20;
  Flow rate: 1 ml / min; UV (nm): 254.
- Qualitative analysis
  Retention time for the starting material 2-naphthol (**4.1**): R (SM) = 3.6 min.
  Retention time for the product **Rac-4.2**: R (product) = 4.2 min.
- Quantitative analysis
  Internal standard: naphthalene
  Equations used:

$$M(Y) = K(Y) \times Area(Y) \qquad \text{(eq. 1)}$$

$$\frac{M(Y)}{M(standard)} = \frac{K(Y)}{K(standard)} \times \frac{Area(Y)}{Area(standard)} \qquad \text{(eq. 2)}$$

$$\frac{K(Y)}{K(standard)} = \frac{Area(standard)}{Area(Y)} \times \frac{M(Y)}{M(standard)} \qquad \text{(eq. 3)}$$

$$M(Y) = \frac{K(Y)}{K(standard)} \times \frac{Area(Y)}{Area(standard)} \times M(standard) \qquad \text{(eq. 4)}$$

Where,

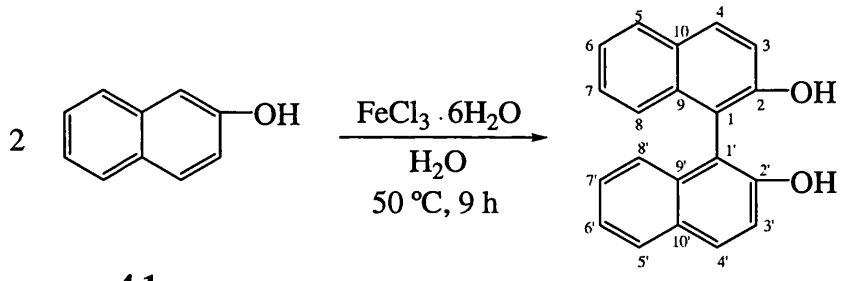
M (Y): the mass of compound Y;

Area (Y): the peak area of compound Y;

K (Y) / K (standard): the correction factor of compound Y. It can be calculated using equation 3.

Results: K (product) / K (standard) = 0.25; K (SM) / K (standard) = 0.31.

Synthetic procedure



4.1 **Rac-4.2**

Compound **4.1** (28.83g, 200mmol), $FeCl_3 \cdot 6H_2O$ (162.18g, 600mmol) and distilled water (600ml) were added to a 1-L beaker. The reaction mixture was sonicated in an ultrasonic bath for 30 min and then stirred at 50 °C (temperature of the heating bath) for 9 h using a mechanical stirrer.

The reaction mixture was cooled to r.t. The solid was collected by suction filtration and washed with distilled water (3 × 54 ml) to remove the Fe^{2+} and Fe^{3+} salts. It was then dried in a vacuum desiccator to give the crude product (30.72 g).

Recrystallization of the crude product from toluene (230 ml) gave the pure product (23.37g; 82% yield).

Melting point (m.p.): 216 - 219 °C (from toluene).

NMR

δ_H (400MHz, $CDCl_3$): 5.00 (s, 2H, -**OH**); 7.07 (d, 2H, **H**-3 and **H**-3', ^3J = 8 Hz); 7.22 (apparent triplet, 2H, **H**-6 and **H**-6', ^3J = 8 Hz); 7.29 (m, 4H, **H**-8, **H**-8', **H**-7 and **H**-7'); 7.81 (d, 2H, **H**-5 and **H**-5', ^3J = 8 Hz); 7.89 (d, 2H, **H**-4 and **H**-4', ^3J = 8 Hz);

δ_C (400MHz, $CDCl_3$): 111.2 (**C**-1 and **C**-1'); 118.2 (**C**-3 and **C**-3'); 124.5 (**C**-6 and **C**-6'); 124.6 (**C**-8 and **C**-8'); 127.9 (**C**-7 and **C**-7'); 128.8 (**C**-5 and **C**-5'); 129.9 (**C**-10 and **C**-10'); 131.8 (**C**-4 and **C**-4'); 133.8 (**C**-9 and **C**-9'); 153.2 (**C**-2 and **C**-2').

IR

ν_{max} (cm^{-1}): 3484 (sharp, HO-); 3398 (HO-, H-bonded); 1616; 1597; 1508; 1471; 1380; 1321; 1209; 1168; 1140;1124; 960; 826; 814; 750.

MS

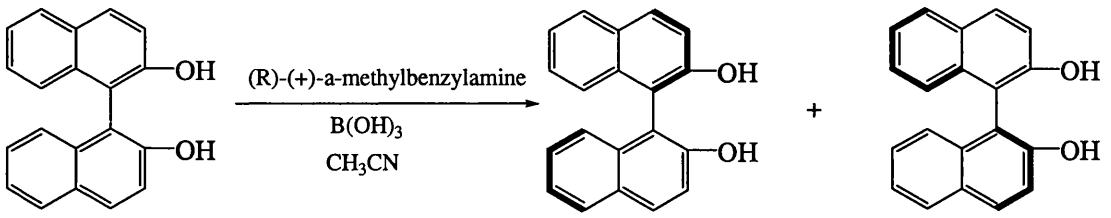
m /z (EI): 286 (M^+, 100%); 257 (22%); 239(23%); 115 (23%); 39 (50%).

m /z (CI, NH_3): 304 ($[M + NH_4]^+$, 100%).

HRMS

Found M^+: 286.0988; $C_{20}H_{14}O_2$ requires: 286.0988.

Resolution of racemic 2,2'-dihydroxy-1,1'-binaphthlene (4.2) using boric acid and (R)-(+)-α-methylbenzylamine



Rac-**4.2** (R)-**4.2** (S)-**4.2**

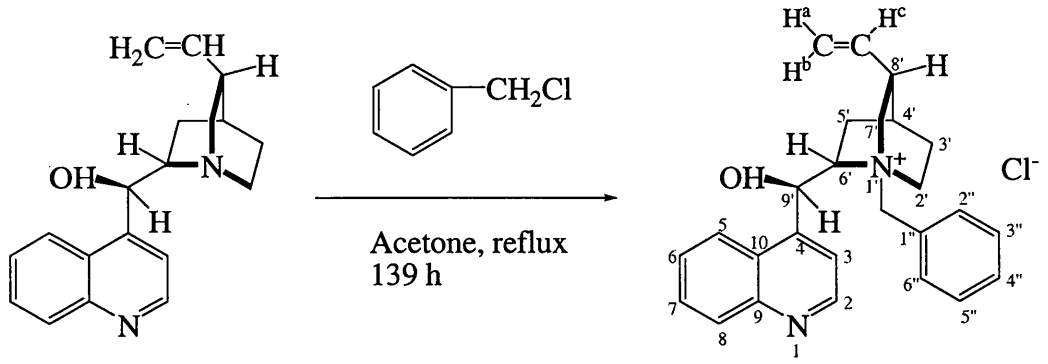
The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower, a condenser and a glass stopper. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. Rac-**4.2** (2.863 g, 10

mmol), $B(OH)_3$ (0.309 g, 5 mmol) and dry CH_3CN (20 ml) were added to the flask and the mixture was stirred for 5 min. (R)-(+)-α-Methylbenzylamine (1.93 ml, 15 mmol) was added by syringe. The mixture was heated under reflux for 12 h, and then kept in a 28 °C water bath for 30 min.

The solid (named as Solid 1) was collected by suction filtration, washed with a little cold CH_3CN and then dried under vacuum (2.362 g). Dry CH_3CN (10 ml) was added to the solid. The mixture was heated under reflux for 6 h and then kept in a 25 °C water bath for 30 min. The solid was again collected by suction filtration, washed with a little CH_3CN and then dried under vacuum (1.968 g). EtOAc (25 ml) and 1 M HCl (20 ml) were added to the solid and the mixture was stirred at r.t. until the solid dissolved. The aqueous layer was separated and then extracted with EtOAc (2 × 20 ml). The combined organic phase was washed with brine (60 ml), dried over anhydrous $MgSO_4$ and filtered. Removal of solvent from the filtrate *in vacuo* and drying of the resulting residue gave partially resolved (S)-(-)-**4.2** {1.604 g, 56% yield, 112% of the theoretical yield of compound (S)-(-)-**4.2**; m.p. 200 - 205 °C; $[\alpha]_D^{20}$ = -11.1 (c 1.06, THF), 32% ee; The ee value was based on $[\alpha]_D^{25}$ = -34.5 (c 1, THF)[12]}.

Removal of solvent from the filtrate, which was obtained after separation of Solid 1, *in vacuo* gave a white solid (1.470 g). Dry THF (20 ml) was added to the solid. The mixture was heated under reflux for 6 h and then kept in a 25 °C water bath for 30 min. The solid was collected by suction filtration, washed with a little THF and dried under vacuum (0.630 g). EtOAc (25 ml) and 1 M HCl (20 ml) were added to the solid and the mixture was stirred at r.t. until the solid dissolved. The aqueous layer was separated and extracted with EtOAc (2 × 20 ml). The combined organic phase was washed with brine (60 ml), dried over anhydrous $MgSO_4$ and filtered. Removal of solvent from the filtrate *in vacuo* and drying of the resulting residue gave (R)-(+)-**4.2** {0.457 g, 16% yield, 32% of the theoretical yield of compound (R)-(+)-**4.2**; m.p. 205 - 207 °C; $[\alpha]_D^{22}$ = +33.8 (c 1.04, THF), 98% ee; The ee value was based on $[\alpha]_D^{25}$ = 34.5 (c 1, THF) [12]}.

Synthesis of (8S,9R)-(-)-*N*-benzylcinchonidinium chloride (4.4)



4.3 **4.4**

The reaction set-up consisted of a 2-L two-necked round bottomed flask equipped with a magnetic follower, a condenser and a glass stopper. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. Compound **4.3** (14.72 g, 50 mmol) and dry acetone (1,200 ml) were added to the flask and heated to reflux. Compound **4.3** dissolved in acetone and remained in solution when the solution was cooled to r.t. Benzyl chloride (5.80 ml, 50 mmol) was added to the solution and the mixture was heated under reflux for 139 h. After being cooled to r.t., the crystalline product was collected by suction filtration, washed with a little acetone and dried under vacuum (10.18g, 48% yield).

Melting point (m.p.): 215 - 217 °C (from acetone).

TLC (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}):

R_f = 0.53 (developing solvent: CH_3OH / CH_3Cl = 1 / 4)

NMR

δ_H (400MHz, $CDCl_3$): 1.03 (m, 1H); 1.57 (m, 1H); 1.89 (m, 2H); 2.09 (m, 2H); 2.44 (m, 1H); 3.10 (m, 2H); 3.68 (m, 1H); 4.03 (t, 1H, **H**-2', J = 9 Hz); 4.70 (m, 1H, **H**-6'); 4.90 (d, 1H, $\mathbf{H^a}$, ^3J = 4 Hz); 5.21 (d, 1H, $\mathbf{H^b}$, J = 17 Hz); 5.39 (m, 1H, $\mathbf{H^c}$); 5.60 (d, 1H, $\mathbf{H^e}$ of PhC$\mathbf{H^d}\mathbf{H^e}$; ^2J = 12 Hz); 5.81 (d, 1H, $\mathbf{H^d}$ of PhC$\mathbf{H^d}\mathbf{H^e}$; ^2J = 12 Hz); 6.50 (d, 1H, **H**-9', ^3J = 4 Hz); 7.13 - 7.23 (m, 5H, others Ar-**H**); 7.49 (d, 1H, J = 6 Hz); 7.62 (d, 2H, **H**-2'' and **H**-6'', ^3J = 7 Hz); 7.83 (d, 1H, **H**-5, ^3J = 4 Hz); 8.15 (d, 1H, **H**-8, ^3J = 8 Hz); 8.79 (d, 1H, **H**-2, ^3J = 4 Hz).

δ_C (400MHz, $CDCl_3$): 22.7 (**C**-5'); 25.5 (**C**-3'); 26.9 (**C**-4'); 38.4 (**C**-8'); 50.7 (**C**-2'); 60.7 (**C**-7'); 63.0 ($\mathbf{C}H_2$Ph); 65.5 (**C**-9'); 68.2 (**C**-6'); 118.2 (**C**-H^a); 120.4 (**C**-3); 123.2

/ 124.3 / 127.5 / 127.8 / 129.2 / 129.3 / 129.7 / 130.4 / 134.4 (Others carbons on the aromatic rings); 136.5 (**C**-H^c); 145.4 (**C**-4); 147.0 (**C**-9); 149.5 (**C**-2).

IR

ν_{max} (cm^{-1}): 3063 (br. CH_2=CH- and Ar-H); 2997 / 2933 / 2889 (CH); 1638; 1588; 1498; 1165; 1135; 1009; 939; 925; 777; 763; 706.

MS

m /z (ES^+): 385 ($[M - Cl]^+$, 100%); 91 ($C_7H_7^+$, 13%).

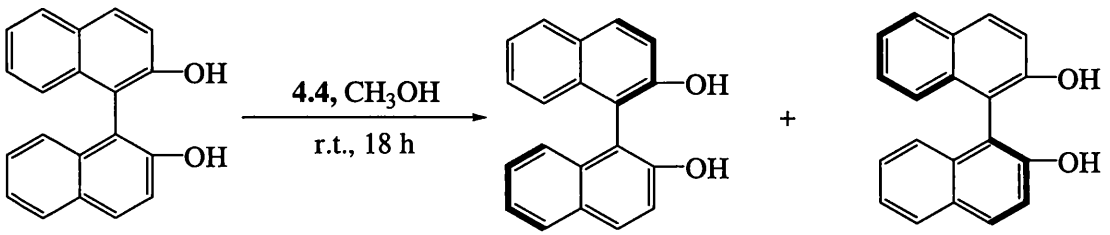
m /z (ES^-): 455 ($[M + Cl]^-$, 100%).

HRMS

Found $[M - Cl]^+$: 385.2274; $C_{26}H_{29}ON_2$ requires: 385.2274.

Specific rotation:
$[\alpha]_D^{28}$ = -181.8 (c 0.51, H_2O).

Resolution of racemic 2,2'-dihydroxy-1,1'-binaphthlene (4.2) using (8S,9R)-(-)-*N*-benzylcinchonidinium chloride(4.4)



Rac-**4.2** (R)-**4.2** (S)-**4.2**

Racemic **4.2** (12.60 g, 44 mmol) and dry MeOH (251 ml) were added to a 500-ml one-necked round bottomed flask and stirred for 10 min. The resolving reagent **4.4** (9.26g, 22 mol) was added to the solution and the mixture was stirred at r.t. for 18 h.

The solid was collected by suction filtration, washed with a little MeOH and dried in a vacuum desiccator containing freshly dried $CaCl_2$ overnight (named as solid 1, 11.86 g). EtOAc (133 ml) and 1 M HCl (133 ml) were added to the solid and the mixture was stirred at r.t. until all solid dissolved. The aqueous layer (containing the

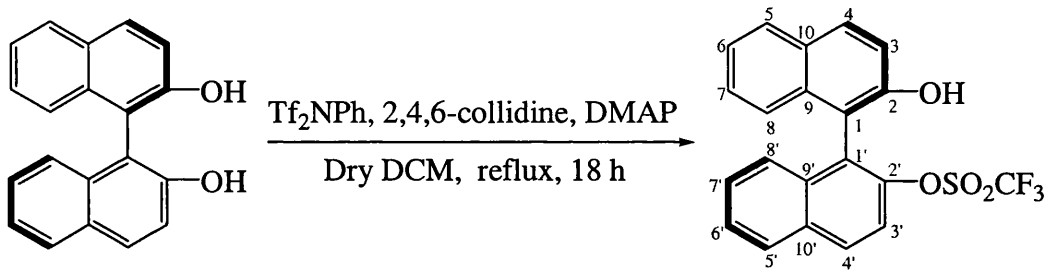
resolving reagent) was separated and then extracted with EtOAc (2 × 133 ml). The combined organic phase was washed with brine (2 × 100 ml), dried over anhydrous $MgSO_4$ and filtered. Removal of solvent from the filtrate *in vacuo* and drying of the resulting residue gave a white solid {4.73 g, m.p. 205 - 208 °C; $[\alpha]_D^{24}$ = +32.3 (c 1.04, THF), 94% ee; The ee value was based on $[\alpha]_D^{25}$ = 34.5 (c 1, THF)[12]}. It was recrystallized from benzene (38 ml) to give pure (R)-**4.2** {3.58 g; 28% yield; 56% of the theoretical yield of compound (R)-**4.2**; m.p. 207 - 210 °C; $[\alpha]_D^{25}$ = +33.7 (c 1.16, THF), 98% ee; The ee value was based on $[\alpha]_D^{25}$ = 34.5 (c 1, THF)[12]}.

The filtrate (named as filtrate 1), which was obtained after separating off solid 1, was evaporated to dryness *in vacuo*. The resulting residue was dried in a vacuum dessicator containing freshly dried $CaCl_2$ overnight (9.92 g). The solid was heated in EtOAc (40 ml) under reflux for 1 h. After cooling to r.t., the solution was separated. The remaining solid was extracted with EtOAc (40 ml) again in the same way. The filtrates were combined (named as filtrate 2). The remaining solid was dried in a vacuum dessicator containing freshly dried $CaCl_2$ overnight (3.39 g). EtOAc (40 ml) and 1M HCl (40 ml) were added to the solid and the mixture was stirred at r.t. until all solid dissolved. The aqueous layer (containing the resolving reagent) was separated and then extracted with EtOAc (2 × 40 ml). The combined EtOAc phase was washed with brine (100 ml), dried over anhydrous $MgSO_4$ and filtered. Removal of solvent from the filtrate *in vacuo* and drying of the resulting residue gave a white solid (1.33 g; m.p. 201 - 207 °C). It was recrystallized from benzene (11 ml) to give another batch of compound (R)-**4.2** {0.99 g; 8% yield; 16% of the theoretical yield of compound (R)-**4.2**; m.p. 209 - 211 °C; $[\alpha]_D^{25}$ = +32.9 (c 1.20, THF), 95% ee; The ee value was based on $[\alpha]_D^{25}$ = 34.5 (c 1, THF)[12]}.

Filtrate 2 was evaporated to dryness *in vacuo*. The resulting residue was dried in a vacuum dessicator containing freshly dried $CaCl_2$ overnight (6.36 g; m.p. 200 - 205 °C). It was recrystallized from benzene (50 ml) to give optically pure (S)-**4.2** {4.42 g; 35% yield; 70% of the theoretical yield of compound (S)-**4.2**; m.p. 209 - 211 °C; $[\alpha]_D^{25}$ = -36.8 (c 1.20, THF), > 99% ee; The ee value was based on $[\alpha]_D^{25}$ = -34.5 (c 1, THF)[12]}.

The resolving reagent **4.4** was recovered by neutralizing the aqueous layers with solid $NaHCO_3$ until the pH reached 8. The solid was collected by suction filtration and then dried in a vacuum dessicatior (8.48 g; 92% recovery).

Synthesis of (R)-2-hydroxy-2'-trifluoromethanesulfonyloxy-1,1-binaphthalene [(R)-4.5]



(R)-4.2 **(R)-4.5**

The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower, a condenser and a glass stopper. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. Compound (R)-**4.2** (3.46 g, 12.1 mmol), Tf_2NPh (4.33 g, 12.1 mmol), DMAP (0.18 g, 1.45 mmol) and dry DCM (50 ml) were added to the flask. Then 2,4,6-collidine (1.60 ml, 12.1 mmol) was added to the solution and the mixture was heated under reflux for 18 h.

After cooling to r.t., the solvent was evaporated off *in vacuo* and the resulting residue was dried in a vacuum desiccator overnight to give a yellow viscous oil (11.45 g). It was then purified by column chromatography (adsorbent: silica 60, 120g; eluting solvent: toluene) to give the product (4.49 g, 89% yield).

TLC (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}):
$R_f = 0.42$ (developing solvent: hexane / ethyl acetate = 3 / 1)

NMR

δ_H (400MHz, $CDCl_3$): 5.30 (br, 1H, O**H**); 7.21 (d, 1H, **H**-3, $^3J = 8$ Hz); 7.36 (m, 2H); 7.41 - 7.47 (m, 2H); 7.58 - 7.63 (m, 2H); 7.70 (d, 1H, $^3J = 9$ Hz); 7.96 (d, 1H, **H**-4, $^3J = 8$ Hz); 8.02 (m, 2H, **H**-5 and **H**-5'); 8.11 (d, 1H, **H**-4', $^3J = 9$ Hz).

δ_C (400MHz, $CDCl_3$): 112.7 (**C**-1); 118.4 (**C**-1'); 120.3; 124.2; 124.4; 124.8; 125.9; 127.0; 127.6; 128.1; 128.8; 129.6; 130.1; 131.9; 132.1; 133.5; 133.8; 134.2 (**C**-9); 138.5 (**C**-9'); 146.7 (**C**-2); 152.3 (**C**-2')

IR

ν_{max} (cm^{-1}): 3533 (sharp, HO-); 3298 (HO-, H-bonded); 3062 (Ar-H); 1622; 1598; 1508; 1496; 1418; 1203; 1135; 1067; 944; 931; 833; 811; 747.

MS

m /z (EI): 418 (M^+, 30%); 285 (44%); 225 (33%); 92 (95%); 69 (100%).

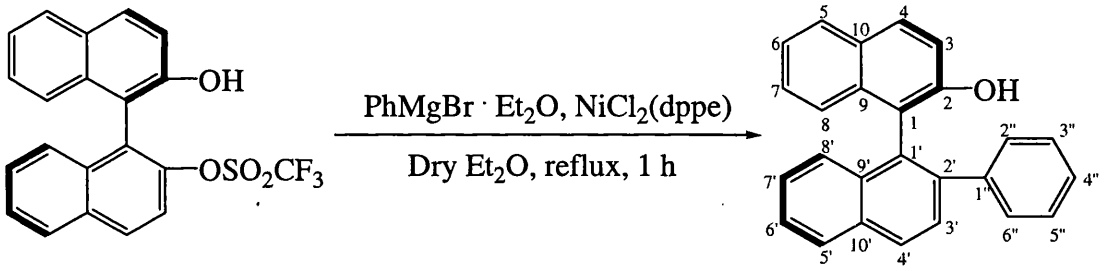
HRMS

Found $[M]^+$: 418.0477; $C_{21}H_{13}O_4F_3S$ requires: 418.0481.

Specific rotation

$[\alpha]_D^{28}$ = +22.9 (c 4.01, CH_3Cl).

Synthesis of (R)-2-hydroxy-2'-phenyl-1,1'-binaphthalene [(R)-4.6]



(R)-4.5 **(R)-4.6**

The reaction set-up consisted of a three-necked round bottomed flask equipped with a magnetic follower, a condenser, a glass stopper and a pressure equalizing addition funnel. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. $NiCl_2$(dppe) (0.11g, 0.2 mmol) and a solution of (R)-**4.5** (4.20 g, 10.1 mmol) in dry Et_2O (37 ml) were added to the flask. PhMgBr·Et_2O (3M; 13.4 ml, 40.2 mmol) was added slowly from the pressure equalizing addition funnel with good stirring. After addition, the reaction mixture was heated under reflux for 1 h.

After cooling to r.t., the reaction was quenched by addition of saturated aqueous NH_4Cl solution (50 ml) and the mixture was extracted with Et_2O (2 × 50 ml). The ethereal extract was washed with aqueous saturated $NaHCO_3$ solution (2 × 50 ml)

and brine (2 × 50 ml). The organic phase was dried over anhydrous $MgSO_4$ and filtered. Removal of solvent from the filtrate *in vacuo* and drying of the resulting residue gave some viscous oil (4.06 g). It was purified by column chromatography (adsorbent: silica 60, 120g; eluting solvent: hexane / toluene = 2 / 3) to give the product (2.22 g, 64% yield).

TLC (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}):

R_f = 0.23 (developing solvent: hexane / toluene = 2 / 3).

R_f = 0.50 (developing solvent: toluene).

NMR

δ_H (400MHz, $CDCl_3$): 4.76 (s, 1H, **H**O-); 6.95 - 7.05 (m, 7H, Ar-**H**); 7.09 - 7.26 (m, 4H, Ar-**H**); 7.42 (m, 1H); 7.60 (d, 1H, **H**-5, ^3J = 9 Hz); 7.67 (m, 2H, **H**-8 and **H**-8'); 7.88 (d, 1H, **H**-5', ^3J = 8 Hz); 7.97 (d, 1H, **H**-4', ^3J = 8 Hz).

δ_C (400MHz, $CDCl_3$): 117.6 (**C**-3); 118.1 (**C**-1); 123.6; 125.5; 125.7; 126.7; 127.0; 127.4; 127.6; 128.1; 128.5; 128.6; 129.0; 129.1 (**C**-10); 129.5; 129.8; 130.3; 133.5 / 133.6 / 134.6 / 138.3 / 141.2 / 142.0 (**C**-9, **C**-1', **C**-2', **C**-9', **C**-10', **C**-1"); 151.4 (**C**-2).

IR

ν_{max} (cm^{-1}): 3501 / 3418 (br. HO-, H-bonded); 3055 (Ar-H); 1619; 1596; 1494; 1444; 1379; 1263; 1204; 1173; 1143; 1128; 1028; 969; 936; 816; 762; 746; 697.

MS

m /z (EI): 346 (M^+, 100%); 239 (33%); 77 (30%).

m /z (CI, NH_3): 364 ($[M + NH_4]^+$, 100%).

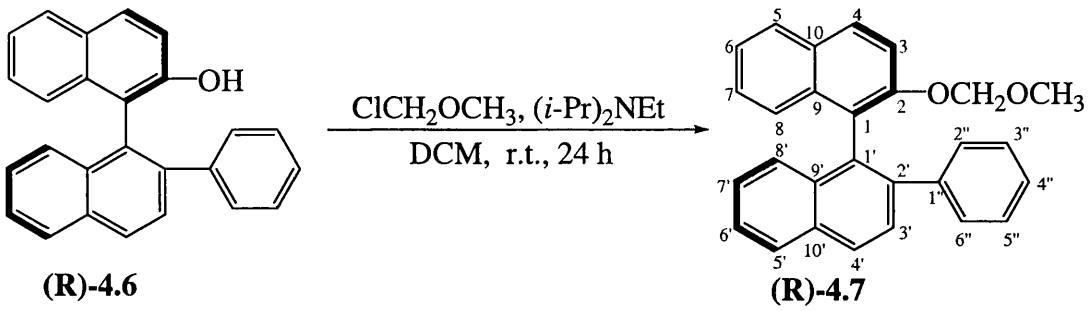
HRMS

Found $[M + NH_4]^+$: 364.1700; $C_{26}H_{22}ON$ requires: 364.1696.

Specific rotation

$[\alpha]_D^{28}$ = +10.8 (c 0.99, CH_3Cl).

Synthesis of (R)-2-methoxymethoxy-2'-phenyl-1,1'-binaphthalene [(R)-4.7]



(R)-4.6 **(R)-4.7**

Drying and purification of DIEA

DIEA was refluxed over anhydrous $CaCl_2$ (5% w /v) for 1 h and then distilled. The fraction of b.p. 126 - 127 °C was collected.

Synthetic procedure

The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower and capped with two septa. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. Compound (R)-**4.6** (2.10 g, 6.07 mmol), DCM (23 ml) and DIEA (3.0 ml, 17.2 mmol) were added to the flask. Then ClMOM (1.3 ml, 17.2 mmol) was added slowly by syringe with good stirring. The resulting solution was stirred for 24 h at r.t.

The reaction was quenched by addition of H_2O (23 ml) and the mixture was extracted with DCM (2 × 23 ml). The DCM extract was washed with H_2O (2 × 23 ml), dried over anhydrous Na_2SO_4 and filtered. Removal of solvent from the filtrate *in vacuo* and drying of the resulting residue gave a viscous oil (2.53 g). It was purified by column chromatography using a *gradient elution* technique (adsorbent: silica 60, 170 g; solvent: hexane / Et_2O = 100 / 0 ~ 95 / 5) to give the product (1.71 g, 73 % yield).

TLC (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}):
R_f = 0.55 (developing solvent: hexane / ethyl acetate = 3 / 1).

NMR

δ_H (400MHz, $CDCl_3$): 3.02 (s, 3H, $\mathbf{H}_3C$-); 4.69 (d, 1H, $\mathbf{H}^b$ of CH^aH^b-, ^2J = 7 Hz); 4.82 (d, 1H, $\mathbf{H}^a$ of CH^aH^b-, ^2J = 7 Hz); 6.92 - 6.95 (m, 3H, Ar-**H**); 7.02 - 7.07 (m, 3H, Ar-**H**); 7.10 - 7.23 (m, 4H, Ar-**H**); 7.34 - 7.39 (m, 2H, Ar-**H**); 7.59 (d, 1H, **H**-5, ^3J = 8 Hz); 7.70 (d, 1H, **H**-8', ^3J = 8 Hz); 7.73 (d, 1H, **H**-8, ^3J = 9 Hz); 7.87 (d, 1H, **H**-5', ^3J = 8 Hz); 7.94 (d, 1H, **H**-4', ^3J = 8 Hz).

δ_C (400MHz, $CDCl_3$): 56.1 ($\mathbf{C}H_3$); 95.4 ($\mathbf{C}H_2$); 116.7 (**C**-3); 123.3 (**C**-1); 124.2; 126.0; 126.2; 126.6; 126.7; 127.2; 127.7; 128.2; 128.3; 128.4; 128.7; 128.8 (**C**-10); 129.2; 129.7; 130.0; 132.2 / 133.2 / 133.6 / 134.8 / 140.4 / 142.4 (**C**-9, **C**-1', **C**-2', **C**-9', **C**-10', **C**-1"); 153.3 (**C**-2).

IR

ν_{max} (cm^{-1}): 3056 (Ar-H); 2956 / 2898 / 2823 (CH); 1622; 1592; 1506; 1495; 1471; 1332; 1240; 1196; 1147; 1080; 1055; 1031; 1011; 920; 904; 810; 762; 746; 700.

MS

m /z (EI): 390 (M^+, 32%); 81 (41%); 45 (100%).

m /z (CI, NH_3): 408 ($[M + NH_4]^+$, 100%).

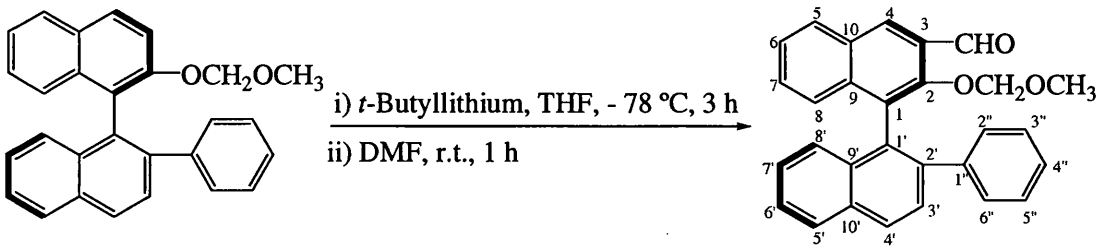
HRMS

Found $[M + NH_4]^+$: 408.1955; $C_{28}H_{26}O_2N$ requires: 408.1958.

Specific rotation

$[\alpha]_D^{27}$ = + 61.3 (c 0.55, CH_3Cl).

Synthesis of (R)-3-formyl-2-methoxymethoxy-2'-phenyl-1,1'-binaphthalene [(R)-4.8]



(R)-4.7 **(R)-4.8**

The reaction set-up consisted of a one-necked round bottomed flask equipped with a magnetic follower and capped with a septum. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. Compound (R)-**4.7**

(1.19 g, 3.05 mmol) and dry THF (13 ml) were added to the flask. The resulting solution was cooled to -78 °C in a dry ice-acetone cooling bath. *t*-Butyllithium (1.7 M in pentane; 4.20 ml, 7.02 mmol) was added slowly to the solution by syringe with good stirring. The resulting solution was stirred at -78 °C for 3 h. Dry DMF (1.20 ml, 15.3 mmol) was then added dropwise by syringe with good stirring. After addition, the reaction mixture was brought to r.t. and stirred for a further 1 h.

The reaction was quenched by addition of saturated aqueous NH_4Cl solution (13 ml) and the mixture was extracted with EtOAc (3 × 13 ml). The EtOAc extract was washed with aqueous $NaHCO_3$ solution (25 ml) and then with brine (15 ml). The organic phase was dried over anhydrous Na_2SO_4 and filtered. Removal of solvent from the filtrate *in vacuo* and drying of the resulting residue gave a viscous oil (1.55 g). It was purified by column chromatography (adsorbent: silica 60, 110 g; solvent: hexane / Et_2O = 19 / 1 ~ 5 / 4) to give the product (1.18 g, 92 % yield).

TLC (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}):
R_f = 0.45 (developing solvent: hexane / diethyl ether = 5 / 4).

NMR

δ_H (400MHz, $CDCl_3$): 2.78 (s, 3H, $\mathbf{H}_3$C-); 4.34 (d, 1H, $\mathbf{H}^b$ of C$\mathbf{H}^a\mathbf{H}^b$-, ^2J = 6 Hz); 4.52 (d, 1H, $\mathbf{H}^a$ of C$\mathbf{H}^a\mathbf{H}^b$-, ^2J = 6 Hz); 6.93 - 6.96 (m, 3H, Ar-**H**); 6.99 - 7.01 (m, 2H, Ar-**H**); 7.15 - 7.42 (m, 6H, Ar-**H**); 7.59 (d, 1H, **H**-8', ^3J = 9 Hz); 7.88 (m, 2H, **H**-5 and **H**-5'); 7.96 (d, 1H, **H**-4', ^3J = 8 Hz); 8.33 (s, 1H, **H**-4); 10.25 (s, 1H, C**H**O-);

δ_C (400MHz, $CDCl_3$): 57.3 (**C**H_3); 100.1 (**C**H_2); 125.9 (**C**-1); 126.2; 126.3; 126.4; 127.0; 127.1; 127.2; 127.9; 128.6; 128.9; 129.2; 129.7 (**C**-3); 129.8; 130.5; 130.6; 131.8; 130.0 / 130.7 / 133.1 / 133.6 / 138.1 / 141.2 / 141.9 (**C**-9, **C**-10', **C**-1', **C**-2', **C**-9', **C**-10', **C**-1"); 153.6 (**C**-2); 191.4 (**C**HO-).

IR

ν_{max} (cm^{-1}): 3044 (Ar-H); 2951 / 2880 / 2824 (CH); 1688 (C=O); 1618; 1586; 1494; 1444; 1352; 1155; 1104; 1068; 1036; 959; 923; 823; 760; 751; 698.

MS

m /z (EI): 418 (M^+, 20%); 315 (25%); 45 (100%).

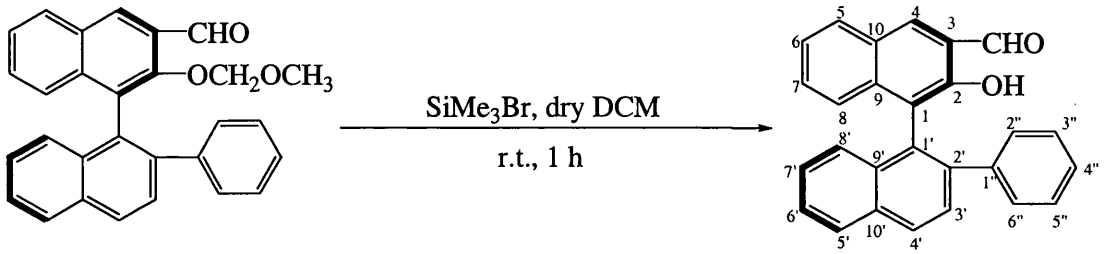
m /z (CI, NH_3): 436 ($[M + NH_4]^+$, 100%); 419 ($[M + H]^+$, 93%); 404 (64%); 387 (83%); 86 (43%).

HRMS:

Found $[M + NH_4]^+$: 436.1912; $C_{29}H_{26}O_3N$ requires: 436.1907.

Specific rotation:
$[\alpha]_D^{30}$ = -19.5 (c 0.19, CH_3Cl).

Synthesis of (R)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene [(R)-4.9]



(R)-4.8 **(R)-4.9**

The reaction set-up consisted of a one-necked round bottomed flask equipped with a magnetic follower and capped with a septum. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. Compound (R)-**4.8** (1.12 g, 2.68 mmol), some activated 4 Å molecular sieves and dry DCM (12 ml) were added to the flask. Then $SiMe_3Br$ (1.43 ml, 10.9 mmol) was added dropwise by syringe with good stirring. After addition, the reaction mixture was stirred at r.t. for 1 h.

The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (30 ml). The liquid layers were separated and the aqueous phase was extracted with DCM (3 × 30 ml). The combined DCM extract was washed H_2O (20 ml), dried over anhydrous $MgSO_4$ and filtered. Removal of solvent from the filtrate *in vacuo* and drying of the resulting residue gave a yellow solid (1.08 g). It was purified by column chromatography (adsorbent: silica 60, 100 g; solvent: hexane / toluene = 3 / 7) to give the product (0.88 g, 88% yield).

TLC (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}):
R_f = 0.32 (developing solvent: hexane / toluene = 3 / 7).

NMR

δ_H (400MHz, $CDCl_3$): 6.91 - 6.94 (m, 3H, Ar-**H**); 7.03 (d, 1H, ^3J = 8 Hz); 7.11 - 7.23 (m, 6H, Ar-**H**); 7.37 (m, 1H, Ar-**H**); 7.56 (d, 1H, **H**-8 or **H**-8', ^3J = 8 Hz); 7.71 (d, 1H, **H**-5, ^3J = 8 Hz); 7.86 (d, 1H, **H**-5', ^3J = 8 Hz); 7.94 (d, 1H, **H**-4', ^3J = 8 Hz); 8.01 (s, 1H, **H**-4); 9.94 (s, 1H, C**H**O-); 10.35 (s, 1H, **H**O-).

δ_C (400MHz, $CDCl_3$): 121.7 (**C**-1); 121.9; 124.6; 125.8; 126.3; 126.5; 126.7; 126.9; 127.0; 127.5 (**C**-3); 127.8 ; 128.7; 128.9; 129.1; 130.1; 130.8; 138.3 (**C**-4); 130.3 / 133.1 / 133.4 / 138.2 / 141.1 / 142.3 (**C**-9, **C**-10', **C**-1', **C**-2', **C**-9', **C**-10, **C**-1"); 154.0 (**C**-2); 197.2 (**C**HO-).

IR

ν_{max} (cm^{-1}): 3180 (br. -OH, H-bonded); 3048 (Ar-H); 2842 (O=**C-H**); 1650 (C=O); 1631; 1506; 1440; 1411; 1385; 1385; 1343; 1290; 1180; 1115; 1027; 940; 894; 822; 763; 747; 704.

MS

m /z (EI): 374 (M^+, 100%); 327 (76%); 326 (67%); 239 (33%); 163 (52%); 156 (51%); 150 (45%); 77 (38%).

m /z (CI, NH_3): 392 ($[M + NH_4]^+$, 100%); 316 (20%).

HRMS:

Found $[M + NH_4]^+$: 392.1648; $C_{27}H_{22}O_2N$ requires: 392.1645.

Specific rotation

$[\alpha]_D^{28}$ = -42.5 (c 1.0, CH_3Cl).

4.5 References for *Chapter 4*

1. a) B. Feringa and H. Wynberg. *J. Org. Chem.,* 1981, 46, 2547; b) J. Brussee, J. L. G. Groenendijk, J. M. Tekoppele and A. C. A. Jansen. *Tetrahedron*, 1985, 41, 3313; c) M. Hovorkova, J. Günterová and J. Závada. *Tetrahedron Lett.,* 1990, 31, 413.
2. F. Toda, K. Tanaka and S. Iwata. *J. Org. Chem.,* 1989, 54, 3007.
3. M. Smrčina, J. Poláková, Š. Vyskočil and P. Kočovsky. *J. Org. Chem.,* 1993, 58, 4534.
4. a) M. Noji, M. Nakajima and K. Koga. *Tetrahedron Lett.,* 1994, 35, 7983; b) M. Nakajima, I. Miyoshi, K. Kanayama and S. Hashimoto. *J. Org. Chem.,* 1999, 64, 2264.

5. K. Ding, Y. Wang, L. Zhang, Y. Wu and T. Matsuura. *Tetrahedron*, 1996, 52, 1005.
6. R. J. Kazlauskas. *J. Am. Chem. Soc.,* 1989, 111, 4953.
7. a) K. Tanaka, T. Okada and F. Toda. *Angew. Chem. Int. Ed. Engl.*, 1993, 32, 1147; b) Q. S. Hu, D. Vitharana and L. Pu. *Tetrahedron: Asymmetry,* 1995, 6, 2123.
8. F. Toda and K. Tanaka. *J. Org. Chem.,* 1988, 53, 3607.
9. a) B. Gong, W. Chen and B. Hu. *J. Org. Chem.,* 1991, 56, 423; b) C. Fabri, G. Delogu and O. De Lucchi. *J. Org. Chem.,* 1995, 60, 6599.
10. a) M. Periasamy, A. S. B. Prasad, J. V. B. Kanth and Ch. K. Reddy. *Tetrahedron: Asymmetry,* 1995, 6, 341; b) M. Periasamy, L. Venkatraman and K. R. J. Thomas. *J. Org. Chem.,* 1997, 62, 4302; c) Z. Shan, Y. Xiong, W. Li and D. Zhao. *Tetrahedron: Asymmetry,* 1998, 9, 3985.
11. M. Smrčina, M. Lorenc, V. Hanus, P. Sedmera and P. Kočovsky. *J. Org. Chem.,* 1992, 57, 1917.
12. M. Periasamy, L. Venkatraman, S. Sivakumar, N. Sampathkumar and C. R. Ramanathan. *J. Org. Chem.,* 1999, 64, 7643.
13. C. H. Liu. *Synthesis and Applications of Polymer-bound Chiral Epoxidation Catalysts.* PhD thesis: University of Wales Swansea, United Kingdom, 2001.
14. S. Colonna, A. Re and H. Wynberg. *J. Chem. Soc., Perkin Trans.,* 1, 1981, 547.
15. a) F. Toda and K. Tanaka. *J. Org. Chem.,* 1994, 59, 5748; b) F. Toda and K. Tanaka. *Chem. Commun.,* 1997, 1087.
16. a) T. Hamada, T. Fukuda, H. Imanishi and T. Katsuki. *Tetrahedron*, 1996, 52, 515; b) H. Sasaki, R. Irie, T. Hamada, K. Suzuki and T. Katsuki. *Tetrahedron,* 1994, 50, 11827.
17. a) V. Farina. In: *Comprehensive Organometallic Chemistry II,* Eds. E. W. Abel, F. G. A. Stone and G. Wilkinson. Pergamon: Oxford, 1995, Vol. 12; b) N. Miyaura and A. Suzuki. *Chem. Rev.,* 1995, 95, 2457.
18. a) T. W. Greene. *Protective Groups in Organic Synthesis*, John Wiley and Sons: New York, 1981; b) G. J. H. Rall, M. E. Oberholzer, D. Ferreira and D. G. Roux. *Tetrahedron Lett.,* 1976, 1033; c) G. Stork and T. Takahashi. *J. Am. Chem. Soc.,* 1977, 99, 1275.
19. G. A. Olah, G. K. S. Prakash and M. Arvanaghi. *Synthesis*, 1984, 228 and references therein.
20. S. Hanessian, D. Delorme and Y. Dufresne. *Tetrahedron Lett.,* 1984, 25, 2515.

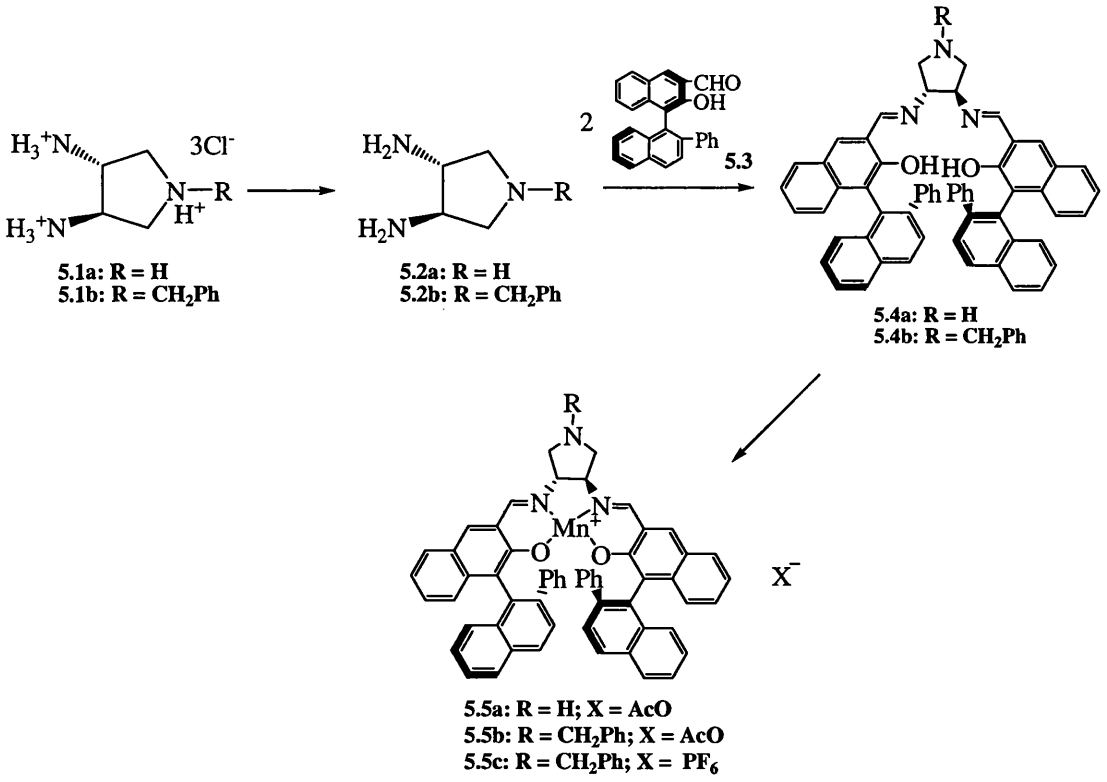
21. a) J. Leonard, B. Lygo and G. Procter. *Advanced practical organic chemistry*, 2nd Ed. Chapman &Hall, 1995; b) B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell. *Vogel's Textbook of Practical Organic Chemistry,* 5th Ed. Longman: Harlow, 1989.

CHAPTER FIVE

PREPARATION OF (SALEN)Mn(III) COMPLEXES AND APPLICATIONS OF THESE COMPLEXES IN ASYMMETRIC EPOXIDATION OF 1,2-DIHYDRONAPHTHALENE

5.1 Introduction

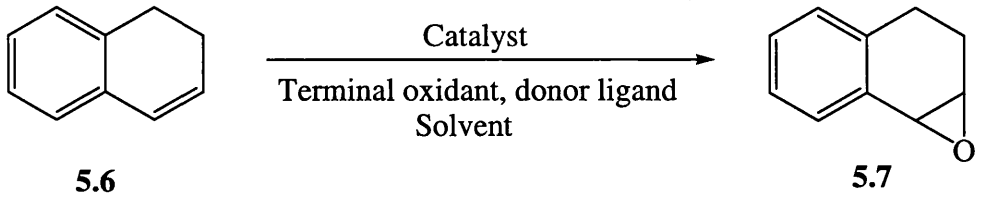
As described in *Chapter 2*, our synthetic targets are salen ligands **5.4** (named as compound **2.5** in *Chapter 2*) and the corresponding Mn(III) complexes **5.5** (named as compound **2.6** in *Chapter 2*). The salen ligands **5.4** would be synthesized by condensation of *trans*-(3R,4R)-diaminopyrrolidine (**5.2a**; named as compound **3.12** in *Chapter 3*) or *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine (**5.2b**; named as compound **3.10** in *Chapter 3*) with two molar equivalents of (R)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene [**5.3**; named as compound (R)-**4.9** in *Chapter 4*]. They would then be converted to the corresponding Mn(III) complexes **5.5** (Scheme 5.1).



Scheme 5.1

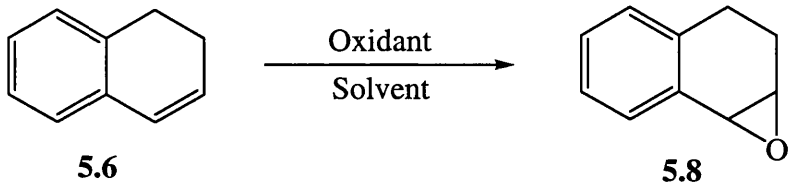
Upon successful preparation of these complexes, their catalytic performances in asymmetric epoxidation of unfunctionalized alkenes would be tested using 1,2-dihydronaphthalene (**5.6**) as the substrate (Scheme 5.2). However, before carrying out these asymmetric syntheses, it would be better to synthesize the corresponding

racemic epoxide **5.8** first (Scheme 5.3) to gain some information about the epoxidation reactions and to use the racemic epoxide to set up the reaction monitoring system.



5.6 **5.7**

Scheme 5.2



5.6 **5.8**

Scheme 5.3

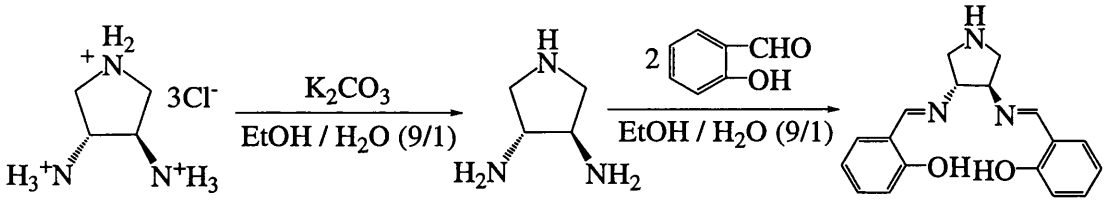
5.2 Discussion and results

5.2.1 Preparation of the target salen ligands 5.4 and the corresponding (salen)Mn(III) complexes 5.5

As described in *Chapter 1* (Section 1.3.2), preparation of chiral C_2 symmetric salen ligands is generally achieved by condensation of an optically pure 1,2-diamine with two molar equivalents of an appropriately substituted salicylaldehyde derivative. Preparation of the corresponding (salen)Mn(III)OAc complex is then readily accomplished by reaction of the salen ligand with one or two molar equivalents of $Mn(OAc)_2 \cdot 4H_2O$ in air. (Salen)Mn(III)OAc complexes can be transformed to (salen)Mn(III)PF_6 complexes by reaction with $NaPF_6$.

5.2.1.1 Preparation of a model salen ligand 5.9

Before synthesizing the target salen ligands **5.4** and the corresponding Mn(III) complexes **5.5**, a simple model compound **5.9** was synthesized first to try to set up an appropriate synthetic route for synthesis of future salen ligands (Scheme 5.4). Optically pure *trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt (**5.1a**; 1mmol) was transformed to the corresponding diamine [*trans*-(3R,4R)-diaminopyrrolidine (**5.2a**)] by refluxing with K_2CO_3 (4 mmol) for 5 min in a mixed solvent system.[1] Since most polyamines are not stable,[2] diamine **5.2a** was not isolated from the reaction mixture. Instead, salicylaldehyde (2 mmol) was added to the reaction mixture and the resulting mixture was heated under reflux for 3 h and then stirred for 13 h at r.t.



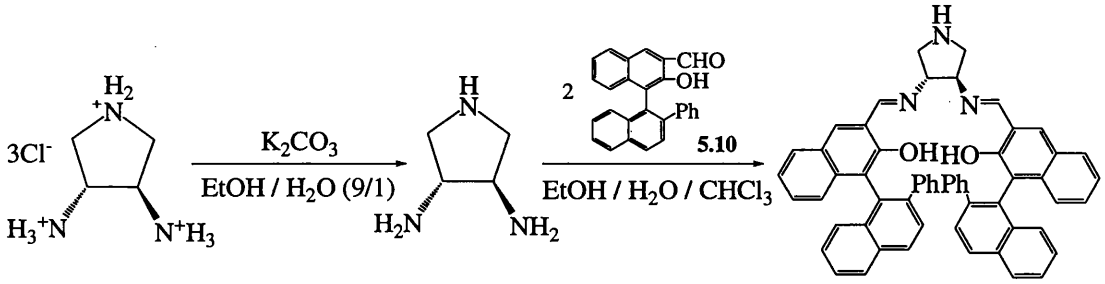
5.1a **5.2a** **5.9**

Scheme 5.4

The condensation reaction of salicylaldehyde with diamine **5.2a** was monitored by tlc. The reaction was found to be quite clean, but incomplete – the spots corresponding to the product and salicylaldehyde were observed after working up the reaction. Purification of the desired product **5.9** was first carried out by flash silica column chromatography. However, it was found that the product **5.9** partially decomposed on silica gel. The purification was therefore carried out again by flash neutral alumina column chromatography. This time the separation was successful; the product **5.9** was obtained in 38% yield and was characterized by NMR, IR and mass spectra. The incompletion of the reaction and decomposition of the product on silica gel might account for the low yield. The detailed experimental procedure and characterization of the product are reported in the *Experimental Section* of this chapter.

5.2.1.2 Preparation of salen ligand 5.11

Before synthesizing the target salen ligand **5.4a**, an analogue salen ligand **5.11** was synthesized, in which the racemic 3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene (**5.10**) was used to react with diamine **5.2a** (Scheme 5.5). The reaction was carried out in a similar way to that used in preparation of the model salen ligand **5.9**. Optically pure *trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt (**5.1a**; 0.07 mmol) was reacted with K_2CO_3 (0.3 mmol) for 30 min at r.t. in a mixed solvent system. Then compound **5.10** (0.13 mmol) was added and the reaction mixture was stirred for 3 h at r.t.



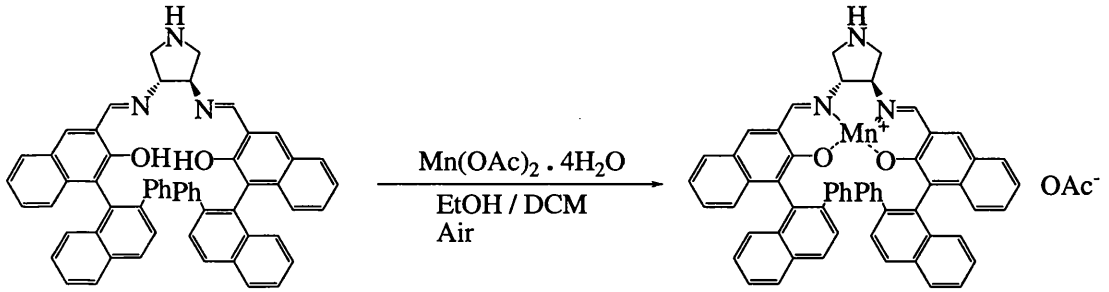
5.1a **5.2a** **5.11**

Scheme 5.5

Unlike in the preparation of the model salen ligand **5.9**, $CHCl_3$ was added to the reaction mixture in this reaction to aid the dissolution of compound **5.10**, so that the condensation reaction could be carried out in a homogeneous solution. Tlc was used to monitor the progress of the condensation reaction. It showed that the reaction was nearly complete after 3 h at r.t. The product **5.11** was obtained in 39% yield after purification by flash neutral alumina column chromatography and was characterized by NMR, IR and mass spectra. No significant decomposition of the product on the alumina column was observed. The detailed experimental procedure and characterization of the product are reported in the *Experimental Section* of this chapter.

5.2.1.3 Preparation of (salen)Mn(III) complex 5.12

(Salen)Mn(III) complex **5.12** was prepared by reaction of the salen ligand **5.11** (0.014 mmol) with $Mn(OAc)_2{\cdot}4H_2O$ for 24 h at r.t. in air, following a general procedure.[3,4] Salen ligand **5.11** was not soluble in ethanol, so DCM was added to the reaction mixture to aid its dissolution (Scheme 5.6).



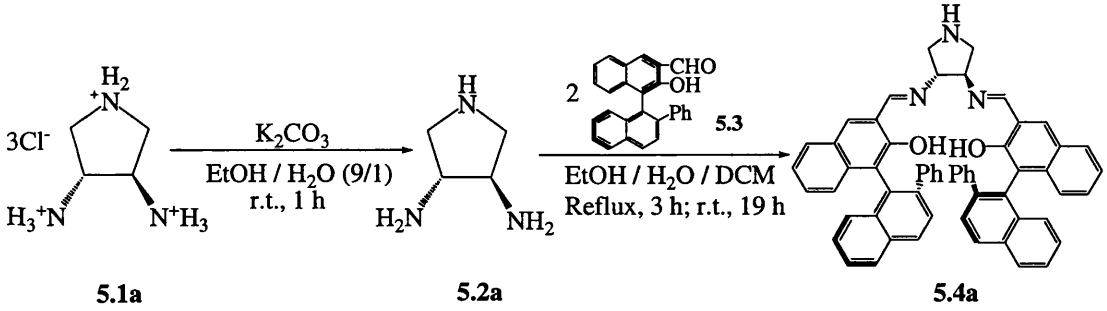
5.11 **5.12**

Scheme 5.6

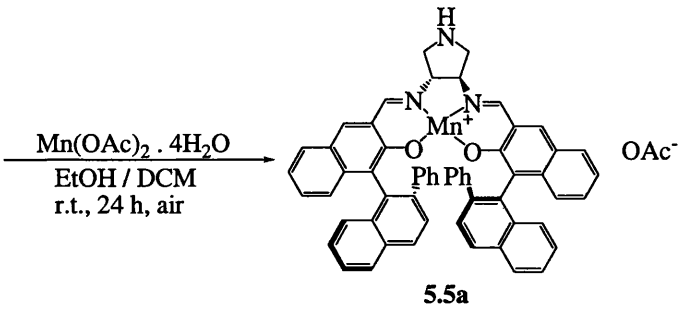
The reaction was carried out in a beaker to maximize contact of the reaction mixture with O_2 in the air. After working up the reaction, DCM was added to the crude product. The unreacted inorganic salt was then removed by filtration. (Salen)Mn(III) complex **5.12** was obtained in 96% yield and was characterized by MS and IR spectra. The low resolution ES^+ and high resolution mass spectra clearly showed the presence of the $[M - OAc]^+$ ion (m/z: 866). Also, the low resolution ES^- showed the presence of AcO^- ion (m/z: 59). The IR spectrum showed the presence of the characteristic imine group (C=N) adsorption at 1626 cm^{-1} and the disappearance of OH- adsorption, which was present in the IR spectrum of the salen ligand **5.11**. The secondary amine group (N-H) was found to be unaffected under the reaction conditions. The detailed experimental procedure and characterization of the product are reported in the *Experimental Section* of this chapter.

5.2.1.4 Preparation of salen ligand 5.4a and the corresponding (salen)Mn(III) complex 5.5a

A similar procedure was used to prepare the target salen ligand **5.4a** and the corresponding (salen)Mn(III) complex **5.5a** (Scheme 5.7). The molar ratios of the reactants were the same as those used in preparation of salen ligand **5.11** and (salen)Mn(III) complex **5.12**. The condensation reaction was carried out by refluxing the reaction mixture for 3 h and then stirring for 19 h at r.t in the hope that these measures would drive the reaction to completion. The salen ligand **5.4a** was obtained in 40% yield after purification by flash neutral alumina column chromatography. And, (salen)Mn(III) complex **5.5a** was obtained in 79% yield by reaction of the salen ligand **5.4a** with $Mn(OAc)_2{\cdot}4H_2O$ in air. The MS and IR spectra of complex **5.5a** were the same as those of complex **5.12**.



5.1a **5.2a** **5.4a**



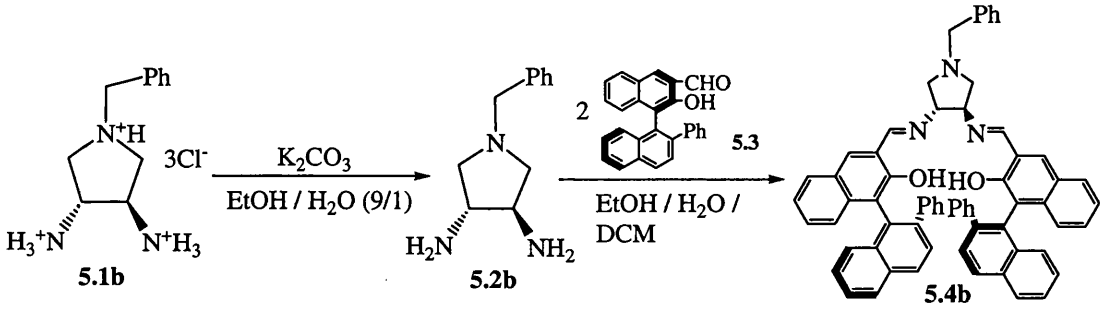
5.5a

Scheme 5.7

5.2.1.5 Preparation of salen ligand 5.4b and the corresponding (salen)Mn(III) complex 5.5b

5.2.1.5.1 Attempt to get the pure salen ligand 5.4b

A similar procedure was used to prepare salen ligand **5.4b** as those used to synthesize salen ligands **5.11** and **5.4a** (Scheme 5.8). *trans*-(3R,4R)-1-Benzyl-3,4-diaminopyrrolidine trihydrochloride salt (**5.1b**; 0.1 mmol) was reacted with K_2CO_3 (0.45 mmol) for 1 h at r.t. in a mixed solvent system. Then compound **5.3** (0.2 mmol) was added and the reaction mixture was stirred for 3 h at r.t.



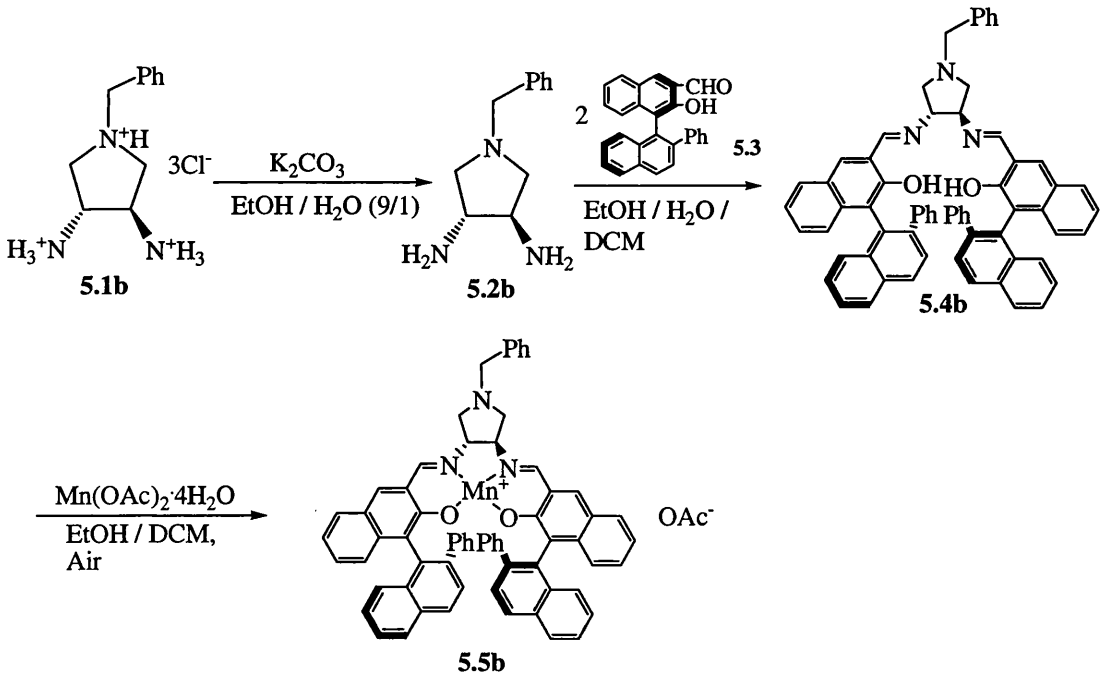
Scheme 5.8

As in the synthesis of salen ligands **5.11** and **5.4a**, DCM was added to the reaction mixture to aid the dissolution of compound **5.3** so that the condensation reaction could be carried out in a homogeneous solution. Two spots were observed by tlc for the crude product, one corresponding to the starting material **5.3** and the other corresponding to the desired salen ligand **5.4b**. Since both salen ligands **5.11** and **5.4a** partially decomposed on a silica column, purification of the product **5.4b** was carried out by flash neutral alumina column chromatography. However, unlike salen ligands **5.11** and **5.4a**, salen ligand **5.4b** was found to decompose on the neutral alumina column. The starting material **5.3** and a little quantity of the desired product, which was confirmed by mass spectra, were obtained after column chromatography.

Since the attempt to get the pure salen ligand **5.4b** failed, we decided to explore the feasibility to prepare (salen)Mn(III) complex **5.5b** directly from the crude salen ligand **5.4b**. Indeed, some (salen)Mn(III) complexes, especially Katsuki-type (salen)Mn(III) complexes, have been prepared in one pot from the chiral diamine and binaphthyl salicylaldehyde analogues without isolation of the salen ligands.[4]

5.2.1.5.2 Preparation of (salen)Mn(III) complex 5.5b

(Salen)Mn(III) complex **5.5b** was prepared according to Scheme 5.9. *trans*-(3R,4R)-1-Benzyl-3,4-diaminopyrrolidine (**5.1b**; 0.15 mmol) was reacted with K_2CO_3 (0.68 mmol) for 1 h at r.t. in a mixed solvent system. Then compound **5.3** (0.3 mmol) was added and the reaction mixture was stirred for 3 h at r.t. After working up the reaction, the crude product was monitored by tlc. Two spots were observed, one corresponding to the starting material **5.3** and the other corresponding to the desired salen ligand **5.4b**. The crude product was dissolved in DCM for complexation with an ethanolic solution of $Mn(OAc)_2{\cdot}4H_2O$ (0.15 mmol) and the mixture was stirred for 24 h at r.t., while air was bubbled into the reaction mixture to facilitate formation of the complex. (Salen)Mn(III) complex **5.5b** was obtained in 63% yield from compound **5.1b**.

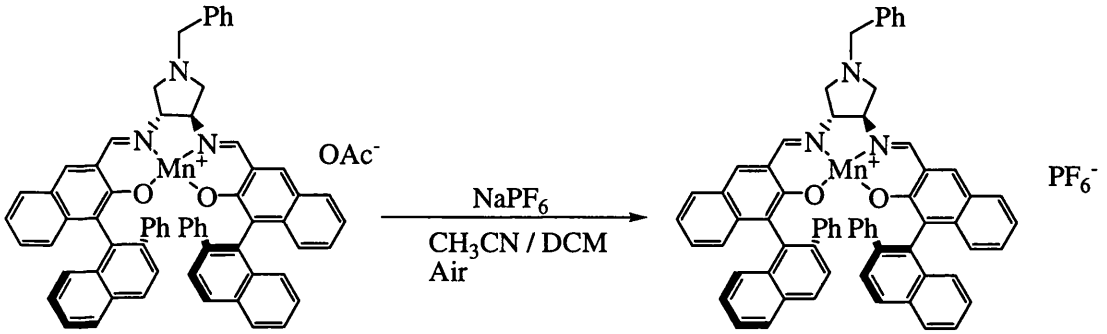


Scheme 5.9

(Salen)Mn(III) complex **5.5b** was characterized by MS and IR spectra. The low resolution ES^+ and high resolution mass spectra clearly showed the presence of the $[M - OAc]^+$ ion (m/z: 956), while the low resolution ES^- mass spectrum showed the presence of AcO^- ion (m/z: 59). The IR spectrum showed the presence of the characteristic imine group (C=N) adsorption at 1626 cm^{-1}. The detailed experimental procedure and characterization of the product are reported in the *Experimental Section* of this chapter.

5.2.1.6 Preparation of (salen)Mn(III) complex 5.5c

(Salen)Mn(III) complex **5.5c** was synthesized by reaction of (salen)Mn(III) complex **5.5b** (0.06 mmol) with $NaPF_6$ (0.57 mmol) in air for 24 h at r.t. (Scheme 5.10). The reaction was carried out following a general procedure.[5]



5.5b **5.5c**

Scheme 5.10

(Salen)Mn(III) complex **5.5c** was obtained in 90% yield and was characterized by its mass and IR spectra. The low resolution ES^+ and high resolution mass spectra clearly showed the presence of the $[M - PF_6]^+$ ion (m/z: 956), while the low resolution ES^- mass spectrum showed the presence of PF_6^- ion (m/z: 150). The IR spectrum showed the presence of the characteristic imine group (C=N) adsorption at 1626 cm^{-1}. The detailed experimental procedure and characterization of the product are reported in the *Experimental Section* of this chapter.

So far, the syntheses of the salen ligands were all carried out in a mixed solvent system, in which H_2O was used as a component of the solvent to aid the

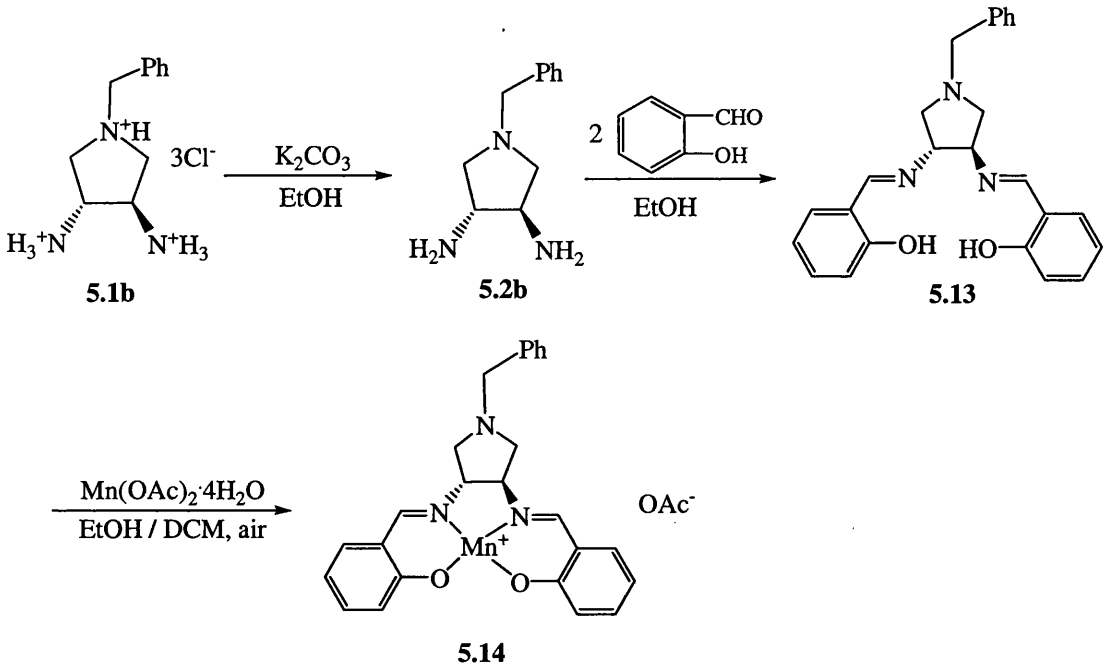
dissolution of K_2CO_3. As it well known, the formation of imines from aldehydes or ketones is usually reversible (Scheme 5.11).[6] The presence of excess H_2O might drive the reaction to the left and therefore disfavour the formation of the imines.

Scheme 5.11

In an attempt to work out the effects of the presence of excess H_2O on the formation of the salen ligands, two experiments were designed, in which the syntheses of salen ligands were carried out under anhydrous conditions.

5.2.1.7 Preparation of a model salen ligand 5.13 and the corresponding (salen)Mn(III) complex 5.14 under anhydrous conditions

Another model salen ligand **5.13** was synthesized under anhydrous conditions, in which no H_2O was added as a component of the solvent system. Also, the presence of excess anhydrous K_2CO_3 was expected to adsorb the H_2O that was produced during the condensation reaction (Scheme 5.12). *trans*-(3R,4R)-1-Benzyl-3,4-diaminopyrrolidine (**5.1b**; 0.15 mmol) was reacted with anhydrous K_2CO_3 (0.68 mmol) for 1 h at r.t. in dry EtOH. Salicylaldehyde (0.3 mmol) was added to the reaction mixture and the resulting mixture was refluxed for 3 h and then stirred for 18 h at r.t. After working up the reaction, the salen ligand **5.13** was dissolved in DCM for the following complexation with an ethanolic solution of $Mn(OAc)_2{\cdot}4H_2O$ (0.15 mmol) and the mixture was stirred for 24 h at r.t., while air was bubbled into the reaction mixture to facilitate the formation of the complex. (Salen)Mn(III) complex **5.14** was obtained in 68% yield from compound **5.1b**.



Scheme 5.12

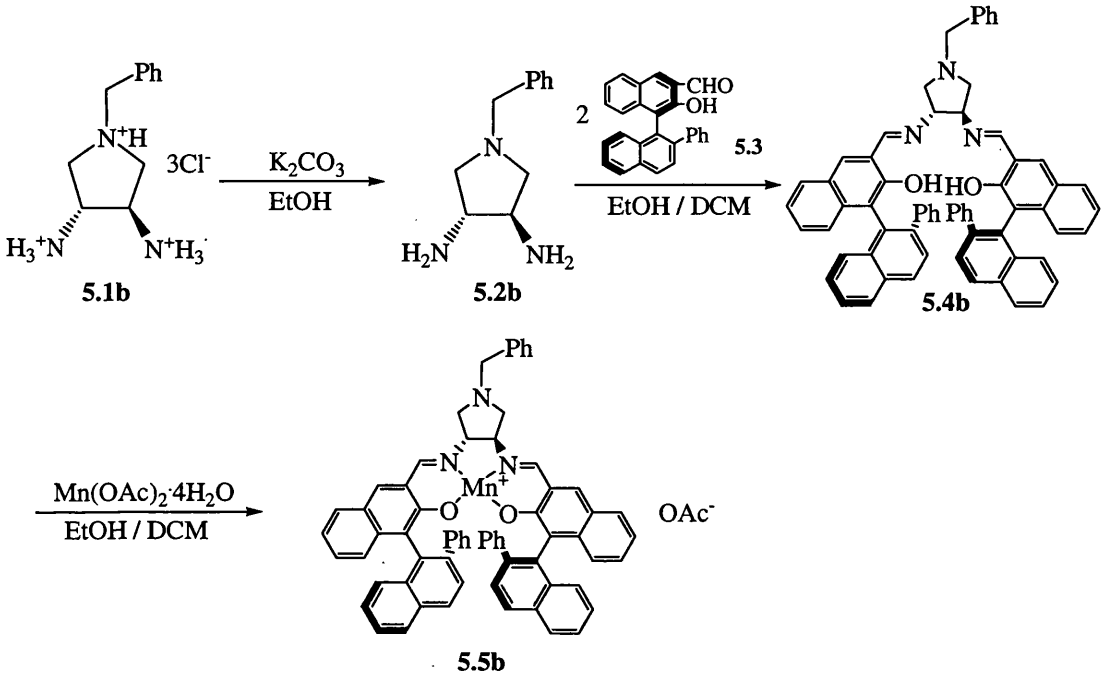
Tlc showed that the condensation reaction was complete. Salen ligand **5.13** was characterized by NMR and mass spectra and (salen)Mn(III) complex **5.14** was characterized by mass and IR spectra. The low resolution ES^+ and high resolution mass spectra clearly showed the presence of the $[M - OAc]^+$ ion (m/z: 452), while the low resolution ES^- mass spectrum showed the presence of OAc^- ion (m/z: 59). The IR spectrum showed the presence of the characteristic imine group (C=N) adsorption at 1623 cm^{-1}. The detailed experimental procedure and characterization of the products are reported in the *Experimental Section* of this chapter.

It appeared that anhydrous reaction conditions worked well for the preparation of salen ligand **5.13**. Therefore, this methodology was used to prepare salen ligand **5.4b**.

5.2.1.8 Preparation of salen ligand 5.4b and the corresponding (salen)Mn(III) complex 5.5b under anhydrous conditions

Salen ligand **5.4b** was synthesized under anhydrous conditions according to Scheme 5.13. *trans*-(3R,4R)-1-Benzyl-3,4-diaminopyrrolidine (**5.1b**; 0.15 mmol) was

reacted with anhydrous K_2CO_3 (0.68 mmol) for 1 h at r.t. in dry EtOH. Compound **5.3** (0.27 mmol) was added to the reaction mixture and the resulting mixture was refluxed for 6 h, and then stirred for 18 h at r.t. Tlc was used to monitor the progress of the condensation reaction. The reaction was found to be incomplete even though the reaction mixture was heated under reflux for 6 h and then stirred at r.t. for a further 18 h. The yield of the crude salen ligand **5.4b** (96%) was slightly higher than that in reaction where the mixed solvent system was used (93%; Section 5.2.1.5.2).



Scheme 5.13

The crude salen ligand was dissolved in DCM for the following complexation with an ethanolic solution of $Mn(OAc)_2 \cdot 4H_2O$ (0.15 mmol) and the mixture was stirred for 24 h at r.t., while air was bubbled into the reaction mixture to facilitate the formation of the complex. (Salen)Mn(III) complex **5.5b** was obtained in 72% yield from compound **5.1b** and was identical to that synthesized in the mixed solvent system. The detailed experimental procedure is reported in the *Experimental Section* of this chapter.

In conclusion, the salen ligands can be prepared in either a mixed solvent system or under anhydrous conditions. The reaction that was carried out under anhydrous conditions produced a higher yield.

Having the target (salen)Mn(III) complexes in hand, the next step would be to test their catalytic performances in the asymmetric epoxidation of 1,2-dihydronaphthalene (**5.6**). However, before carrying out the asymmetric syntheses, it would be better to prepare the corresponding racemic epoxide first using a similar method in order to get some information about the reaction and to set up tlc and hplc reaction monitoring systems and a product characterization system (especially the method to determine the enantiomeric excess of the product).

5.2.2 Synthesis of racemic 1,2-epoxy-1,2,3,4-tetrahydronaphthalene (5.8) by direct epoxidation of 1,2-dihydronaphthalene (5.6)

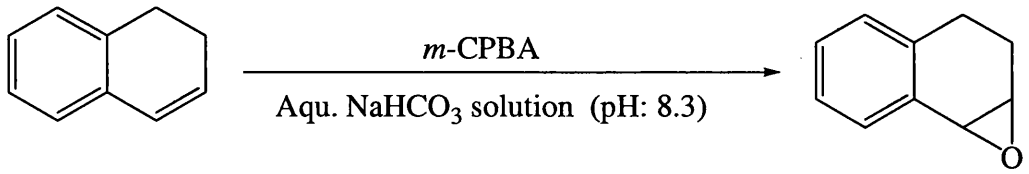
Preparation of aryl epoxides is usually difficult because the products are sensitive to acids and therefore unstable under the usual epoxidizing conditions.[7] The epoxidation reactions are usually carried out in the presence of a buffer, such as sodium carbonate, sodium bicarbonate, or sodium hydrogen phosphate.[8]

In the present work, three reaction systems were used to synthesise racemic 1,2-epoxy-1,2,3,4-tetrahydronaphthalene (**5.8**) from 1,2-dihydronaphthalene (**5.6**). These included: epoxidation in a buffered aqueous solution; epoxidation in a biphasic solvent system; and epoxidation in an organic solvent.

5.2.2.1 Epoxidation of 1,2-dihydronaphthalene (5.6) with *m*-CPBA in an aqueous sodium bicarbonate solution

It has been reported that labile aryl epoxides can be synthesized using *m*-CPBA in the presence of an aqueous sodium bicarbonate solution (pH = 8.3). The reactions have been found to proceed rapidly and produce the epoxides in good to

excellent yield.[9] Therefore, it was decided to follow this method to synthesize 1,2-epoxy-1,2,3,4-tetrahydronaphthalene (**5.8**) first (Scheme 5.14).



5.6 **5.8**

Scheme 5.14

Three experiments were carried out following the literature procedure.[9] The reactions were carried out at 0 °C. The molar ratio of *m*-CPBA to compound **5.6** was 1. And, *m*-CPBA was pre-cooled to 0 °C prior to use and added from a solid addition tube in small portions.

It has been reported that identical results are obtained for epoxidation reactions using commercial *m*-CPBA and those using the purified *m*-CPBA.[9] The first experiment was carried out on a 2 mmol scale of 1,2-dihydronaphthalene (**5.6**). Commercial *m*-CPBA was used without further purification. The buffer solution worked well – the pH of the reaction mixture remained at about 8 throughout the reaction. Tlc showed that the reaction was incomplete after 45 min and a by-product with a lower R_f was present. A gradient elution technique was used to purify the crude product by silica column chromatography. However, it was found that the product decomposed on silica gel under such operation conditions. Decomposition of the product on silica gel might account for the low yield obtained (10%).

m-CPBA was purified prior to use in the second experiment and should have been free from 3-chlorobenzoic acid. The reaction was carried out under the same conditions as those used in the first experiment, but on a 3 mmol scale of 1,2-dihydronaphthalene (**5.6**). As in the first experiment, a small quantity of by-product having a lower R_f was observed by tlc. Flash silica column chromatography was employed to purify the crude product. It worked well – no significant decomposition of the product was observed. However, the product was still

obtained in low yield (28%) after purification. It appeared that the protocols used in the work-up procedure might play very important roles in determining the yield of the reaction.

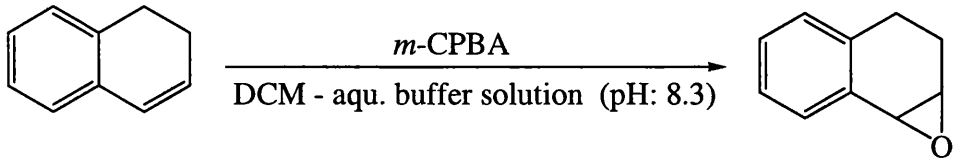
A third experiment was carried out on a 2 mmol scale of 1,2-dihydronaphthalene (**5.6**) under the same conditions. However, some modifications were made during the work-up procedure. For example, the volume of the 10% NaOH solution, which was used to wash the organic phase, was adjusted to such an extent that the organic phase remained in a neutral or slightly basic condition rather than a strongly basic condition, in the hope that this would prevent the occurrence of base-catalyzed ring-opening reactions of the epoxide. These modifications had a desired effect – the yield of the epoxide was increased to 47% after purification by flash silica column chromatography. The detailed experimental procedure and characterization of the product are reported in the *Experimental Section* of this chapter.

It is interesting to note that the reactants, both 1,2-dihydronaphthalene and *m*-CPBA, are insoluble in the aqueous buffered solution. Also, water is known to decrease the rate of alkene epoxidation.[8a] However, the system was still reactive enough to epoxidize the substrate **5.6** to its corresponding epoxide **5.8**.

5.2.2.2 Epoxidation of 1,2-dihydronaphthalene (4.6) with *m*-CPBA in an alkaline two-phase solvent system

It has also been reported that acid-sensitive aryl epoxides can be prepared by direct epoxidation of alkenes with *m*-CPBA in a two-phase solvent system. The two-phase solvent systems usually include DCM and an aqueous buffer solution, such as phosphate buffer solution or sodium bicarbonate solution. The reactions have been reported to be very clean and efficient, and good to excellent yields can be realized in syntheses of a series of acid-sensitive epoxides. Also, the method has been reported to be superior to the single organic solvent method in epoxidation of acid-sensitive compounds.[8b,10]

Two experiments were carried out using this methodology on 2 mmol scale of the starting material **5.6** (Scheme 5.15). The molar ratio of *m*-CPBA to the starting material **5.6** was 2. Also, *m*-CPBA was pre-cooled to 0 °C prior to use and added from a solid addition tube in small portions. The reaction conditions and the results are summarized in Table 5.1.



5.6 **5.8**

Scheme 5.15

Table 5.1 Epoxidation of 1,2-dihydronaphthalene (4.6) using *m*-CPBA in an alkaline biphasic solvent system according to Scheme 5.15

Entry	Quantities (mmol)		Temp. (Reaction time)	Yield (%)[c]
	m-CPBA	DCM / buffer solution		
1	4[a]	20 ml / 20 ml (phosphate buffer solution, pH: 8.0)	r.t. (21 h)	0
2	4[b]	20 ml / 20 ml ($NaHCO_3$ solution, pH: 8.3)	0 °C (6 h)	51

a. Commercial *m*-CPBA was used without further purification and added in two equal batches.
b. *m*-CPBA was purified prior to use and added in two equal batches.
c. Isolated yield after purification by silica column chromatography.

The first experiment was carried out following a literature procedure (Entry 1).[4] A phosphate buffer solution (pH: 8.0) was used as the aqueous component for the two-phase solvent system. The starting material **5.6** was added in two equal batches. One batch was added at the beginning; the other batch was added after 7 h. It was found that the starting material **5.6** was totally consumed. However, no desired product was obtained after purification by silica column chromatography; a complicated mixture of oxidized products was obtained instead. A possible reason for the failure to get the target epoxide might be due to the acidic nature of the reaction

mixture – it was found that the buffer solution did not work. The pH of the reaction mixture was about 3 - 5, which could result in decomposition of the product due to acid-catalyzed ring-opening reactions. Also, compared to the epoxidation reactions carried out in aqueous solution (Section 5.2.2.1), the prolonged reaction time (21 h) could not be beneficial to the formation of the product due to its instability, especially in the presence of an acidic aqueous solution.

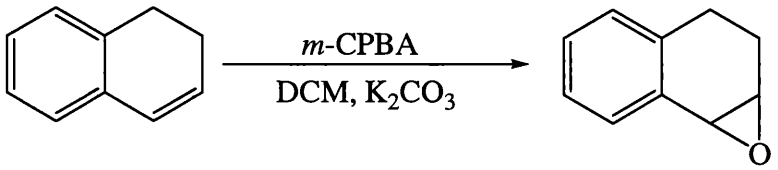
A second experiment was carried out in which some modifications were made to minimise the possibilities of occurrences of side reactions and decomposition of the product (Entry 2). These included: a) a sodium bicarbonate solution (pH = 8.3) was used as the buffer solution instead of a phosphate buffer solution; b) *m*-CPBA was purified prior to use; c) the reaction time was reduced to 6 h; d) the reaction temperature was lowered to 0 °C instead of r.t. Hplc was used to monitor the progress of the reaction and it showed that the reaction was complete after 6 h. The product was obtained in 51% yield after purification by flash silica column chromatography. The detailed experimental procedure is reported in the *Experimental Section* of this chapter.

It is important to note that *m*-CPBA was added in two equal batches instead of one in both experiments. In the second experiment, one batch was added at the beginning and the other was added after 4 h (Entry 2) whereas in the first experiment the second batch was added after 7 h. The reason for doing this was because it had been reported that this addition method was crucial for complete conversion of the starting material in epoxidation reactions – if one molar equivalent of *m*-CPBA was used, the reaction was found to be incomplete; when a second equivalent was added, all the alkene present was consumed; if two equivalents were added initially in one portion, the epoxidation was found to be incomplete.[10]

5.2.2.3 Epoxidation of 1,2-dihydronaphthalene (5.6) with *m*-CPBA in DCM in the presence of solid potassium carbonate

The epoxidation reaction was also carried out under anhydrous conditions, in which DCM was used as the solvent and solid potassium carbonate was used as a

solid buffer (Scheme 5.16). *m*-CPBA was purified prior to use. The reaction conditions and the results are summarized in Table 5.2.



5.6 **5.8**

Scheme 5.16

Table 5.2 Epoxidation of 1,2-dihydronaphthalene (5.6) with *m*-CPBA in the presence of solid buffer according to Scheme 5.16[a]

Entry	Quantities (mmol)			Temp. (Reaction time)	Yield (%)[d]
	5.6	*m*-CPBA	K_2CO_3		
1[b]	3	6	10	-78 °C (24 h) / 0 °C (24 h)	50
2[c]	2	5.6	6	0 °C (24 h) / r.t. (19 h)	82

a. The reactions were carried out under anhydrous conditions.
b. Tlc was used to monitor the reaction progress. *m*-CPBA was added in one batch at the beginning of the reaction.
c. *m*-CPBA was added in two equal batches. Hplc was used to monitor the reaction progress.
d. Isolated yield after purification by silica column chromatography.

It has been reported that asymmetric epoxidation of unfunctionalized alkenes using a combination of *m*-CPBA and NMO is rapid and clean both at 0 °C and at -78 °C. Also, the enantioselectivities and the *cis* / *trans* epoxide ratios increase significantly at low temperature.[11] Since this method would be used for future asymmetric epoxidation reactions, the reaction here was tried at low temperature first (Entry 1). However, it was found by tlc that the reaction proceeded very slowly at -78 °C; when the reaction temperature was raised to 0 °C, the reaction rate was found to increase singnificantly. The tlc chromatograms of the reaction mixture were similar to those in the epoxidation reactions using the above-mentioned two methods. The reaction was found to be still incomplete after 24 h at 0 °C by tlc. Nevertheless it was worked up and the epoxide **5.8** was obtained in 50% yield after purification by flash silica column chromatography.

It is important to note that the solid buffer worked very well – the pH of the reaction mixture remained slightly basic (pH: ~ 8). The slightly basic nature of the reaction mixture and the absence of added H_2O could minimize the possibilities of the occurrences of some side reactions, such as ring-opening reactions of the product.

A second experiment was carried out in which some modifications were made to try to drive the reaction to completion and increase the reaction rate (Entry 2). These included: a) the molar ratio of *m*-CPBA to starting material **5.6** was increased to 2.8; b) as that in the above-mentioned two methods, *m*-CPBA was added in two equal batches; and c) the reaction temperature was raised to r.t. after 24 h at 0 °C. These measures had a desirable effect – the product was obtained with an isolated yield of 82% after purification by flash silica column chromatography.

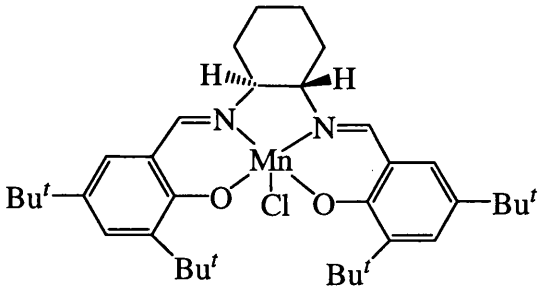
It has been claimed that the two-phase solvent system and the aqueous buffer solution system are superior to the solid buffer-single solvent system in epoxidation of acid-sensitive alkenes or alkenes yielding acid-sensitive epoxides.[9,10] However, this was not the case in our hands. The best result for epoxidation of 1,2-dihydronaphthalene (**5.6**) with *m*-CPBA was obtained in the reaction that was carried out in a single organic solvent system (DCM). The detailed experimental procedure is reported in the *Experimental Section* of this chapter.

In conclusion, racemic 1,2-epoxy-1,2,3,4-tetrahydronaphthalene (**5.8**) was synthesised *via* direct epoxidation of 1,2-dihydronaphthalene (**5.6**) in three different reaction media. An efficient procedure has been established to carry out the epoxidation reaction in DCM in the presence of a solid buffer.

Upon successfully set up the reaction monitoring system and the product characterization system. The next step would be to carry out the asymmetric syntheses.

5.2.3 Asymmetric epoxidation of 1,2-dihydronaphthalene (5.6)

Before using the synthesized (salen)Mn(III) complexes as catalysts to carry out the asymmetry epoxidation of 1,2-dihydronaphthalene (**5.6**), a commercially available (salen)Mn(III) complex **5.15**, also known as Jacobsen's catalyst, was used first.

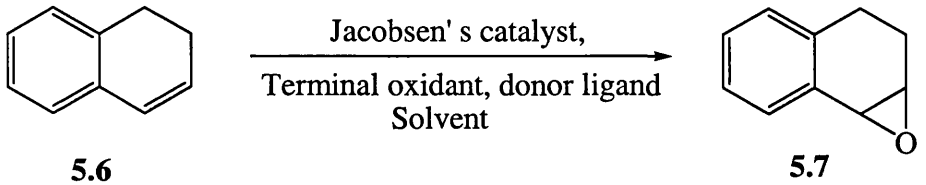


5.15

5.2.3.1 Asymmetric epoxidation of 1,2-dihydronaphthalene (5.6) using Jacobsen's catalyst

As described in *Chapter 1* (Section 1.3.3), epoxidation reactions are usually carried out using a small amount of catalyst (0.5 - 10 mol %) in a suitable solvent at temperatures between 0 °C and r.t. The terminal oxidant is usually used in excess (the molar ratio of the oxidant to the substrate is 1 - 2). Two types of terminal oxidants have been widely used. One is a buffered NaOCl solution (bleach). Reaction conditions for NaOCl epoxidation have been well developed into a two-phase system, with an aqueous buffered NaOCl solution phase and an organic phase composed of a substrate, a catalyst and a donor ligand in a suitable solvent.[12] The other widely used oxidant is *m*-chloroperbenzoic acid (*m*-CPBA). The reactions are usually carried out under anhydrous conditions at low temperature (typically -78 ~ 0°C) in the presence of an added ligand, such as *N*-methylmorpholine-*N*-oxide (NMO), which takes up an axial orientation. It has been found that a wide range of unfunctionalized alkenes are epoxidized with an increase in enantioselectivitiy under these conditions compared to the biphasic reactions employing bleach as the oxidant.[11]

The asymmetric epoxidations of 1,2-dihydronaphthalene (**5.6**) using Jacobsen's catalyst were carried out in the above-mentioned two different reaction systems (Scheme 5.17). The molar ratios of the catalyst and the oxidant to the substrate were 0.05 and 2, respectively. The reactions were carried out at 0 °C using DCM as the organic solvent. The reaction conditions and the results are summarized in Table 5.3.



5.6 **5.7**

Scheme 5.17

Table 5.3 Asymmetric epoxidation of 1,2-dihydronaphthalene (5.6) using Jacobsen's catalyst according to Scheme 5.17

Entry	Donor ligand (Molar ratio to **5.6**)	Terminal oxidant	Reaction time (h)	Yield (%)	ee [e] (%)
1	NMO (5)	*m*-CPBA [a]	24	68 [c]	83
2 [b]	NMO (5)	*m*-CPBA [a]	24	50 [c] (78) [d]	88
3	4-PPNO (0.25)	NaOCl	3.5	26 [c] (47) [d]	87

a. *m*-CPBA was purified prior to use.
b. Solid K_2CO_3 was added as a solid buffer.
c. Isolated yield after purification by flash silica column chromatography.
d. Calculated by hplc result from the crude product using 2-naphthol as the internal standard.
e. ee% was determined by integration of the peak areas of the enantiomers in the ^{1}HNMR spectrum following addition of the chiral shift reagent Eu(hfc)$_3$.

The first asymmetric epoxidation reaction was carried out using *m*-CPBA as the oxidant, NMO as the donor ligand and dry DCM as the solvent (Entry 1). Since it had been found that the reaction proceeded very slowly at the low temperature (-78 °C) in the synthesis of racemic epoxide **5.8** (Section 5.2.2.3), the asymmetric epoxidation was carried out at 0 °C. Hplc was used to monitor the progress of the reaction. It showed that the reaction proceeded slowly and was still incomplete after 24 h. However, the yield of the epoxide, which was calculated by hplc, was found to

be nearly unchanged for the sample taken at 12 h and that taken at 24 h. So the reaction was stopped and worked up. The product was obtained in 68% yield after purification by flash silica column chromatography. Its enantiomeric excess (ee %) was determined as 83% by integration of peak areas of the enantiomers in the ^{1}HNMR spectrum following addition of the chiral shift reagent Eu(hfc)$_3$. It was verified by measuring its specific rotation and then comparing it with the highest value reported using the equation {ee (%) = $[\alpha]_{obs}$ / $[\alpha]_{ref}$ × 100%}. In this case, it was calculated as 82% ee. The absolute configuration of the product should be (+)-(1R,2S) by comparison of its specific rotation sign with that in the literature. The detailed experimental procedure is reported in the *Experimental Section* of this chapter.

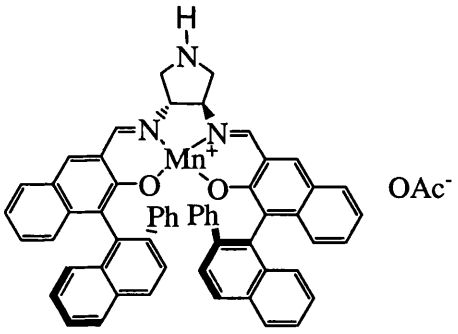
Since good results had been obtained in the synthesis of racemic epoxide **5.8** using *m*-CPBA in DCM in the presence of solid sodium carbonate (Section 5.2.2.3), a second experiment was tried in which solid K_2CO_3 was added as a solid buffer (Entry 2). No significant differences were observed by hplc between the asymmetric epoxidation reaction with or without the presence of solid K_2CO_3. The ee% value of the product was slightly increased; however, the yield was decreased.

The asymmetric epoxidation was also carried out in a buffered biphasic system using a combination of NaClO and 4-PPNO (Entry 3). The concentration of a commercial NaClO solution was analyzed by iodometric titration. It was then diluted with a phosphate buffer solution (0.05 M) to the desired concentration. The pH of the buffered NaClO solution was adjusted to 11.8 by adding 1 M HCl. The reaction conditions were similar to those reported by Jacobsen *et al.*[12] Hplc results showed that the yield of the product began to decrease after 3 h. So the reaction was stopped and worked up. The epoxide **5.7** was obtained in 26% yield after purification by flash silica column chromatography. Its ee value was calculated as 87%. The absolute configuration of the epoxide was also (+)-(1R,2S). The detailed experimental procedure is reported in the *Experimental Section* of this chapter.

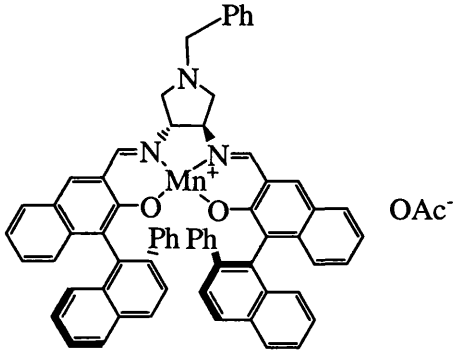
Having set up the asymmetric synthetic methods using Jacobsen's catalyst (**5.15**), the next step would be to test the performances of the synthesized catalysts in a similar way.

5.2.3.2 Asymmetric epoxidation of 1,2-dihydronaphthalene (5.6) using synthesized (salen)Mn(III) complexes 5.5 as the catalysts

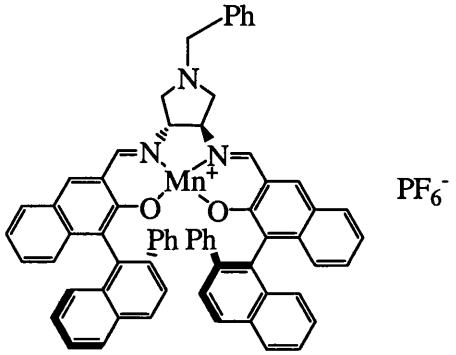
The synthesized (salen)Mn(III) complexes **5.5** were used as the catalysts to carry out the asymmetric epoxidation of 1,2-dihydronaphthalene (**5.6**) (Scheme 5.18). *m*-CPBA was purified prior to use. The reactions were carried out at 0 °C and hplc was used to monitor the progress of these reactions. The reaction conditions and the results are summarized in Table 5.4.



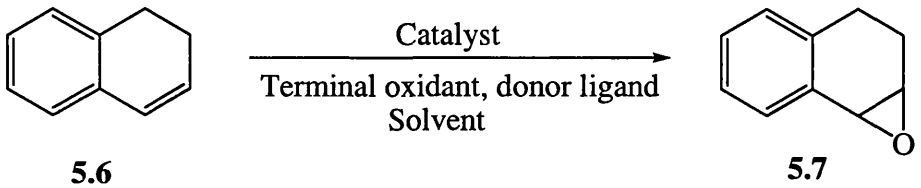
5.5a



5.5b



5.5c



5.6 **5.7**

Scheme 5.18

Table 5.4 Asymmetric epoxidation of 1,2-dihydronaphthalene (5.6) using the synthesized (salen)Mn(III) complexes 5.5 as catalysts according to Scheme 5.18

Entry	Molar ratio to compound **5.6**			Reaction time (h)	Yield (%)	ee [c] (%)
	Catalyst	Donor ligand	Terminal oxidant			
1	5% (**5.5c**)	5 (NMO)	2 (*m*-CPBA)	6	13 [a] (21) [b]	1
2	2.8% (**5.5b**)	2.8 (NMO)	2 (*m*-CPBA)	24	28[a] (36) [b]	4
3	3.2% (**5.5b**)	0.2 (4-PPNO)	5 (NaClO)	24	12 [a] (19) [b]	6
4	3% (**5.5a**)	0.2 (4-PPNO)	5 (NaClO)	24	51[a]	2

a. Isolated yield after purification by flash silica column chromatography.
b. Calculated by hplc from the crude product using 2-naphthol as the internal standard.
c. ee% was determined by integration of peak areas of the enantiomers in the ^{1}HNMR spectrum following addition of the chiral shift reagent Eu(hfc)$_3$.

The reaction was first carried out under anhydrous conditions using complex **5.5c** as the catalyst, *m*-CPBA as the oxidant, NMO as the donor ligand and dry DCM as the solvent (Entry 1). Hplc showed that the yield of the epoxide began to decrease after 6 h. So the reaction was stopped and worked up. Hplc also showed that a large broad peak appeared, which had a retention time of 4.42 min and was absent in the asymmetric epoxidations using Jacobsen's catalyst. The epoxide was obtained in low yield (13%) after purification by flash silica column chromatography. And even worse, it was almost a racemate.

(Salen)Mn(III) complex **5.5b** was also tested under similar reaction conditions (Entry 2). The reaction was found to proceed slowly and to be incomplete after 24 h. A large broad peak with the retention time of 4.42 min was also observed. The epoxide was obtained with a relatively higher yield (28%) after purification by flash silica column chromatography. The ee %, however, was still very low (4%).

At this stage, there was a possibility that the catalysts might not be robust enough to withstand the epoxidation conditions using *m*-CPBA as the oxidant. A third experiment was carried out in a two-phase solvent system because the two-phase solvent system using NaClO as the oxidant has normally been considered as a milder

epoxidation system than the *m*-CPBA / NMO system (Entry 3). Unlike the epoxidation reactions using Jacobsen's catalyst (Table 5.13, Entry 3), hplc results showed that the reaction proceeded very slowly and was incomplete after 24 h. The epoxide was obtained in low yield (12%) after purification by flash silica column chromatography. The ee, although slightly higher, was still far from satisfaction (6%).

(Salen)Mn(III) complex **5.5a** was also tested for epoxidation of 1,2-dihydronaphthalene (**5.6**) in the two-phase solvent system (Entry 4). Similary, the reaction was found to proceed slowly. The epoxide was obtained with a higher yield (51%) after purification by flash silica column chromatography. However, the ee value was disappointing (2%).

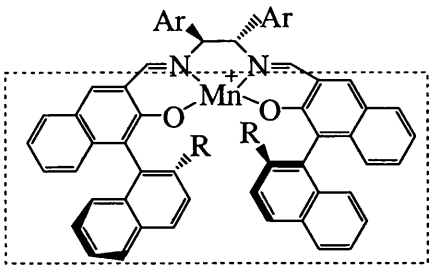
In comparison with the asymmetric epoxidation reactions using Jacobsen's catalyst, two conclusions could be made: a) the disappointing results for the synthesized (salen)Mn(III) complexes **5.5** were not due to the epoxidation methods or quality of the related chemicals because good results had been obtained in reactions using Jacobsen's catalyst; therefore, b) the disappointing results for the synthesized (salen)Mn(III) complexes **5.5** were probably due to the catalysts themselves.

Possible reasons for the poor performances of the synthesized (salen)Mn(III) complexes (**5.5a**, **5.5b**, and **5.5c**) in the asymmetric epoxidation of 1,2-dihydronaphthalene (**5.6**) might be attributed to the several factors.

1) The catalysts might not be robust enough to withstand the epoxidation reaction conditions. The building blocks, both optically pure diaminopyrrolidines and (R)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene (**5.3**), have been proven to be effective components for construction of the salen ligands and the corresponding Mn(III) complexes. Also, the catalysts were synthesized following general procedures. As a result, they should, at least in principle, catalyze the asymmetric epoxidation reactions. However, both the activities and the enantioselectivities were found to be very poor in reality. A possible explanation is that the catalysts might decompose under the reaction conditions. A piece of indirect evidence, which might support this assumption, was that, as described in Section 5.2.1, the synthesized salen

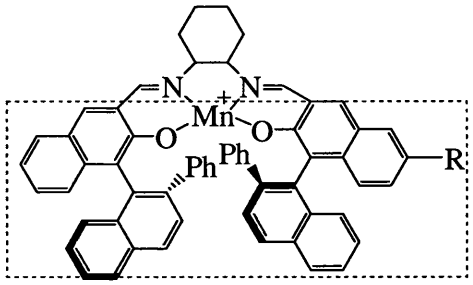
ligands had a tendency to decompose during column chromatography, especially on silica columns. Also, decomposition of (salen)Mn(III) complexes under the epoxidation reaction conditions has been reported since the emergence of such kinds of catalysts.[12] If this explanation is the case, these synthesized catalysts (**5.5a**, **5.5b**, and **5.5c**) might still find some use in other asymmetric reactions such as cyclopropanation or the Diels-Alder reaction.[13]

2) The presence of the (substituted) pyrrolidine moiety in the catalysts structure might have adverse effects on their catalytic performance. As described in *Chapter 1* (Section 1.3.4), (R)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene (**5.3**) has been proven to be an effective component to construct the (salen)Mn(III) complexes, like (salen)Mn(III) complexes **5.16** synthesized by Katsuki *et al.*,[14] and (salen)Mn(III) complexes **5.17** synthesized by Smith.[15] The significant structural difference between the synthesized (salen)Mn(III) complexes **5.5** and catalysts **5.16b** and **5.17b** lies in the chiral pyrrolidine moiety. However, Song[16] has reported the preparation and applications of the (pyrrolidine salen)Mn(III) complex **5.18** and the supported (pyrrolidine salen)Mn(III) complex **5.19**, which exhibited good catalytic performances in asymmetric epoxidation of unfunctionalized alkenes. The results suggested that the chiral pyrrolidine salen moiety was an appropriate chiral scafford for the asymmetric epoxidation catalyst. The supported catalyst **5.19**, however, was also reported to decompose partially under the epoxidation reaction conditions.



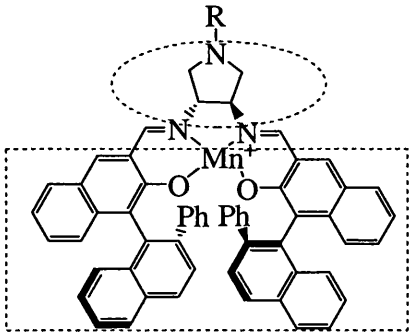
AcO^- or PF_6^-

5.16a: Ar, Ar = Ph, Ph; R = Me
5.16b: Ar, Ar = Ph, Ph; R = Ph
5.16c: Ar, Ar= 3,5-$Me_2C_6H_3$, 3,5-$Me_2C_6H_3$; R = Ph



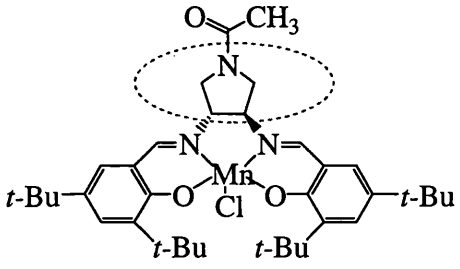
PF_6^-

5.17a: R = $CH_2CH_2CH_2OH$
5.17b: R = H
5.17c: R = $CH_2CH_2CH_2OCOC_6H_4$-P

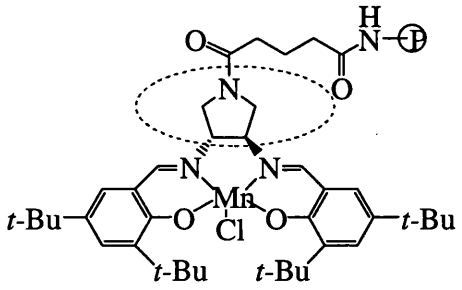


X

5.5a: R = H; X = AcO^-
5.5b: R = CH_2Ph; X = AcO^-
5.5c: R = CH_2Ph; X = PF_6^-



5.18



5.19

It might be argued that the *N* atom in catalyst **5.18** and **5.19** is attached to a carbonyl group. Its lone pair electrons can therefore conjugate with the π electrons of the carbonyl group to make it more 'neutral'- unlikely to donate its lone pair of electrons. However, in catalysts **5.5**, the N atom is attached to a H atom or benzyl group. As a result, it would be more 'basic'- more likely to donate its lone pair of electrons. There was therefore a possibility that the *N* atom in catalyst **5.5** might react

with the oxidant during the reaction. At the moment, there was no evidence to prove whether any reaction between the *N* atom and the oxidant occurred or not. However, some points appeared to be clear: a) the catalysts were used in small quantities (2.8 – 0.05 molar equivalents relative to the substrate) whereas the terminal oxidant was used in large quantities (2 - 5 equivalents relative to the substrate). This meant that the oxidant could not be used up by reaction with the *N* atom *if* there was some kind of oxidation reaction of the catalyst; b) *if* any reaction occurred between the *N* atom of the catalyst **5.5** and the oxidant, and *if* the reaction could not destroy the basic structure of the salen complex, the resulting product might still have the capability to catalyze the aymmetric epoxidation reaction because the pathway by which the alkene approaches to the oxo (salen)manganese(V) complexes appeared unaffected. A piece of indirect evidence to support this assumption was that the presence of a large and complicated group attached to the *N* atom in catalyst **5.19** seemed to have no adverse effects on its performance.[16]

In short, the main possible reason for the poor performances of the (salen)Mn(III) complexes **5.5** might be due to their instability – the combination of (substituted) diaminopyrrolidine moiety with (R)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene moiety somehow increased the instability of the resulting salen ligands and the corresponding (salen)Mn(III) complexes. The (salen)Mn(III) complexes decomposed under the reaction conditions and lost the salen complex structure.

5.3 Conclusions

- A new pyrrolidine-type salen ligand **5.4a** was synthesized by condensation of *trans*-(3R,4R)-diaminopyrrolidine (**5.2a**) with two molar equivalents of (R)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene (**5.3**) in 40% yield from *trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt (**5.1a**). The corresponding (salen)Mn(III)OAc complex **5.5a** was obtained in 79% yield by reaction of the salen ligand **5.4a** with $Mn(OAc)_2 \cdot 4\ H_2O$ in air.

- Pure pyrrolidine-type salen ligand **5.4b** could not be obtained. It decomposes on both silica and alumina column.
- A new pyrrolidine-type (salen)Mn(III)OAc complex **5.5b** was prepared by condensation of *trans*-(3R,4R)-1-benzyl-3,4–diaminopyrrolidine (**5.2b**) with two molar equivalents of (R)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene (**5.3**) and then by reaction of the crude salen ligand **5.4b** with $Mn(OAc)_2 \cdot 4\ H_2O$ in air. Complex **5.5b** was obtained in 63% yield from *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine trihydrochloride salt (**5.1b**) when the ligand **5.4b** was synthesized in a mixed solvent system (EtOH / H_2O = 9 / 1). A better yield (72%) was obtained from *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine trihydrochloride salt (**5.1a**) when the ligand **5.4b** was synthesized under anhydrous conditions. It seemed that the presence of excess water disfavoured the formation of salen ligands.
- A new pyrrolidine-type (salen)Mn(III)PF_6 complex **5.5c** was synthesized in a yield of 90% by reaction of (salen)Mn(III)OAc complex **5.5b** with $NaPF_6$ in a mixed solvent system (CH_3CN / DCM).
- Racemic 1,2-epoxy-1,2,3,4-tetrahydronaphthalene (**5.8**) was synthesised *via* direct epoxidation of 1,2-dihydronaphthalene (**5.6**) using *m*-CPBA in three different reaction media: a buffered aqueous solution; a biphasic solvent system; or dry DCM. An efficient procedure has been established to carry out the epoxidation reaction with a yield of 82% in DCM in the presence of anhydrous K_2CO_3.
- Jacobsen's catalyst **5.15** was used to catalyze the asymmetric epoxidation of 1,2-dihydronaphthalene (**5.6**) in two different reaction systems. The epoxide **5.7** was obtained with an 88% ee using the *m*-CPBA / NMO system under anhydrous conditions. Also, the epoxide **5.7** was obtained with an 87% ee using a buffered NaClO solution in a two-phase solvent system.
- The synthesized pyrrolidine-type (salen)Mn(III) complexes **5.5a**, **5.5b**, and **5.5c** were also used as catalysts to carry out aymmetric epoxidation reactions. The results were disappointing. When complex **5.5b** was used as the catalyst, the epoxide was obtained with 6% ee using a buffered NaClO solution in a two-phase solvent system. It was obtained in 4% ee using the *m*-CPBA / NMO

system under anhydrous conditions. When the complex **5.5c** was used as the catalyst, the epoxide obtained was nearly racemic (1% ee) using a *m*-CPBA / NMO system under anhydrous conditions. Also, when complex **5.5a** was used as the catalyst, the epoxide obtained was nearly racemic (2% ee) using a buffered NaClO solution in a two-phase solvent system.

- The poor performances of the synthesized pyrrolidine-type (salen)Mn(III) complexes **5.5a**, **5.5b**, and **5.5c** might be attributed to their instability. They might not be robust enough to withstand the reaction conditions and therefore decomposed.

5.4 Experimental section

See also *Experimental Section 3.4* in *Chapter 3* and *Experimental Section 4.4* in *Chapter 4* for related experimental details.

Neutral alumina gel was purchased from Aldrich (activated Brockmann I grade; 150 mesh).

Purification of m-CPBA

The commercial product (5 g; from Aldrich, 77%, the remainder being 3-chlorobenzoic acid and water) was dissolved in benzene (100 ml). The solution was washed with an aqueous NaH_2PO_4 / NaOH buffer solution (pH: 7.4; 5 × 10 ml), dried over anhydrous $MgSO_4$ and filtered. The filtrate was evaporated to dryness *in vacuo* (necessary care was taken when evaporating the solution in case of explosion).

Hplc analysis of 1,2-epoxy-1,2,3,4-tetrahydronaphthalene

- Hplc conditions
  Column: hp hypersil, 3μ, 60 × 4.6 mm; solvent: hexane / EtOAc = 100 / 5; flow rate: 0.75 ml / min; UV (nm): 270.
- Qualitative analysis

Retention time for the starting material 1,2-dihydronaphthalene (**5.6**): R (SM) = 1.1 min.

Retention time for the epoxide **5.8** or **5.7**: R (product) = 2.2 min.

- Quantitative analysis

  Internal standard: 2-naphthol.

  Equations used:[17]

$$M(Y) = K(Y) \times \text{Area}(Y) \qquad \text{(eq. 1)}$$

$$\frac{M(Y)}{M(\text{standard})} = \frac{K(Y)}{K(\text{standard})} \times \frac{\text{Area}(Y)}{\text{Area}(\text{standard})} \qquad \text{(eq. 2)}$$

$$\frac{K(Y)}{K(\text{standard})} = \frac{\text{Area}(\text{standard})}{\text{Area}(Y)} \times \frac{M(Y)}{M(\text{standard})} \qquad \text{(eq. 3)}$$

$$M(Y) = \frac{K(Y)}{K(\text{standard})} \times \frac{\text{Area}(Y)}{\text{Area}(\text{standard})} \times M(\text{standard}) \qquad \text{(eq. 4)}$$

Where,

M (Y): the mass of compound Y;

Area (Y): the peak area of compound Y;

K (Y) / K (standard): the correction factor of compound Y. It can be calculated using equation 3.

Results: K (product) / K (standard) = 29.4; K (SM) / K (standard) = 0.46.

Calculation of the enantiomeric excess (ee%) of epoxide 5.7

The enantiomeric excess (ee%) of the epoxide **5.7** was determined by integration of peak areas of the enantiomers in the ^{1}HNMR spectrum following addition of a chiral shift reagent, $Eu(hfc)_3$. The equation used was:

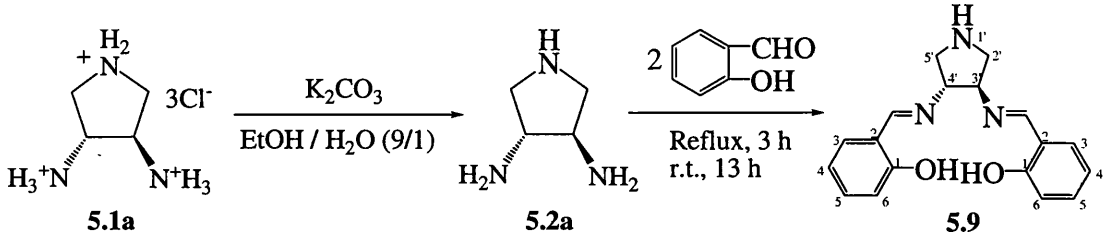
$$ee(\%) = \frac{A(\text{major enantiomer}) - A(\text{minor enantiomer})}{A(\text{major enantiomer}) + A(\text{minor enantiomer})} \times 100$$

Where,

A (major enantiomer): the peak area of the major enantiomer;

A (minor enantiomer): the peak area of the minor enantiomer.

Preparation of model salen ligand 5.9



5.1a **5.2a** **5.9**

The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower, a condenser and a glass stopper. Compound **5.1a** (0.21 g, 1 mmol), K_2CO_3 (0.55 g, 4 mmol) and a mixture of EtOH / H_2O (9:1, 120 ml) were added to the flask. The mixture was heated under reflux for 5 min. After cooling to r.t., salicylaldehyde (0.22 ml, 2 mmol) was added by syringe. The reaction mixture was heated under reflux for 3 h and then stirred at r.t. for 13 h.

The solid was filtered off. The filtrate was poured into brine (100 ml) and then extracted with DCM (3 × 50 ml). The DCM extract was washed with brine (50 ml), dried over anhydrous Na_2SO_4 and filtered. Removal of DCM from the filtrate *in vacuo* and drying of the resulting residue gave a yellow solid (0.319 g). The crude product was first purified by silica column chromatography (adsorbent: silica 60, 40g; eluting solvent: Et_2O / hexane = 2 / 1 ~ $CHCl_3$ / MeOH = 3 / 1). However, it was found that the product partially decomposed on the silica column under such operation to give the starting material (salicylaldehyde). Therefore, the mixture (0.18 g) collected after the first column was purified by flash neutral alumina column chromatography [adsorbent: neutral alumina, 14 g; H_2O (5% w / w) was added to make it to Brockmann II – III grade; eluting solvent: Et_2O / hexane = 2 / 1 ~ MeOH] to give the product (0.112 g, 38% yield).

TLC (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}):

$R_f = 0.53$ (developing solvent: CH_3OH / $CHCl_3$ = 1 / 6).

NMR

δ_H (400MHz, $CDCl_3$): 3.59 (br, 2H, **H**-2′ [a] and **H**-5′ [a]); 3.91 (br, 2H, **H**-2′ [b] and **H**-5′[b]); 4.24 (br, 2H, **H**-3′ and **H**-4′); 7.14 (apparent triplet, 2H, **H**-4, ^3J = 8 Hz); 7.22 (d, 2H, **H**-6, ^3J = 8 Hz); 7.47 (dd, 2H, **H**-3, ^3J = 8 Hz, ^4J = 1 Hz); 7.58 (apparent triple doublet, 2H, **H**-5, ^3J = 8 Hz, ^4J = 1 Hz); 8.59 (s, 2H, N=C-**H**); 13.0 (s, 2H, **H**O-).

δ_C (400MHz, $CDCl_3$): 51.9 (**C**-2′ and **C**-5′); 75.4 (**C**-3′ and **C**-4′); 116.7 (**C**-6); 118.9 (**C**-2); 119.2 (**C**-4); 132.3 (**C**-3); 133.0 (**C**-5); 160.8 (**C**-1); 167.7 (**C**=N).

IR

ν_{max} (cm^{-1}): 2879 (br. H-bonded -OH; Ar-H; CH); 1626 (C=N); 1579; 1494; 1460; 1404; 1276; 753.

MS

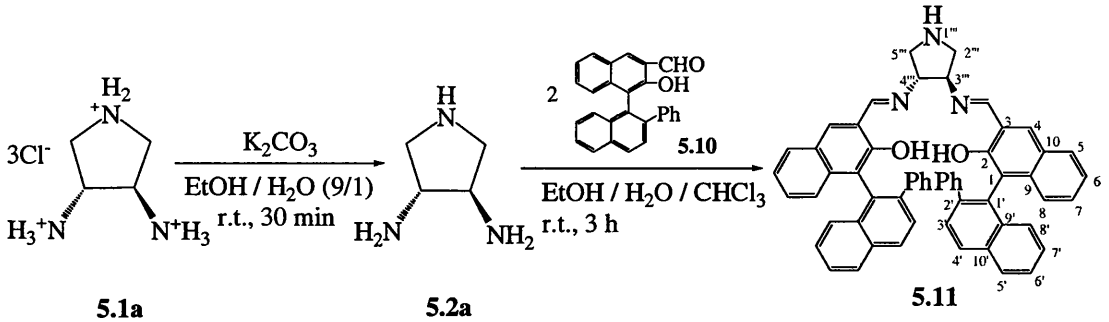
m /z (EI): 309 (M^+, 2%); 44 (52%); 40 (100%).

m /z (CI, NH_3): 310 ($[M + H]^+$, 8%); 243 (44%); 226 (31%); 198 (100%).

HRMS

Found $[M + H]^+$: 310.1554; $C_{18}H_{20}O_2N_3$ requires: 310.1550.

Synthesis of salen ligand 5.11



5.1a **5.2a** **5.11**

The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower and capped with two septa. Compound **5.1a** (0.014 g, 0.07 mmol), K_2CO_3 (0.042 g, 0.3 mmol) and EtOH / H_2O (9:1, 6 ml) were added to the flask and the mixture was stirred for 30 min at r.t. A solution of compound **5.10** (0.050 g, 0.13 mmol) in $CHCl_3$ (2 ml) was added. The reaction mixture was stirred at

r.t. for 3 h. Tlc (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}; developing solvent: hexane / toluene = 3 / 7) was used to monitor the reaction progress and showed the reaction was complete.

The reaction mixture was poured into brine (6 ml) and then extracted with DCM (3 × 20 ml). The DCM extract was washed with brine (50 ml), dried over anhydrous Na_2SO_4 and filtered. Removal of DCM from the filtrate *in vacuo* and drying of the resulting residue gave the crude product (0.042 g). It was purified by flash column chromatography [adsorbent: neutral alumina, 10 g; H_2O (0.5 g, 5% w / w) was added to make it to Brockmann II - III grade; eluting solvent: Et_2O ~ Et_2O / MeOH = 5 /1] to give the product (0.021 g, 39% yield).

TLC (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}):

R_f = 0.61 (developing solvent: CH_3OH / $CHCl_3$ = 1 / 6).

NMR

δ_H (400MHz, $CDCl_3$): 3.01 (br, 2H, **H**-2‴ [a] and **H**-5‴ [a]); 3.31 (br, 2H, **H**-2‴ [b] and **H**-5‴ [b]); 3.70 (apparent triplet, 2H, **H**-3‴ and **H**-4‴, J = 5 Hz); 6.87 (m, 4H, Ar**H**); 6.97 (m, 2H, Ar**H**); 7.04 - 7.26 (m, 14H, Ar**H**); 7.35 (m, 2H, Ar**H**); 7.56 (m, 6H, Ar**H**); 7.84 (d, 2H, ^3J = 8 Hz, Ar**H**); 7.92 (d, 2H, ^3J = 8 Hz, Ar**H**); 8.20 (s, 2H, N=C-**H**); 12.3 (s, 2H, **H**O-).

IR

ν_{max} (cm^{-1}): 3051 (Ar-H); 3008 (br, H-bonded -OH); 2922 / 2868 (CH); 1624 (C=N); 1494; 1442; 1342; 1183; 1147; 1116; 1028; 940; 820; 744; 698.

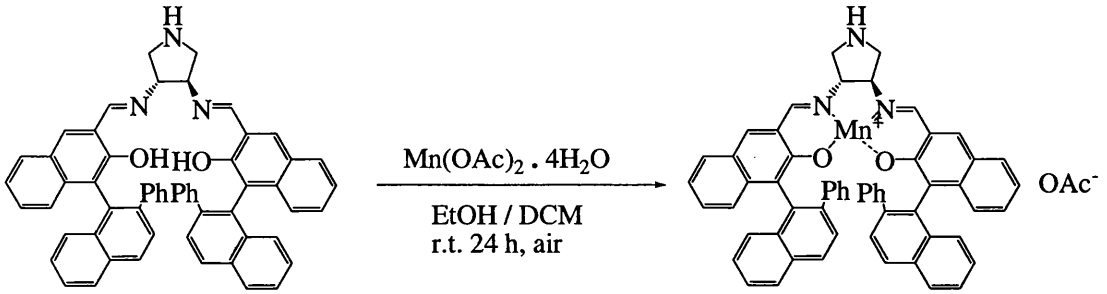
MS

m /z (ES^+): 814 ($[M + H]^+$, 100%); 458 (58%); 374 (33%); 359 (71%).

HRMS

Found $[M + H]^+$: 814.3430; $C_{58}H_{44}O_2N_3$ requires: 814.3428.

Preparation of (salen)Mn(III) complex 5.12



5.11 **5.12**

$Mn(OAc)_2 \cdot 4\ H_2O$ (0.009 g, 0.037 mmol) and EtOH (3 ml) were added to a 10-ml beaker. A solution of compound **5.11** (0.011 g, 0.014 mmol) in DCM (1.5 ml) was then added. The reaction mixture was stirred at r.t. for 24 h in air.

The solid, which precipitated from the reaction mixture, was collected by suction filtration, washed with a little EtOH / DCM (2 / 1) and then dried in a vacuum dessicator to give the product **5.12** (0.007 g, 50% yield). Removal of solvent from the filtrate *in vacuo* and drying of the resulting residue gave some brown solid (0.015 g). DCM (10 ml) was added to the solid and the mixture was stirred for 30 min. The solid was filtered off. Removal of DCM from the filtrate *in vacuo* and drying of the resulting residue gave another batch of the product **5.12** (0.006 g, 46% yield).

IR

ν_{max} (cm^{-1}): 3054 (Ar-H); 2913 / 2866 (CH); 1626 (C=N); 1494; 1442; 1345; 1291; 1185; 1148; 1118; 1028; 941; 821; 761; 746; 698.

MS

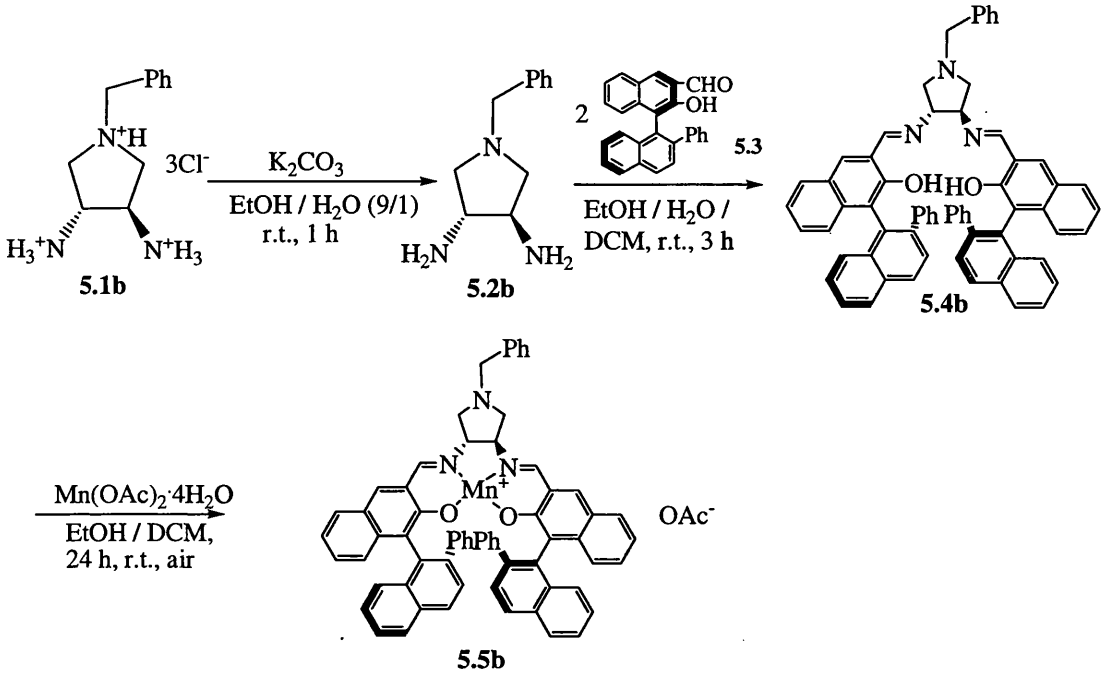
m /z (ES^+): 866 ($[M - OAc]^+$, 8%); 814 (47%); 458 (100%); 375 (19%).

m /z (ES^-): 59 (AcO^-, 100%).

HRMS

Found $[M - OAc]^+$: 866.2568; $C_{58}H_{41}O_2N_3Mn^+$ requires: 866.2574.

Preparation of (salen)Mn(III) complex 5.5b



The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic stirrer and capped with two septa. Compound **5.1b** (0.045 g, 0.15 mmol), K_2CO_3 (0.093 g, 0.68mmol) and EtOH / H_2O (9:1, 15 ml) were added to the flask and the mixture was stirred for 1 h at r.t. A solution of compound **5.3** (0.112 g, 0.3 mmol) in DCM (5 ml) was added. The reaction mixture was stirred at r.t. for 3 h. It was then poured into brine (10 ml) and extracted with DCM (3 × 15 ml). The DCM extract was washed with brine (30 ml), dried over anhydrous Na_2SO_4 and filtered. Removal of DCM from the filtrate *in vacuo* and drying of the resulting residue gave salen ligand **5.4b** (0.125 g).

Salen ligand **5.4b** was transferred to a small two-necked round bottomed flask and dissolved in a mixture of EtOH and DCM (5 ml / 2 ml). $Mn(OAc)_2 \cdot 4\ H_2O$ (0.037 g, 0.15 mmol) was added. Air was bubbled into the reaction mixture and it was stirred for 24 h at r.t. The reaction mixture was evaporated to dryness *in vacuo* to give a dark brown solid (0.11 g). DCM (15 ml) was added to the solid and the mixture was stirred for 2 h at r.t. The solid was filtered off. Removal of DCM from the filtrate *in vacuo* and drying of the resulting residue gave (salen)Mn(III) complex **5.5b** (0.096 g, 63% yield).

IR

ν_{max} (cm^{-1}): 3049 (Ar-H); 2913 / 2792 (CH); 1626 (C=N); 1494; 1442; 1341; 1291; 1182; 1147; 1116; 1028; 940; 821; 745; 698 .

MS

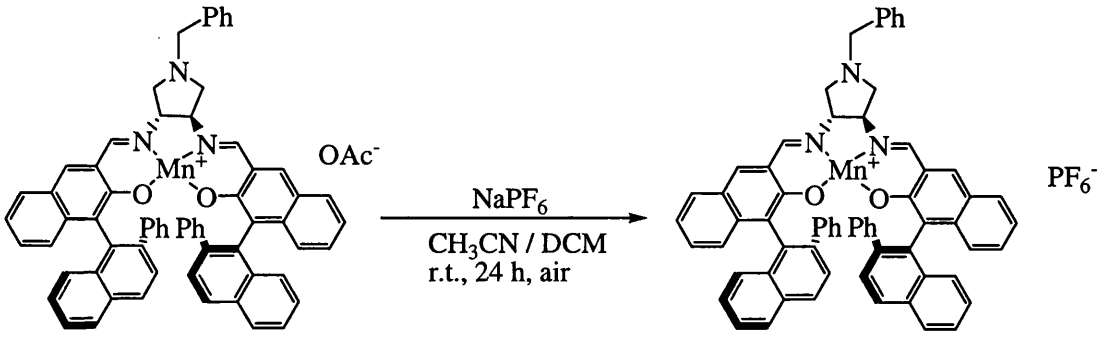
m /z (ES^+): 956 ($[M - OAC]^+$, 37%); 904 (26%); 397 (41%); 375 (100%); 204 (40%); 64 (61%).

m /z (ES^-): 59 (AcO^-, 100%).

HRMS

Found $[M - OAC]^+$: 956.3041; $C_{65}H_{47}O_2N_3Mn^+$ requires: 956.3043.

Preparation of (salen)Mn(III) complex 5.5c



5.5b **5.5c**

(Salen)Mn(III) complex **5.5b** (0.058 g, 0.057 mmol) was dissolved in a mixture of CH_3CN and DCM (15 ml / 2 ml). A solution of $NaPF_6$ (0.096 g, 0.57 mmol) in CH_3CN (3 ml) was added. The reaction mixture was stirred for 24 h in air at r.t. and then evaporated to dryness *in vacuo* to give a dark brown solid (0.15 g). DCM (15 ml) was added to the solid and the mixture was stirred for 30 min. The solid was filtered off. Removal of DCM from the filtrate *in vacuo* and drying of the resulting residue gave (salen)Mn(III) complex **5.5c** (0.057 g, 90% yield).

IR

ν_{max} (cm^{-1}): 3053 (Ar-H); 2846 / 2784 (CH); 1626 (C=N); 1494; 1442; 1339; 1291; 1182; 1147; 1116; 1028; 940; 821; 745; 697.

MS

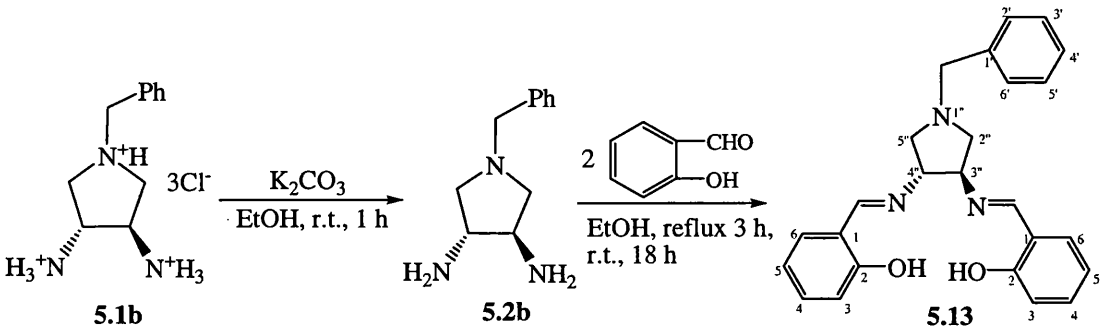
m /z (ES^+): 956 ($[M - PF_6]^+$, 14%); 904 (11%); 375 (100%); 204 (32%).

m /z (ES^-): 150 (PF_6^-, 100%).

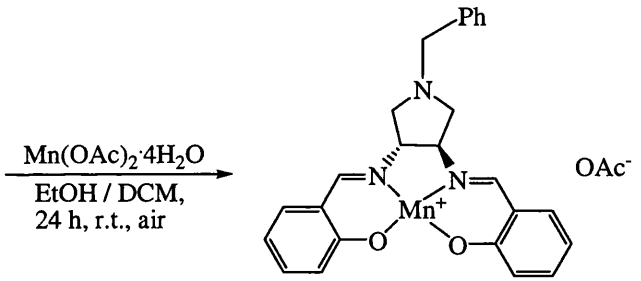
HRMS

Found $[M - PF_6]^+$: 956.3049; $C_{65}H_{47}O_2N_3Mn^+$ requires: 956.3043.

Preparation of salen ligand 5.13 and the corresponding (salen)Mn(III) complex 5.14 under anhydrous conditions.



5.1b **5.2b** **5.13**



5.14

The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower, a condenser and a glass stopper. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. Compound **5.1b** (0.045 g, 0.15 mmol), K_2CO_3 (0.093 g, 0.68 mmol) and EtOH (15 ml) were added to the flask and the mixture was stirred for 1 h at r.t. Salicylaldehyde (0.03 ml, 0.30 mmol) was added by syringe. The reaction mixture was heated under reflux for 3 h and then stirred for 18 h at r.t.

The reaction mixture was evaporated to dryness *in vacuo*. DCM (15 ml) was added to the residual solid and the mixture was stirred for 20 min. The solid was

filtered off. Removal of DCM from the filtrate *in vacuo* and drying of the resulting residue gave the salen ligand **5.13** (0.051 g, 85% yield).

The salen ligand was transferred to a small two-necked round bottomed flask and dissolved in a mixture of EtOH / DCM (5 ml / 1 ml). $Mn(OAc)_2 \cdot 4\ H_2O$ (0.037 g, 0.15 mmol) was then added. Air was bubbled into the reaction mixture and it was stirred for 24 h at r.t., and then evaporated to dryness *in vacuo* to give a dark brown solid (0.077 g). DCM (10 ml) was added to the solid and the mixture was stirred for 30 min. The solid was filtered off. Removal of DCM from the filtrate *in vacuo* and drying of the resulting residue gave (salen)Mn(III) complex **5.14** (0.052 g, 68% yield).

Characterization of salen ligand 5.13:

TLC (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}):
$R_f = 0.18$ (developing solvent: Et_2O / hexane = 1 / 3).

NMR

δ_H (400MHz, $CDCl_3$): 2.84 (dd, 2H, **H**-2″ [a] and **H**-5″ [a], ^2J = 10 Hz, ^3J = 5 Hz); 3.06 (dd, 2H, **H**-2″ [b] and **H**-5″ [b], ^2J = 10 Hz, ^3J = 5 Hz); 3.63 (d, 1H, $\mathbf{H}^c$ of PhC$\mathbf{H}^c\mathbf{H}^d$, ^2J = 13 Hz); 3.68 (d, 1H, $\mathbf{H}^d$ of PhC$\mathbf{H}^c\mathbf{H}^d$, ^2J = 13 Hz); 3.90 (apparent triplet, 2H, **H**-3″ and **H**-4″, ^3J = 5 Hz); 6.77 (apparent triple doublet, 2H, **H**-5, ^3J = 8 Hz, ^4J = 1 Hz); 6.88 (d, 2H, **H**-3, ^3J = 8 Hz); 7.10 (dd, 2H, **H**-2′ and **H**-6′, ^3J = 8 Hz, ^4J = 1 Hz); 7.16 - 7.30 (m, 7 H, Ar-**H**); 8.17 (s, 2H, N=C-**H**); 13.0 (s, 2H, **H**O-).

δ_C (400MHz, $CDCl_3$): 60.4 (**C**-2″ and **C**-5″); 60.5 (**C**H_2Ph); 75.7 (**C**-3″ and **C**-4″); 117.4 (**C**-3); 118.9 (**C**-1); 119.3 (**C**-5); 127.6 (**C**-4′); 128.8 (**C**-3′ and **C**-5′); 129.2 (**C**-2′ and **C**-6′);132.0 (**C**-6); 133.0 (**C**-4); 138.3 (**C**-1′); 161.3 (**C**-2); 165.8 (**C**=N).

MS

m /z (EI): 399 (M^+, 1%); 160 (23%); 91 ($C_7H_7^+$, 100%).

m /z (CI, NH_3): 400 ($[M + H]^+$, 26%); 158 (80%); 122 (100%); 106 (52%); 52 (75%).

HRMS

Found $[M + H]^+$: 400.2020; $C_{25}H_{26}O_2N_3^+$ requires: 400.2020.

Characterization of (salen)Mn(III) complex 5.14

IR

ν_{max} (cm^{-1}): 3053 (Ar-H); 2971 / 2795 (CH); 1623 (C=N); 1494; 1446; 1394; 1277; 1150; 1121; 1028; 816; 753; 699.

MS

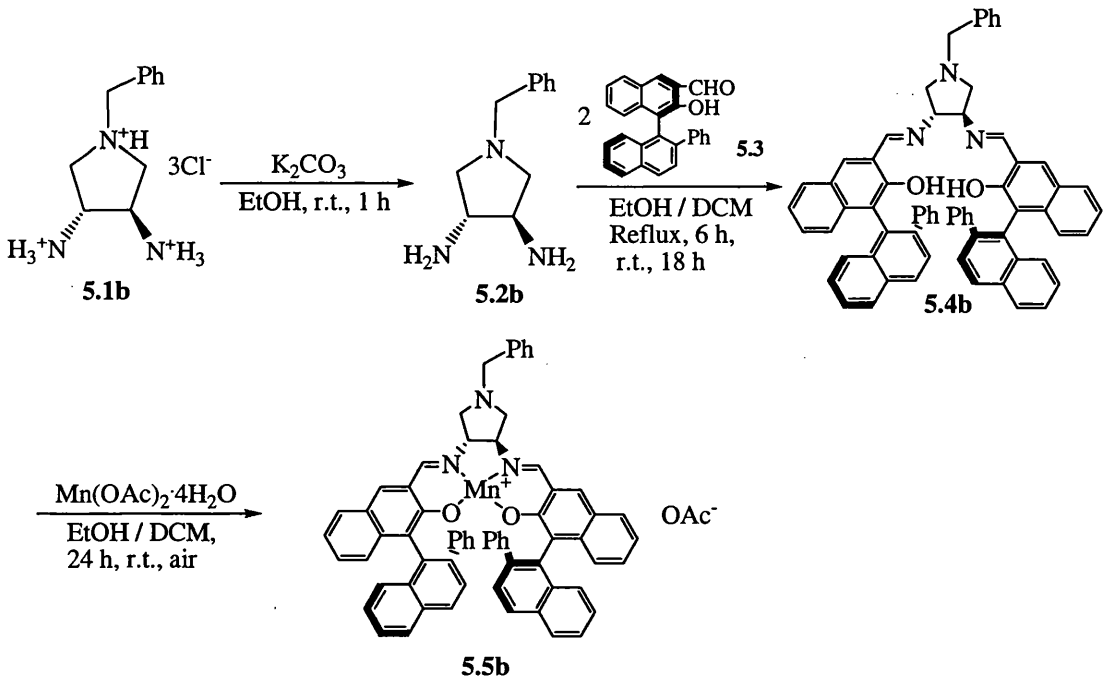
m /z (ES^+): 452 ($[M - OAc]^+$, 100%).

m /z (ES^-): 59 (OAc^-, 100%).

HRMS

Found $[M - OAc]^+$: 452.1160; $C_{25}H_{23}O_2N_3Mn^+$ requires: 452.1165.

Synthesis of (salen)Mn(III) complex 5.5b under anhydrous conditions



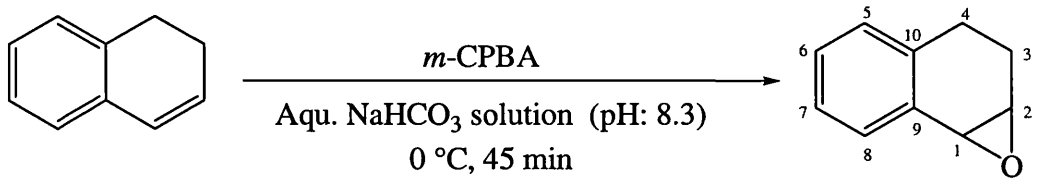
The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower, a condenser and a glass stopper. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. Compound **5.1b** (0.045 g, 0.15 mmol), K_2CO_3 (0.093 g, 0.68mmol) and EtOH (5 ml) were added to the flask and the mixture was stirred for 1 h at r.t. A solution of compound **5.3** (0.100 g, 0.27

mmol) in DCM (2 ml) was added. The reaction mixture was heated under reflux for 6 h, stirred at r.t. for 18 h and then evaporated to dryness *in vacuo*. DCM (20 ml) was added to the residual solid and the mixture was stirred for 20 min. The solid was filtered off. Removal of DCM from the filtrate *in vacuo* and drying of the resulting residue gave the salen ligand **5.4b** (0.129 g).

The salen ligand was transferred to a small two-necked round bottomed flask and dissolved in a mixture of EtOH / DCM (10 ml / 7 ml). $Mn(OAc)_2 \cdot 4\ H_2O$ (0.073 g, 0.30 mmol) was then added. Air was bubbled into the reaction mixture and it was stirred for 24 h at r.t. The reaction mixture was evaporated to dryness *in vacuo* to give a dark solid. DCM (10 ml) was added to the solid and the mixture was stirred for 30 min. The solid was filtered off. Removal of DCM from the filtrate *in vacuo* and drying of the resulting residue gave (salen)Mn(III) complex **5.5b** (0.099 g, 72% yield).

***The product** was identical with the batch of (salen)Mn(III) complex **5.5b** synthesized in the mixed solvent system.*

Epoxidation of 1,2-dihydronaphthalene (5.6) with *m*-CPBA in aqueous sodium bicarbonate solution



5.6 **5.8**

The reaction set-up consisted of a three-necked round bottomed flask equipped with a magnetic follower, a solid addition tube, a glass stopper and a septum. Compound **5.6** (0.26 ml, 2 mmol) and aqueous $NaHCO_3$ solution (0.3 M, pH 8.3, 12 ml) were added to the flask. The mixture was cooled to 0 °C in a water-ice bath. The pre-cooled *m*-CPBA (0.35 g, 2 mmol) was added from the solid addition tube in small

portions over a period of 5 - 10 min. The reaction mixture was then stirred at 0 °C for 45 min.

The reaction mixture was brought to r.t. and extracted with Et_2O (3 × 15 ml). The combined ethereal extract was washed with a pre-cooled 10% NaOH solution (15 ml) and brine (30 ml). It was then dried over anhydrous Na_2SO_4 and filtered. Removal of Et_2O from the filtrate *in vacuo* and drying of the resulting residue gave a yellow oil (0.319 g). It was purified by flash silica chromatography (adsorbent: silica 60, 30g; eluting solvent: Et_2O / hexane = 5 / 95) to give the product (0.136 g, 47% yield).

TLC (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}):
R_f = 0.43 (developing solvent: hexane / EtOAc = 5 / 1).

NMR

δ_H (400MHz, $CDCl_3$): 1.69 (apparent triple doublet, 1H, **H**-3^a, ^2J = 15 Hz, ^3J = 6 Hz); 2.34 (m, 1H, **H**-3^b); 2.47 (dd, 1H, **H**-4^a, ^2J = 15 Hz, ^3J = 6 Hz); 2.71 (apparent triple doublet, 1H, **H**-4^b, ^2J = 15 Hz, ^3J = 6 Hz); 3.64 (m, 1H, **H**-2); 3.76 (d, 1H, **H**-1, ^3J = 4 Hz); 7.01 (d, 1H, **H**-5, ^3J = 7 Hz); 7.12 (apparent triple doublet, 1H, **H**-6 or **H**-7 , ^3J = 7 Hz, ^4J = 1 Hz); 7.17 (apparent triple doublet, 1H, **H**-6 or **H**-7 , ^3J = 7 Hz, ^4J = 1 Hz); 7.32 (dd, 1H, **H**-8, ^3J = 7 Hz, ^4J = 1 Hz).

δ_C (400MHz, $CDCl_3$): 22.2 (**C**-3); 24.8 (**C**-4); 53.2 (**C**-2); 55.5 (**C**-1); 126.5 (**C**-5); 128.8 / 129.0 (**C**-6 and **C**-7); 130.0 (**C**-8); 133.0 (**C**-10); 137.1 (**C**-9).

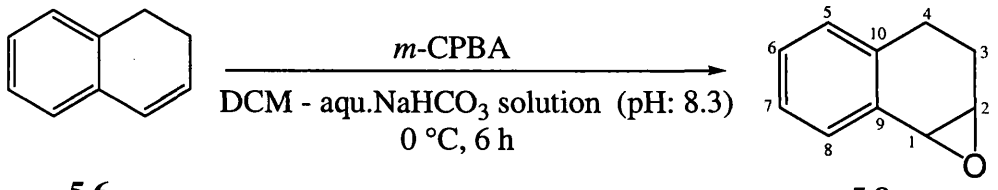
MS

m /z (EI): 146 (M^+, 100%); 131 (28%); 117 (50%); 104 (85%); 91 ($C_7H_7^+$, 23%).

HRMS

Found $[M]^+$: 146.0724; $C_{10}H_{10}O^+$ requires: 146.0726.

Epoxidation of 1,2-dihydronaphthalene (5.6) with *m*-CPBA in a biphasic solvent system



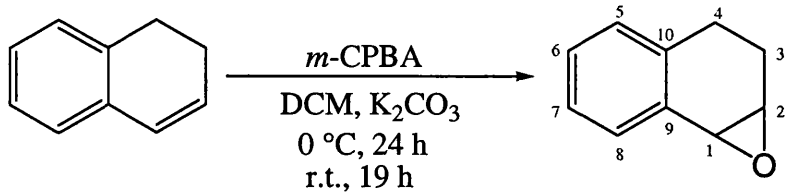
5.6 **5.8**

The reaction set-up consisted of a three-necked round bottomed flask equipped with a magnetic follower, a solid addition tube, a glass stopper and a septum. Compound **5.6** (0.26 ml, 2 mmol), DCM (20 ml) and an aqueous $NaHCO_3$ solution (0.3 M, pH 8.3, 20 ml) were added to the flask. The mixture was cooled to 0 °C in a water-ice bath. The pre-cooled *m*-CPBA (0.35 g, 2 mmol) was added from the solid addition tube in small portions over a period of 5 - 10 min. The reaction mixture was then stirred for 4 h at 0 °C. A second batch of the pre-cooled *m*-CPBA (0.35 g, 2 mmol) was added in the same way as the first batch and the reaction mixture was stirred for a further 2 h.

The reaction mixture was brought to r.t. The aqueous phase was separated off. The DCM phase was washed with saturated sodium thiosulfate (15 ml), a pre-cooled 10% NaOH solution (5 ml), distilled water (15 ml) and brine (20 ml). It was then dried over anhydrous Na_2SO_4 and filtered. Removal of DCM from the filtrate *in vacuo* and drying of the resulting residue gave a yellow oil (0.303 g). It was purified by flash silica chromatography (adsorbent: silica 60, 30g; eluting solvent: Et_2O / hexane = 5 / 95) to give the product (0.147 g, 51% yield).

***The product** was identical to the epoxide synthesized in aqueous sodium bicarbonate solution with m-CPBA.*

Epoxidation of 1, 2-dihydronaphthalene with *m*-CPBA in DCM in the presence of anhydrous potassium carbonate



5.6 **5.8**

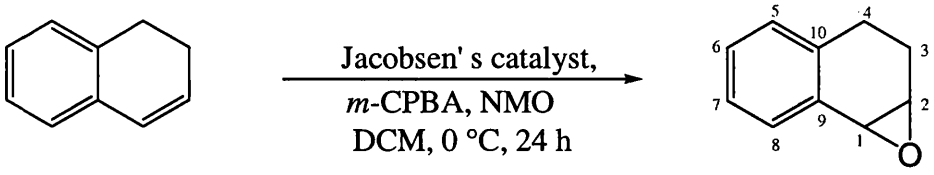
The reaction set-up consisted of a three-necked round bottomed flask equipped with a magnetic follower, a solid addition tube, a glass stopper and a septum. It was

assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. Anhydrous K_2CO_3 (0.83 g, 6 mmol), compound **5.6** (0.26 ml, 2 mmol) and dry DCM (20 ml) were added to the flask. The mixture was cooled to 0 °C in a water-ice bath. The pre-cooled *m*-CPBA (0.62 g, 3.6 mmol) was added from the solid addition tube in small portions over a period of 5 – 10 min. The reaction mixture was then stirred at 0 °C for 24 h. A second batch of pre-cooled *m*-CPBA (0.35 g, 2 mmol) was added in the same way as the first batch. The reaction mixture was brought to r.t. and stirred for a further 19 h.

The reaction mixture was cooled to 0 °C. A pre-cooled dimethyl sulfide solution in DCM (0.68 ml, 1.8 mmol) was added. Then a pre-cooled 2 M NaOH solution (20 ml) was added. The aqueous phase was separated off. The organic phase was washed with distilled water (20 ml) and brine (20 ml). It was then dried over anhydrous Na_2SO_4 and filtered. Removal of DCM from the filtrate *in vacuo* and drying of the resulting residue gave a yellow oil (0.514 g). It was purified by flash silica chromatography (adsorbent: silica 60, 30g; eluting solvent: Et_2O / hexane = 5 / 95) to give the product (0.239 g, 82% yield).

***The product** was identical to the epoxide synthesized using the above-mentioned two methods.*

Asymmetric epoxidation of 1,2-dihydronaphthalene (5.6) with *m*-CPBA using Jacobsen's catalyst



5.6 **5.7**

The reaction set-up consisted of a three-necked round bottomed flask equipped with a magnetic follower, a solid addition tube, a glass stopper and a septum. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t.

Jacobsen's catalyst (0.06 g, 0.1 mmol), NMO (1.17 g, 10 mmol), compound **5.6** (0.26 ml, 2 mmol) and dry DCM (20 ml) were added to the flask. The mixture was cooled to 0 °C in a water-ice bath. The pre-cooled *m*-CPBA (0.70 g, 4 mmol) was added from the solid addition tube in small portions over a period of 5 - 10 min. The reaction mixture was then stirred at 0 °C for 24 h.

A pre-cooled solution of dimethyl sulfide in DCM (0.68 ml, 1.8 mmol) was added to the reaction mixture. Then a pre-cooled 2 M NaOH solution (20 ml) was added. The aqueous phase was separated off. The organic phase was washed with distilled water (25 ml) and brine (25 ml). It was then dried over anhydrous Na_2SO_4 and filtered. Removal of DCM from the filtrate *in vacuo* and drying of the resulting residue gave a dark brown oil (0.52 g). It was purified by flash silica chromatography (adsorbent: silica 60, 30g; eluting solvent: Et_2O / hexane = 5 / 95) to give the product (0.19 g, 65% yield).

TLC (silica plate: 0.20 mm, silica gel 60 with fluorescent indicator UV_{254}):
$R_f = 0.44$ (developing solvent: hexane / EtOAc = 5 / 1).

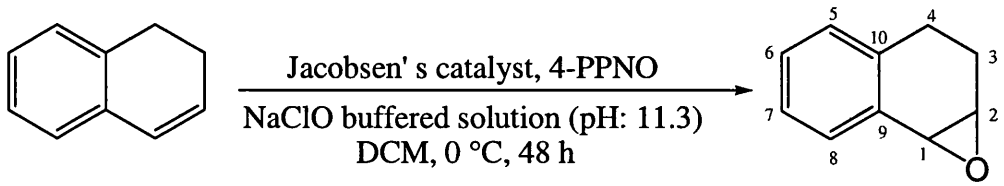
Specific rotation

$[\alpha]_D^{24} = 109.6$ (c. 0.72, $CHCl_3$).

Enantiomeric excesses (ee %): 83.

The spectral properties were virtually the same as those recorded for previously obtained samples of racemic epoxide **5.8**.

Asymmetric epoxidation of 1,2-dihydronaphthalene (5.6) with NaClO in a biphasic solvent system using Jacobsen's catalyst



5.6 **5.7**

Analysis of NaOCl solution by iodometric titration

NaOCl solution (5 ml, from Lancaster Synthesis Ltd.) was transferred to a 500-ml volumetric flask and diluted to 500 ml with distilled water. An aliquot (50 ml) of the diluted solution was transferred to a 100-ml Erlenmeyer flask containing potassium iodide (2 g) and a magnetic stirring bar. HCl (6 M; 3 ml) was added and the mixture was immediately titrated with a standard sodium thiosulfate solution (1.1024 M) until the color of the solution changed to pale yellow. A starch indicator solution (5 ml) was added. Titration was continued until the color changed to colorless.

$$OCl^- + 2\,S_2O_3^{2-} + 2\,H^+ \longrightarrow S_4O_6^{2-} + Cl^- + H_2O$$

Thus, 1 mmol of OCl^- = 1 mmol of I_2 = 2 mmol of $S_2O_3^{2-}$

Result: V ($Na_2S_2O_3$): 1st 9.50 ml; 2nd 9.40 ml; 3rd 9.20 ml.

The concentration of the commercial NaOCl solution was calculated as 0.96 M.

Preparation of a buffered 0.55 M NaOCl solution

NaOCl solution (0.96 M, 57.3 ml) was placed in a 100-ml volumetric flask and diluted with a phosphate buffer solution (Na_2HPO_4, 0.05 M) to 100 ml. A few drops of 1 M HCl were added to adjust the pH of the solution to 11.3.

Asymmetric synthesis

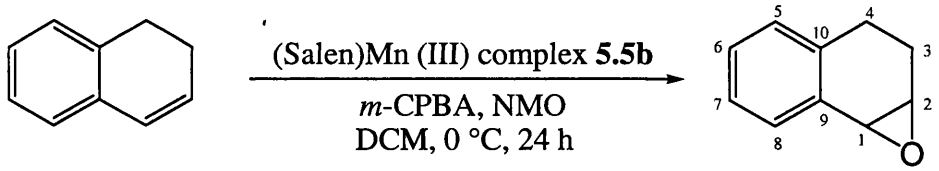
The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower and capped with a glass stopper and a septum. Jacobsen's catalyst (0.030 g, 0.05 mmol), 4-PPNO (0.038 g, 0.23 mmol), compound **5.6** (0.12 ml, 0.90 mmol) and DCM (2.5 ml) were added to the flask. The mixture was cooled to 0 °C in a water-ice bath. A buffered NaClO solution (3.3 ml, 1.80 mmol) was then added. The reaction mixture was stirred at 0 °C for 3.5 h.

The reaction mixture was brought to r.t. DCM (5 ml) was added. The aqueous phase was separated and then extracted with DCM (10 ml). The combined DCM solution was washed with distilled water (30 ml) and brine (30 ml). It was then dried over anhydrous Na_2SO_4 and filtered. Removal of DCM from the filtrate *in vacuo* and drying of the resulting residue gave a dark oil (0.213 g). It was purified by flash silica chromatography (adsorbent: silica 60, 30 g; eluting solvent: Et_2O / hexane = 5 / 95) to give the product (0.033 g, 26% yield).

Enantiomeric excess (ee %): 87.

The NMR and mass spectra of the epoxide synthesized were the same as those of the product synthesized from the reactions using *m*-CPBA as the oxidant.

Asymmetric epoxidation of 1,2-dihydronaphthalene (5.6) with *m*-CPBA using (salen)Mn(III) complex 5.5b



5.6 **5.7**

The reaction set-up consisted of a three-necked round bottomed flask equipped with a magnetic follower, a solid addition tube, a glass stopper and a septum. It was assembled while the glassware was hot, and flushed with Ar while it cooled to r.t. (Salen)Mn(III) complex **5.5b** (0.026 g, 0.03 mmol), NMO (0.295 g, 2.52 mmol), compound **5.6** (0.120 g, 0.90 mmol) and dry DCM (9 ml) were added to the flask. The mixture was cooled to 0 °C in a water-ice bath. The pre-cooled *m*-CPBA (0.310 g, 1.80 mmol) was added from the solid addition tube in small portions over a period of 5 -10 min. The reaction mixture was then stirred at 0 °C for 24 h.

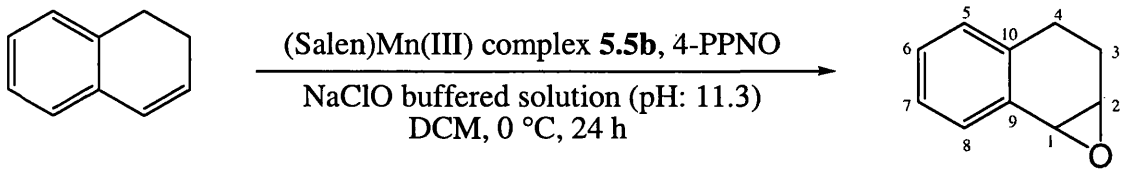
A pre-cooled solution of dimethyl sulfide in DCM (0.31 ml, 0.90 mmol) was added to the reaction mixture. Then a pre-cooled 2 M NaOH solution (9 ml) was added. The aqueous phase was separated off. The organic phase was washed with

distilled water (12 ml) and brine (12 ml). It was then dried over anhydrous Na_2SO_4 and filtered. Removal of DCM from the filtrate *in vacuo* and drying of the resulting residue gave a dark oil (0.154 g). It was purified by flash silica chromatography (adsorbent: silica 60, 33g; eluting solvent: Et_2O / hexane = 5 / 95) to give the product (0.036 g, 28% yield).

Enantiomeric excesses (ee %): 4.

The NMR spectra of the epoxide synthesized were the same as those of the product synthesized from the reactions using Jacobsen's catalyst.

Asymmetric epoxidation of 1,2-dihydronaphthalene (4.6) with NaClO in a biphasic solvent system using (salen)Mn(III) complex 5.5b



5.6 **5.7**

The reaction set-up consisted of a two-necked round bottomed flask equipped with a magnetic follower and capped with a glass stopper and a septum. (Salen)Mn(III) complex **5.5b** (0.025 g, 0.02 mmol), 4-PPNO (0.026 g, 0.15 mmol), compound **5.6** (0.10 ml, 0.77 mmol) and DCM (1 ml) were added to the flask. The mixture was cooled to 0 °C in a water-ice bath. A buffered NaClO solution (2.8 ml, 1.54 mmol) was then added. The reaction mixture was stirred at 0 °C for 3 h. A second batch of the buffered NaClO solution (4.2 ml, 2.31 mmol) was added. The reaction mixture was stirred at 0 °C for a further 21 h.

The reaction mixture was brought to r.t. DCM (5 ml) was added. The aqueous phase was separated and then extracted with DCM (10 ml). The combined organic phase was washed with distilled water (15 ml) and brine (20 ml). It was then dried over anhydrous Na_2SO_4 and filtered. Removal of DCM from the filtrate *in vacuo* and drying of the resulting residue gave a dark oil (0.114 g). It was purified by flash silica

chromatography (adsorbent: silica 60, 30 g; eluting solvent: Et_2O / hexane = 5 / 95) to give the product (0.014 g, 12% yield).

Enantiomeric excesses (ee %): 6.

The NMR spectra of the epoxide synthesized were the same as those of the product synthesized from the reactions using Jacobsen's catalyst.

5.5 References for *Chapter 5*

1. R. G. Konsler, J. Karl and E. N. Jacobsen. *J. Am. Chem. Soc.,* 1998, 120, 10780.
2. H. Sasaki and T. Katsuki. *Tetrahedron,* 1994, 50, 11835.
3. C. Kokubo and T. Katsuki. *Tetrahedron*, 1996, 52, 13895.
4. H. Sasaki, R. Irie, T. Hamada, K. Suzuki and T. Katsuki. *Tetrahedron,* 1994, 50, 11827.
5. C. H. Liu. *Synthesis and Applications of Polymer-bound Chiral Epoxidation Catalysts.* PhD thesis: University of Wales Swansea, United Kingdom, 2001.
6. J. McMurry. *Organic Chemistry*, 5th edn. Brooks / Cole: Pacific Grove, 1999.
7. N. C. Yang, W. Chiang, D. Leonov, E. Leonov, I. Bilyk and B. Kim. *J. Org. Chem.,* 1978, 43, 3425.
8. a) D. Swern. In: *Organic Peroxides*, Vol. II, D. Swern, Ed., Wiley-Interscience: New York, 1971, 355; b) W. K. Anderson and T. Veysoglu. *J. Org. Chem.,* 1973, 38, 2267.
9. F. Fringuelli and F. Pizzo. *Org. Prep. Proced. Int.,* 1989, 21, 757.
10. M. Imuta and H. Ziffer. *J. Org. Chem.,* 1979, 44, 1351.
11. M. Palucki, G. J. McCormick and E. N. Jacobsen. *Tetrahedron Lett.,* 1995, 36, 5457.
12. W. Zhang and E. N. Jacobsen. *J. Org. Chem.,* 1991, 56, 2296.
13. Y. N. Ito and T. Katsuki. *Bull. Chem. Soc. Jpn.,* 1999, 72, 603.
14. a) H. Sasaki, R. Irie and T. Katsuki. *Synlett,* 1994, 356; b) H. Sasaki, R. Irie, T. Hamada, K. Suzuki and T. Katsuki. *Tetrahedron,* 1994, 50, 11827; c) N. Hosoya, A. Hatakeyama, R. Irie, H. Sasaki and T. Katsuki. *Tetrahedron,* 1994, 50, 4311; d) T. Fukuda, R. Irie and T. Katsuki. *Synlett*, 1995, 197; e) D. Mikame, T.

Hamada, R. Irie and T. Katsuki. *Synlett*, 1995, 827.

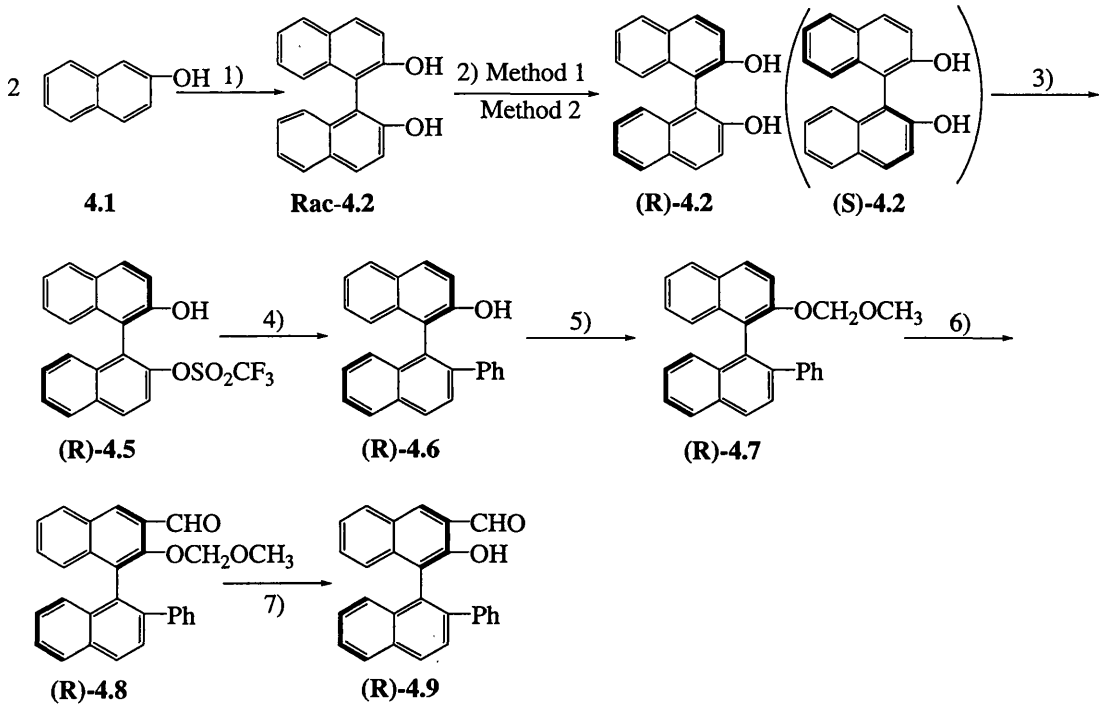
15. K. Smith and C. H. Liu. *Chem. Commun.*, 2002, 886.
16. C. E. Song, E. J. Roh, B. M. Yu, D. Y. Chi and S. C. Kim and K. -J. Lee. *Chem. Commun.*, 2000, 615.
17. J. Leonard, B. Lygo and G. Procter. *Advanced practical organic chemistry*, 2nd edn. Chapman &Hall, 1995.

CHAPTER SIX

CONCLUSION

The target of the work reported in this thesis was to prepare new chiral pyrrolidine-type salen ligands **5.4** and their corresponding Mn(III) complexes **5.5**. Salen ligands **5.4** were synthesized by condensation of *trans*-(3R,4R)-diaminopyrrolidine (**3.12**) or *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine (**3.10**) with two equivalents of (R)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene [(R)-**4.9**]. (Salen)Mn(III) complexes **5.5** were prepared from their corresponding salen ligands with $Mn(OAc)_2 \cdot 4\ H_2O$ following a general procedure. The synthetic routes and the best results for each transformation step are described in Schemes 6.1 - 6.4.

(R)-3-Formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene [(R)-**4.9**] was synthesized from 2-naphthol (**4.1**) in 9% overall yield according to Scheme 6.1. The optimized reaction conditions and the results are also listed.



Scheme 6.1

Reaction conditions and the results

1) $FeCl_3 \cdot 6\ H_2O$, H_2O, 50 °C, 9 h; 82% yield.

2) (Optical resolution) *Method 1*: $B(OH)_3$, (R)-(+)-α-methylbenzylamine, CH_3CN, reflux, 12 h; (R)-**4.2**: 16% yield, 98% ee; (S)-**4.2**: 56% yield, 32% ee.

Method 2: (8S,9R)-(-)-*N*-benzylcinchonidinium chloride, CH_3OH, r.t., 18 h; (R)-**4.2**: 28% yield, 98% ee; (S)-**4.2**: 35% yield, >99% ee.

3) Tf_2NPh, 2,4,6-collidine, DMAP, dry DCM, reflux, 18 h; 89% yield.

4) $PhMgBr{\cdot}Et_2O$, $NiCl_2(dppe)$, dry Et_2O, reflux, 1 h; 70% yield.

5) $ClCH_2OCH_3$, $(i\text{-}Pr)_2NEt$, dry DCM, r.t., 24 h; 73% yield.

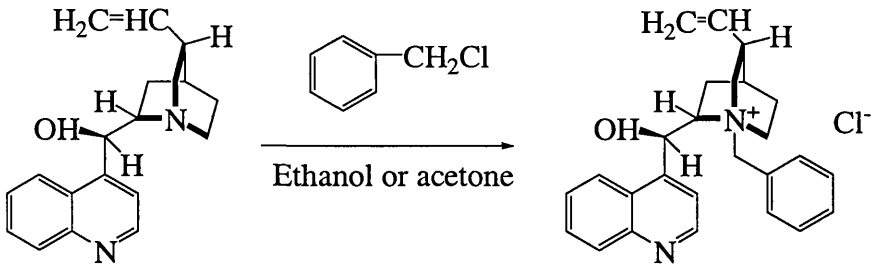
6) a. *t*-BuLi, dry THF, -78 °C, 3 h; b. DMF, r.t., 1 h; 92% yield.

7) $SiMe_3Br$, dry DCM, r.t., 1 h; 88% yield.

2,2'-Dihydroxy-1,1'-binaphthalene (Rac-**4.2**) was synthesized by oxidative coupling of 2-naphthol (**4.1**) in an aqueous Fe^{3+} solution. Several factors that affect the yield of the reaction were investigated. These factors included: the particle size of 2-naphthol; the reaction vessel type; the reaction temperature; and the molar ratio of oxidant (Fe^{3+}) to 2-naphthol. The reaction was effectively applied to a large scale synthesis, which produced an 82% yield.

Racemic 2,2'-dihydroxy-1,1'-binaphthalene (Rac-**4.2**) was resolved into its enantiomers using two methods. The method using boric acid and (R)-(+)-α-methylbenzylamine as the resolving reagent gave unsatisfactory results; only one optically pure enantiomer [(R)-**4.2**] was obtained, but in a low yield (16%). Conversely, a simple, practical and efficient method has been developed using synthesized (8S,9R)-(-)-*N*-benzylcinchonidinium chloride (**4.4**) as the resolving reagent. Both (R)-**4.2** and (S)-**4.2** were obtained in optically pure form. This is especially important for (S)-**4.2**, which has normally been only partially resolved or has been obtained in optically pure form only after using specialized techniques.

Two different solvents were used to synthesize the resolving reagent (8S,9R)-(-)-*N*-benzylcinchonidinium chloride (**4.4**) (Scheme 6.2). A simple procedure has been developed to prepare the pure product in 48% yield using dry acetone as the solvent. However, when dry ethanol was used as the solvent, the product was found to be contaminated with some dark coloured impurities, which were presumed to derive from decomposition of the product at high temperature.



4.3 **4.4**

Scheme 6.2

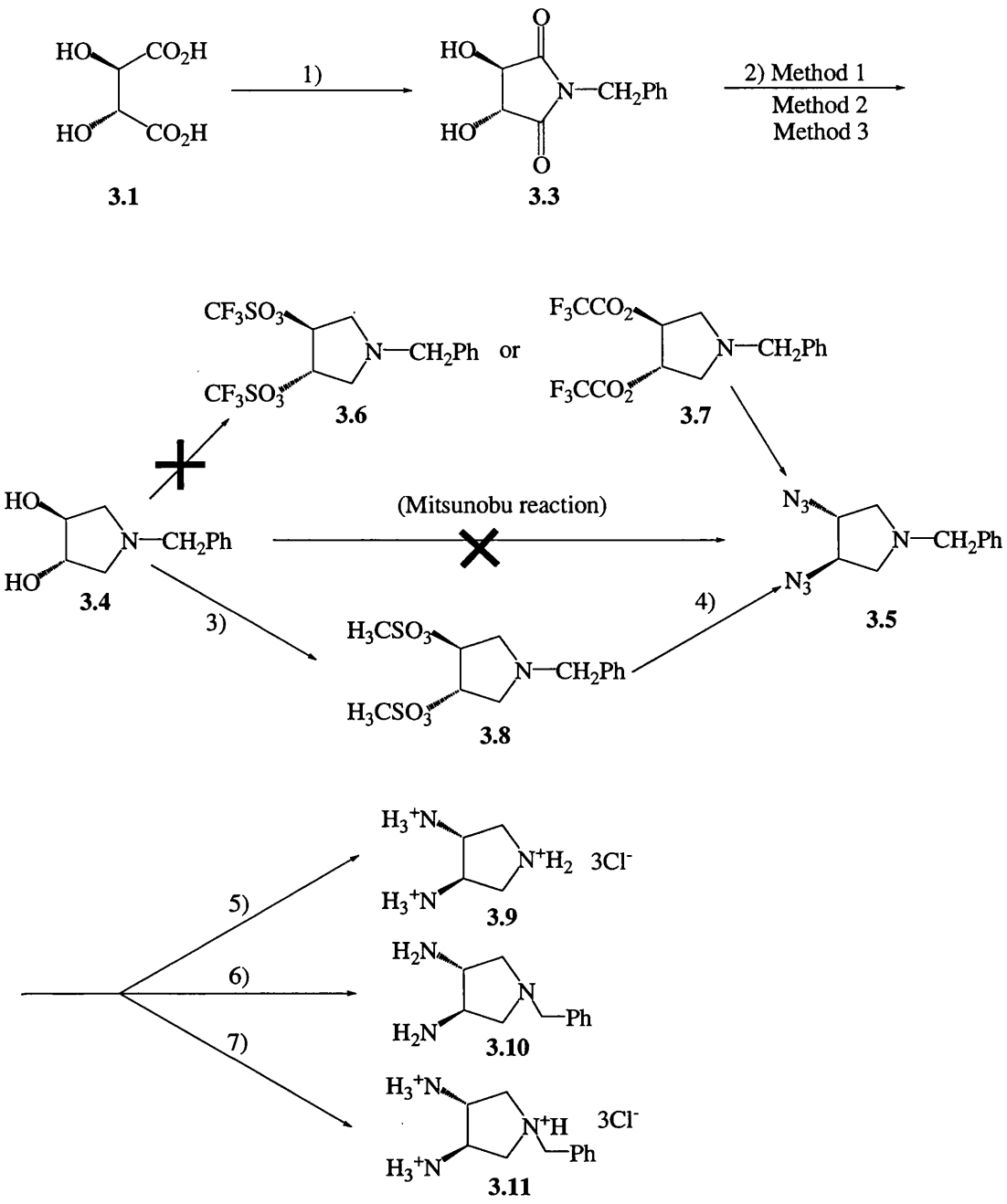
Reaction conditions and the results

Method 1: Ethanol, reflux, 20 h; 73% yield (contaminated with dark coloured impurities).

Method 2: Acetone, reflux, 139 h; 48% yield.

Before using compound (R)-**4.2** as the starting material to carry out the following transformations, Rac-**4.2** was used as the starting material first. The transformations were successful; racemic 3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthalene (Rac-**4.9**) was synthesized with an overall yield of 28%. The transformations were next carried out on compound (R)-**4.2**. The target compound (R)-**4.9** was obtained in 37% yield.

trans-(3R,4R)-Diaminopyrrolidine trihydrochloride salt (**3.9**), *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine (**3.10**) and its trihydrochloride salt (**3.11**) were synthesized from (2R,3R)-(+)-tartaric acid (**3.1**) according to Scheme 6.3. The reaction conditions and the results are listed.



Scheme 6.3

Reaction conditions and the results

1) Benzylamine, xylene, Dean-Stark trap, reflux; 71% yield.

2) *Method 1*: $NaBH_4$, I_2, dry THF, 0 °C (2.5 h), reflux (6 h); 64% yield.

Method 2: BH_3·THF, BF_3·Et_2O, dry THF, 0 °C (3.3 h), reflux (36 h); 51% yield.

Method 3: $NaBH_4$, BF_3·Et_2O, dry diglyme, 70 °C, 4 h; 71% yield.

3) CH_3SO_2Cl, Et_3N, dry DCM, 0 °C (25 min), 23 °C (40 min); 93% yield.

4) *Method 1*: NaN_3, dry DMF, 100 °C, 8 h; 56% yield.

Method 2: a. NaN_3, LiCl, dry DMF, r.t., 12 h; b. 80 °C (4 h), 100 °C (2 h); 55% yield.

5) a. H_2, Pd / C, CF_3CO_2H / EtOH (1 / 4), 4.3 atm, r.t., 28 h; b. conc. HCl; 82% yield.

6) H_2, Pd / C, EtOH, 1.2 atm, r.t., 1 h; 100% yield.

7) a. $LiAlH_4$, dry THF, reflux, 2 h; b. conc. HCl; 66% yield.

The reduction of (3R,4R)-1-benzyl-3,4-dihydroxy-2,5-pyrrolidinedione (**3.3**) to diol (3S,4S)-1-benzyl-3,4-dihydroxypyrrolidine (**3.4**) was intensively investigated using three reduction systems: $NaBH_4$ / I_2 / THF system, BH_3·THF complex and $NaBH_4$ / BF_3·Et_2O / diglyme system. The best result was obtained using the $NaBH_4$ / BF_3·Et_2O / diglyme reduction system, which produced a 71% isolated yield. A new method was attempted in which BH_3·THF complex was used as the reductant, and this resulted in a 51% isolated yield.

Since the Mitsunobu reaction failed to transform diol **3.4** to diazide **3.5**, an indirect transformation approach was adopted. The initial attempt to convert diol **3.4** to bistriflate **3.6** gave unsatisfactory results, and attempts to convert diol **3.4** to compound **3.7** failed. Fortunately, transformation of diol **3.4** to dimesylate **3.8** was successfully achieved.

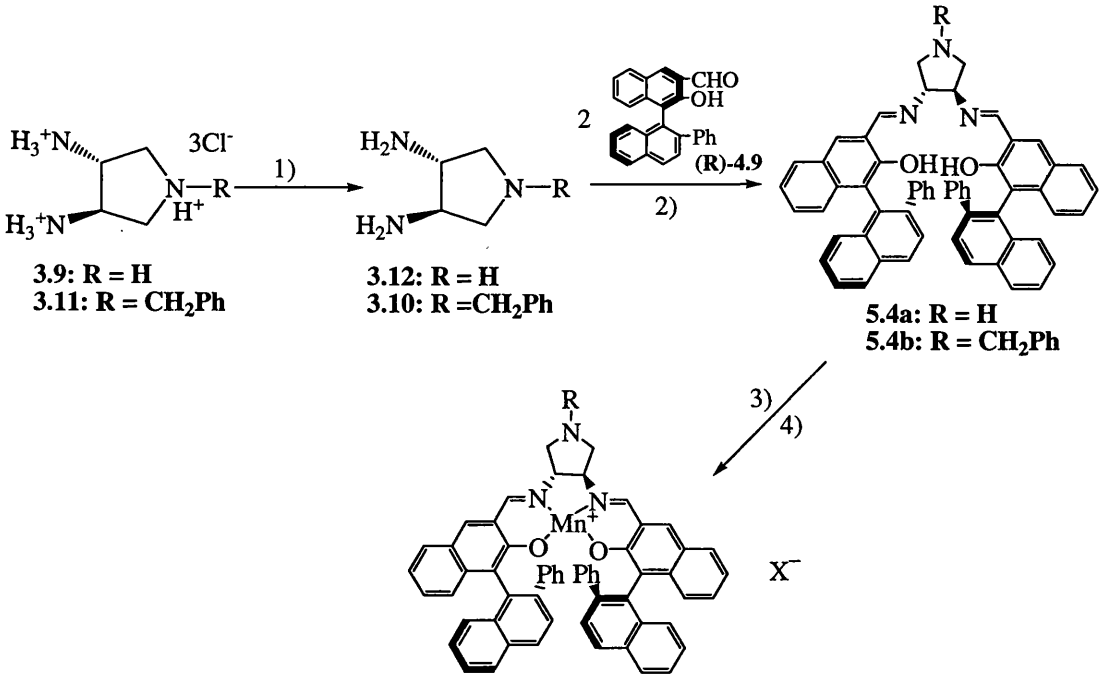
Dimesylate **3.8** was successfully transformed into diazide **3.5** by reaction with sodium azide or lithium azide. The influences of reaction parameters, such as reaction temperature, solvent, and catalyst, on the yield of the reaction were investigated. The best isolated yield obtained was 56% using sodium azide as the azide source.

Diazide **3.5** was successfully reduced to the target compound *trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt **(3.9)** by a simple hydrogenation procedure. The reaction was complete and clean. The best isolated yield obtained was 82%.

A simple, clean and efficient method has been developed to synthesize the target compound *trans*-(3R,4R)-diaminopyrrolidine trihydrochloride salt **(3.9)** directly from dimesylate **3.8**, which produced a 47% isolated yield.

Diazide **3.5** was reduced to the target compound *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine **(3.10)** quantitatively and cleanly by a hydrogenation method. It was also reduced to *trans*-(3R,4R)-1-benzyl-3,4-diaminopyrrolidine trihydrochloride salt **(3.11)** in 66% yield using $LiAlH_4$ as the reductant.

The salen ligands **5.4** and their corresponding Mn(III) complexes **5.5** were synthesized according to Scheme 6.4. The reaction conditions and the results are listed.



3.9: R = H
3.11: R = CH_2Ph

3.12: R = H
3.10: R = CH_2Ph

5.4a: R = H
5.4b: R = CH_2Ph

5.5a: R = H; X = AcO
5.5b: R = CH_2Ph; X = AcO
5.5c: R = CH_2Ph; X = PF_6

Scheme 6.4

Reaction conditions and the results

- Preparation of complex **5.5a**: 1) K_2CO_3, EtOH / H_2O (9 / 1), r.t., 1 h; 2) EtOH / H_2O / DCM, reflux (3 h), r.t. (19 h); 40% yield (from compound **3.9**); 3) $Mn(OAc)_2 \cdot 4\ H_2O$, EtOH / DCM, r.t., 24 h, air; 79% yield (from salen ligand **5.4 a**).

- Preparation of complex **5.5b** (*Method 1*): 1) K_2CO_3, EtOH / H_2O (9 / 1), r.t., 1 h; 2) EtOH / H_2O / DCM, r.t., 3 h; 3) $Mn(OAc)_2 \cdot 4\ H_2O$, EtOH / DCM, r.t., 24 h, air; 63% yield (from compound **3.11**).
- Preparation of complex **5.5b** under anhydrous conditions (*Method 2*): 1) K_2CO_3, EtOH, r.t., 1 h; 2) EtOH / DCM, reflux (6 h), r.t., 18 h; 3) $Mn(OAc)_2 \cdot 4\ H_2O$, EtOH / DCM, r.t., 24 h, air; 72% yield (from compound **3.11**).
- Preparation of complex **5.5c:** 1) K_2CO_3, EtOH / H_2O (9 / 1), r.t., 1 h; 2) EtOH / H_2O / DCM, r.t., 3 h; 3) $Mn(OAc)_2 \cdot 4\ H_2O$, EtOH / DCM, r.t., 24 h, air; 4) $NaPF_6$, CH_3CN / DCM, r.t., 24 h, air; 57% yield (from compound **3.11**)

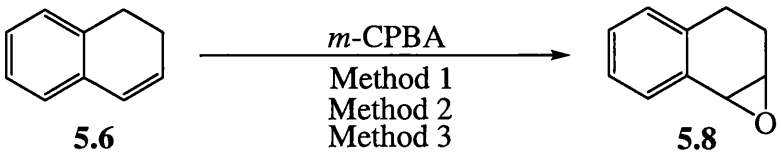
The synthetic route to salen ligand **5.4** was first tested by preparation of two model salen ligands **5.9** and **5.11**. Salen ligand **5.4a** was obtained in 40% yield after purification by alumina column. (Salen)Mn(III) complex **5.5a** was obtained from salen ligand **5.4a** in 79% yield.

Salen ligand **5.4b** was found to decompose on both silica and alumina columns. It was therefore not purified; the crude product was used for the following complexation instead. (Salen)Mn(III) complex **5.5b** was prepared in such a way from compound **3.11** and compound (R)-**4.9** with a yield of 63%. Since there was a possibility that the presence of excess H_2O would disfavour the formation of salen ligands, (salen)Mn(III) complex **5.5b** was also prepared under anhydrous conditions, which produced a 72% yield (from compound **3.11**).

(Salen)Mn(III) complex **5.5c** was prepared from (salen)Mn(III) complex **5.5b** in 90% yield.

Racemic 1,2-epoxy-1,2,3,4-tetrahydronaphthalene (**5.8**) was synthesised *via* direct epoxidation of 1,2-dihydronaphthalene (**5.6**) using *m*-CPBA in three different reaction media: a buffered aqueous solution, a biphasic solvent system, or dry DCM (Scheme 6.5). The optimized reaction conditions and the results are listed as below. An efficient procedure has been established in which the epoxidation reaction was

carried out in dry DCM in the presence of anhydrous K_2CO_3 and an 82% yield of the product was obtained.



5.6 **5.8**

Scheme 6.5

Reaction conditions and the results

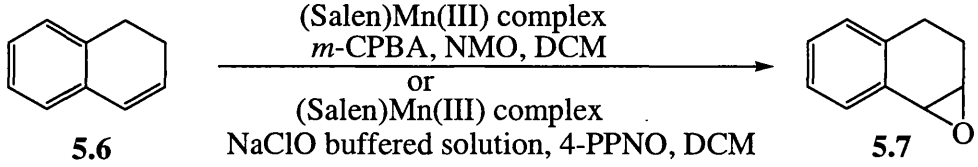
Method 1: *m*-CPBA, aqu. $NaHCO_3$ solution (pH: 8.3), 0 °C, 45 min; 47% yield.

Method 2: *m*-CPBA, DCM / aqu. $NaHCO_3$ solution (pH: 8.3), 0 °C, 6 h; 51% yield.

Method 3: *m*-CPBA, DCM, K_2CO_3, 0 °C (24 h), r.t.(19 h); 82% yield.

A commercially available (salen)Mn(III) complex, Jacobsen's catalyst **5.15**, was used to catalyze the asymmetric epoxidation of 1,2-dihydronaphthalene (**5.6**) in two different reaction systems. The epoxide **5.7** was obtained in 88% ee using a *m*-CPBA / NMO oxidation system under anhydrous conditions. Also, the epoxide **5.7** was obtained in 87% ee using a buffered NaClO solution as the oxidant in a two-phase solvent system.

The synthesized pyrrolidine-type (salen)Mn(III) complexes **5.5a**, **5.5b**, and **5.5c** were also used as catalysts for the aymmetric epoxidation reactions (Scheme 6.6). The results were disappointing. When complex **5.5b** was used as the catalyst, the epoxide was obtained in 6% ee using a buffered NaClO solution as the oxidant in a two-phase solvent system. Also, the epoxide was obtained in 4% ee using a *m*-CPBA / NMO system under anhydrous conditions. When complex **5.5c** was used as the catalyst, the epoxide obtained was nearly a racemate (1% ee) using a *m*-CPBA / NMO system under anhydrous conditions. When complex **5.5a** was used as the catalyst, the epoxide obtained was also nearly a racemate (2% ee) using a buffered NaClO solution in a two-phase solvent system.



5.6 **5.7**

Scheme 6.6

Reaction conditions and the results

- Complex **5.5b** (3.2 mol %), NaClO buffered solution (pH: 11.3), 4-PPNO, DCM, 0 °C, 24 h; 12% isolated yield, 6 % ee.

The poor performances of the synthesized pyrrolidine-type (salen)Mn(III) complexes **5.5a**, **5.5b**, and **5.5c** might be due to their instability. They might not be robust enough to withstand the reaction conditions and consequently might have decomposed. Alternatively, it is possible that the presence of a basic N atom capable of inversion might have undesirable consequences for asymmetric induction during epoxidation reaction. Whatever the precise explanation, there was insufficient time available to allow the design and synthesis of alternative catalysts.