Salen Coordination Compounds as Lewis Acid Catalysts

Submitted to the University of Leicester

By

Pedro R. Villuendas

A thesis submitted

In candidature for the degree of

PhD

University *of* Leicester

2007

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Statement of Originality

The experimental work in this thesis has been carried out by the author in the department of chemistry at the University of Leicester between September 2003 and November 2006. The work has not been submitted, and is not presently being submitted, for any other degree at this or any other university.

Signed..... Date.....

Pedro R. Villuendas
University of Leicester
University Road,
Leicester.
LE1 7RH

Salen Coordination Compounds as Lewis Acid catalysts

Pedro R. Villuendas

Abstract

In this research a range of salen ligands have been synthesised with a variety of diamine backbones. These compounds have been characterised by ^{1}H, ^{19}F, ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis.

Derivatives of these ligands [M= Ni(II), Zn(II), Cu(II)] have subsequently been prepared and have been characterised by ^{1}H, ^{19}F NMR spectroscopy, mass spectrometry and elemental analysis. These metal complexes were used as catalysts in the synthesis of enaminodiones, the enantioselective alkylation of carbonyls and imines, the enantioselective trifuoromethylation and the enantioselective Reformatsky reaction.

Yields better than 90% were achieved for the enaminodione reaction for zinc salen derivatives in 24 hours and reactivities across a range of substrates were established. Once the best catalysts and conditions were determined, experiments were carried out in order to determine the recyclability of the catalyst by supporting it on silica gel or FRPSG (Fluorous Reverse Phase Silica Gel). Most catalysts could not be recycled, but the best catalyst could be recovered four times without loosing activity. In all these experiments large losses of zinc to the organic phase were identified using ICP/MS, suggesting catalyst decomposition. Experiments were carried out in order to determine the cause of this decomposition.

In the enantioselective addition of $ZnEt_2$ to benzaldehyde, the conversion was calculated by ^{1}H NMR spectroscopy and the enantioselectivity was calculated using chiral GC. Generally, the non-fluorous zinc salen complex demonstrated enhanced enantioselectivity to the fluorous ones. However, recycling experiments using FPSE were demonstrated for one of the zinc fluorous salen catalysts.

In the enantioselective trifluoromethylation of benzaldehyde, the enantioselective Reformatsky reaction and the enantioselective addition of $ZnEt_2$ to benzaldehyde, conversions were calculated by ^{1}H NMR spectroscopy and enantioselectivities were determined by chiral GC, NMR spectroscopy with a chiral solvent and HPLC respectively. Poor enantioselectivities were obtained in the trifluoromethylation and metallosalen complexes were demonstrated not to be catalysts for this reaction. No enantioselectivity was induced by these catalysts in the other reactions.

Acknowledgments

I have many thanks to give to everyone I have met in the last three years and who have made this thesis possible. Firstly, much appreciation and gratitude to my supervisors, Alison and Eric, for giving me this opportunity and for all their guidance support and encouragement. Without the technical and secretarial support from the University of Leicester, the research would have been much more difficult. Special thanks goes to Gerry Griffin (NMR), Graham Eaton (MS), Kuldip Singh and John Fawcett (X-Ray), Mick Lee (HPLC and GC) and K. Sharkey (ICP).

Next I would like to say thanks to the fluorine group at the University of Leicester, to Carla, James, Dan, Jose, Andy, Dave, Nicholas, Kate, Duncan and Sam, for all those good moments we have shared in the department and outside the department. Last but no least, I want to say thanks to my family who are always unconditionally there for me.

Finally, I want to thank University of Leicester for funding.

Contents

Abbreviations

BTF	Benzotrifluoride
d	Doublet
DCM	Dichloromethane
dd	Doublet of doublets
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulphoxide
EI	Electron impact
ES	Electrospray
FAB	Fast atom bombardment
FBC	Fluorous biphasic catalysis
FRPSG	Fluorous reverse phase silica gel
FSPE	Fluorous solid phase extraction
GC	Gas chromatography
Hz	Hertz
ICP-OES	Inductively coupled plasma optical emission spectroscopy
IL	Ionic liquid
IR	Infrared
J	Coupling constant

m	Multiplet
mp	Melting point
NMR	Nuclear magnetic resonance
Ph	Phenyl fragment
PP3	Perfluoro-1,3-dimethylcyclohexane
ppm	Parts per million
Rf	Perfluoroalkyl group
RT	Room temperature
s	Singlet
SAPC	Supported aqueous phase catalysis
$scCO_2$	Supercritical carbon dioxide
SCF	Supercritical fluid
SOPC	Supported organic phase catalysis
t	Triplet
TBAB	Tetrabutylammonium bromide
TfO	Triflate
THF	Tetrahydrofuran
wt	Weight
TBHP	*tert*-Butyl hydroperoxide

1 Introduction.

1.1 Homogeneous and heterogeneous catalysis.

One of the main objectives of chemistry today is the development of environmentally friendly technologies. Here, it is necessary to use reagents and solvents that are not harmful to the environment and produce high yields and selectivities. An excellent way to achieve these objectives is to use a catalyst. A catalyst is a substance that increases the rate of a chemical reaction without being consumed itself. Typically, the catalyst reacts with the reagents to yield some intermediate compounds through steps, that are part of a catalytic cycle, and make the transformation into products easier. The effect of the catalyst is only kinetic, accelerating a reaction that is thermodynamically possible. However, a catalyst can affect the distribution of the products, catalysing competitive reactions with different rates. The use of homogeneous catalysts has been a key factor in improvements in the fine chemistry industry in the last forty years.[1]

A catalyst is said to be homogeneous if it is in the same phase as the reactants, or heterogeneous if it is in a different phase from the reactants. In heterogeneous catalysis the catalyst is normally a solid, whilst the reactants are in either the liquid or gaseous phase. In this case, the catalytic reaction occurs at the catalyst surface. The advantages and disadvantages of homogeneous and heterogeneous catalysis are compared in **Table 1.1**.

	Homogeneous	**Heterogeneous**
Reaction conditions	Mild	Hard
Separation of products	Difficult	Easy
Catalyst recovery	Expensive	Cheap
Thermal stability of catalyst	Low	High
Catalyst Lifetime	Variable	High
Activity of catalyst	High	Variable
Selectivity of catalyst	High	Low
Poisoning of catalyst	Low	High
Determination of steric and electronic properties of catalyst	Possible	Very difficult
Determination of the mechanism	Possible	Very difficult
Diffusion problems	Low	Important

Table 1.1.

The most important advantages of homogeneous catalysis are the high selectivity, high activity and mild conditions of the reactions. However, the main obstacle that limits the industrial applications of homogeneous catalysis is the separation of the metal catalyst from the products. If the catalyst could be heterogenised, then it could be easily separated from the product, providing the best of both homogeneous and heterogeneous catalysis.

1.2 Techniques for facile product separation.

1.2.1 Supercritical Fluids.

Although supercritical fluids (SCFs) have been known since 1822,[2] and homogeneous catalysis in SCFs has been known since Ipatiev's experiments in 1913,[3] intensive research on homogeneous catalysis in SCFs by multiple research groups did not begin until the mid-1990s.[4] Supercritical fluids, which are either pure compounds or mixtures heated and pressurised beyond their critical points, have many advantages for homogeneous catalysis. A few of these advantages are true for all the SCFs and essentially all reactions: mass transfer (the physical process that involves molecular and convective transport of atoms and molecules within physical systems) is very rapid, the solvent is completely miscible with the gaseous reactants and the solvent is easy to remove from the product. Some advantages are specific to supercritical CO_2 ($scCO_2$): it is non-toxic, non-flammable, non-halogenated, it does not pollute and does not cause cancer or other long term problems. It has also been shown that $scCO_2$ can act as both a solvent and a protecting group.[5] Finally, some advantages are specific to certain combinations of SCFs and reactions. Polar SCFs, like fluoroform, have variable dielectric constants allowing the reaction conditions to be tuned.[6] Quite commonly, SCFs serve as both reactant and solvent; the homogeneously catalysed polymerisation of supercritical ethene is an industrialised example.[7]

Supercritical fluids can, in theory, overcome the problem of catalyst/substrate separation due to the differing solubilities of the catalysts, substrates and products. When the system is below the "crossover pressure", the density of the SCF can be reduced by increasing the temperature, decreasing substrate solubility and is known as "retrograde behaviour." When the system is above the "crossover pressure" the solubility of the solutes can be increased by raising the temperature and, therefore, the solubility increases.[8] Assuming that the components of the system have suitably different solubilities, changing the pressure or the temperature of the system could selectively precipitate each of the components, which could then be isolated and, in the case of the catalyst, reused.

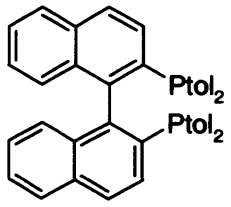
1.2.1.1 Development of CO_2-soluble catalysts.

Most homogeneous catalysts are notoriously insoluble in supercritical CO_2 and similarly non-polar SCFs; for example $PdCl_2$, organometallic complexes containing aromatic ligands, and charged catalysts of any type have very low solubility in $scCO_2$. However, neutral catalysts or precursors that are either volatile (such as HCl) or contain CO_2-philic groups (such as carbonyl ligands,[9] highly fluorinated ligands,[10] trialkylphosphines[11] and trialkylphosphites[12]) can be sufficiently non-polar to be soluble or usable in $scCO_2$.

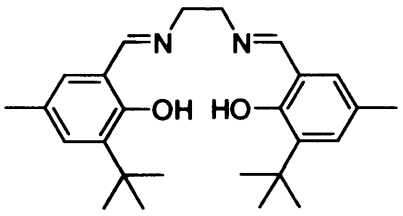
Ligands that tend not to make CO_2-soluble complexes are aromatic ligands such as the ubiquitous triphenylphosphine and other ligands (**Figure 1.1**), although some strategies to make these soluble have been developed. There are four basic strategies:

1) Switch to more soluble phosphines such as trialkylphosphines, despite their greater basicity.
2) Switch to the more soluble but not particularly basic tri(2-furyl)phosphine.
3) Add co-solvents or surfactants to increase the solubility of the complex.
4) Add CO_2-philic substituents to the *meta-* or *para-* positions of the aromatic rings.

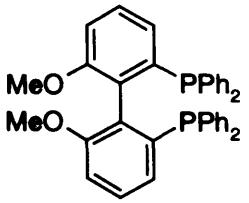
For example, adding either fluorine atoms[13] or fluorinated chains[14] dramatically increases the solubility of the ligand. This is not only true for phosphine ligands but also for phosphite and cyclopentadienyl ligands as well.



tolBINAP



H_2Salen

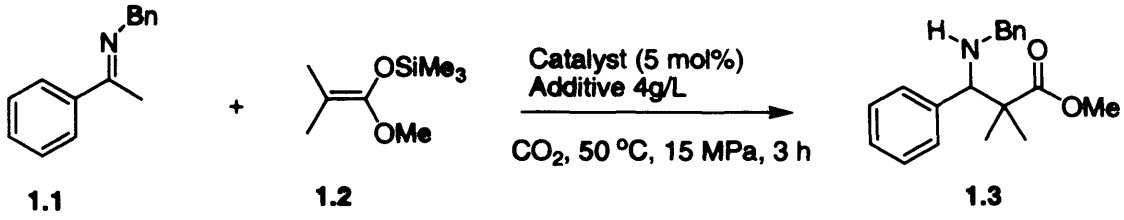


MeOBIPHEP

Figure 1.1.

1.2.1.2 Uses of Supercritical Fluids.

There are plenty of examples of the use of supercritical fluids in catalysis.[15] One report describes Aldol and Mannich reactions using $Sc(OTf)_3$ (**Scheme 1.1**).[16] In this work the importance of additives was studied (**Table 1.2**), and it was shown that when no catalyst was added poor yields were obtained. However, when poly(ethylene glycol) (PEG) was added or the catalyst was tuned by adding fluorous chains good yields were obtained because the solubility of the catalyst was increased.



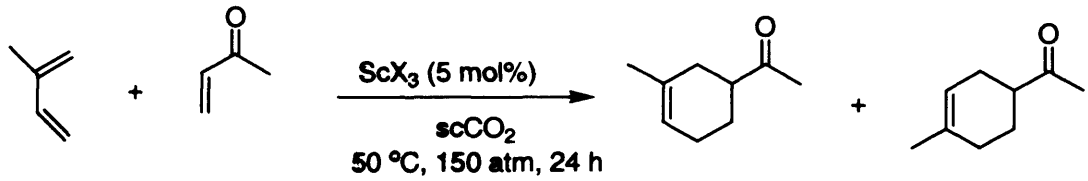
1.1 1.2 1.3

Scheme 1.1

Catalyst	Additive	Yield (%)
$Yb(OTf)_3$	None	10
$Yb(OTf)_3$	PEG	72
$Yb(OTf)_3$	DCM	36
$Yb(OSO_2C_4F_9)_3$	None	47
$Yb(OSO_2C_4F_9)_3$	PEG	62

Table 1.2. Yields for an aldol reaction in $scCO_2$.

Another example of the use of supercritical fluids in catalysis is the Diels-Alder cyclisation. The reaction between 2-methyl-1,3-butadiene and methylvinylketone (MVK) is a classic example of this reaction (**Scheme 1.3**). The major problem when Lewis acids are used in $scCO_2$ is their low solubility. This problem was solved by adding perfluoroalkyl chains to the ligands. As the results show (**Table 1.3**), the reaction gave higher yields and selectivities with the fluorinated ligands and the longer the alkyl chain the better the results.



1.4 1.5 1.6 1.7

Scheme 1.2.

ScX_3	Yield (%)	1.6/ 1.7
None	4	80/20
$Sc(OTf)_3$	41	93/7
$Sc(OSO_2C_4F_9)_3$	64	94/6
$Sc(OSO_2C_8F_{17})_3$	74	94/6

Table 1.3. Yields for a Dies-Alder in $scCO_2$.

1.2.1.3 Supercritical Fluids-Conclusions.

The examples described so far in this chapter show that SCFs are useful solvents with the advantage that there are no mass-transport concerns in reactions where diffusion is an issue and, if CO_2 is employed, the solvent is cheap, non-toxic and non-flammable. The separation of the products from the catalysts theoretically can be easily achieved by reducing the pressure of the system and there are no problems with solvent residues.

One of the problems with this approach at present is that it is necessary to modify the catalyst to make it soluble in $scCO_2$. When modification of the ligand is not possible, the addition of surfactants seems like a sensible way to solubilise the catalyst, but, by doing this, contaminants are added to the reaction system that may be difficult to separate at the end of the reaction. The major problem of this technique is the cost associated with the high pressure equipment for industrial applications. However, if good yields, selectivities and good separation of the catalyst are obtained then the use in industrial processes will become more attractive.

1.2.2 Ionic Liquids.

Ionic liquids (ILs) are a class of novel solvents with very interesting properties, which are attracting the attention of a growing number of scientists and engineers. This is shown by the increasing number of papers published in this area in recent years.[17] As a consequence of their peculiar properties, such as negligible vapour pressure, ability to dissolve organic, inorganic and polymeric materials and high thermal stability, ILs have gained popularity as "green" alternatives to volatile organic solvents (VOCs).

"Ionic liquid" is now the commonly accepted term for low-melting salts (melting points typically <100 °C) obtained by the combination of large organic cations with a variety of anions. Although estimates vary, there is no doubt that the number of combinations of anions and cations that can give rise to potential ILs is vast.

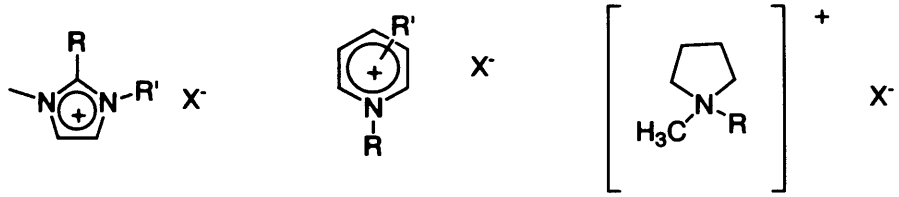
1.2.2.1 Properties of Ionic Liquids.

The properties of ILs such as phase transitions, viscosity and density, can be tailored over a wide range to suit the system in which they will be employed. Relatively little is known about the microscopic physical properties of these solvents or chemical properties for every reaction.

On the basis of the anion, ILs can be divided into four groups:

1) systems based on $AlCl_3$ and organic salts such as 1-butyl-3-methylimidazolium chloride [bmim][Cl]
2) Systems based on anions such as $[PF_6]^-$, $[BF_4]^-$ and $[SbF_6]^-$
3) Systems based on anions such as $[CF_3SO_3]^-$, $[(CF_3SO_3)_2N]^-$ and similar
4) Systems based on anions such as alkylsulfates and alkylsulfonates

The cation is generally a bulky organic structure with low symmetry. Those described are based on substituted ammonium (**1.11**), sulfonium (**1.12**), phosphonium (**1.13**), imidazolium (**1.8**), pyridinium (**1.9**), picolinium, pyrrolidinium and pyrazolium cations (**Figure 1.2**). Concerning the cation structure, it is generally assumed that non-symmetrical *N,N*-dialkylimidazolium cations give salts having low melting points, even though dibutyl-, dioctyl-, dinonyl- and didecyl-imidazolium hexafluorophosphates are liquid at room temperature. 1-butyl-3-methyl and 1-ethyl-3-methylimidazolium cations ($[bmim]^+$ and $[emim]^+$) are probably the most investigated structures of this type.



1.8 **1.9** **1.10**

$[NR_xH_{4-x}]^+$ $[SR_xH_{3-x}]^+$ $[PR_xH_{4-x}]^+$

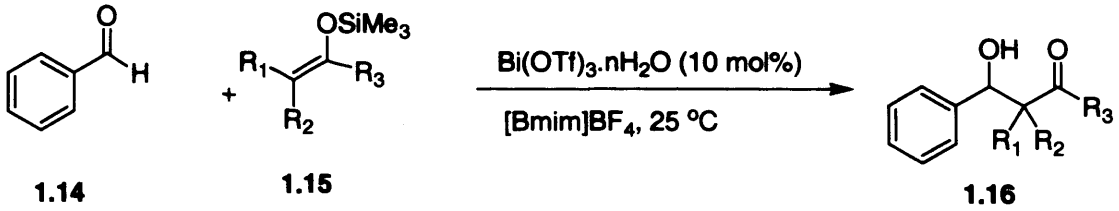
x=1- 4 x= 1- 3 x= 1- 4

1.11 **1.12** **1.13**

Figure 1.2.

1.2.2.2 Uses of Ionic Liquids.

The first example of the use of ionic liquids to be discussed was the use of bismuth(III) salts as catalysts in Mukaiyama-Aldol reactions.[18] In this approach a variety of silylenol ethers were studied and good yields were obtained for most of them using $Bi(OTf)_3.nH_2O$. This method offers several advantages including mild reaction conditions and no formation of by-products. The *β*-hydroxycarbonyl products obtained were easily purified.



1.14 **1.15** **1.16**

Scheme 1.3.

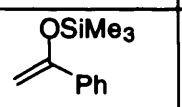
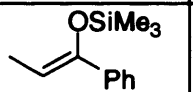
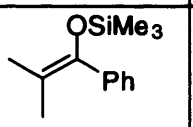
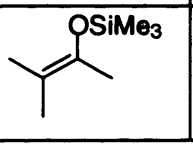
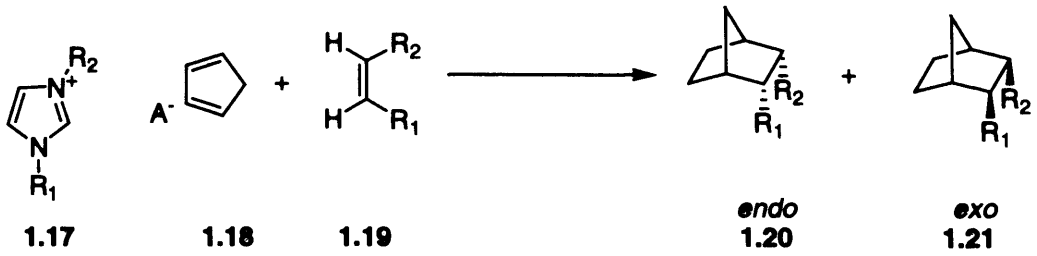
Silyl enolate	Time[h]	Yield (%)
	5	92
	8	83
	23	77
	22	63

Table 1.4. Yields obtained for an Aldol-Mukaiyama reaction in ionic liquids.

Another example of the use of ionic liquids was in an asymmetric Diels-Alder reaction.[19] The reaction was performed with a large variety of different ILs. The yields and selectivities of the reactions in salicylates and lactates of 1-alkyl- and 1-alkoxy-methylimidazolium (**Figure 1.3**) were dependent upon the type of dienophile (**Table 1.5**). It is clear that elongation of the alkyl substituent on the cation resulted in no significant alterations in the course of the reaction even though the

viscosity of the ILs was markedly increased. The type of anion employed was found to be significant by affecting the overall selectivity of the reaction.



1.17 **1.18** **1.19** **1.20** **1.21**

Figure 1.3. **Scheme 1.4.**

R_1	R_2	Anion	Yield (%)	Ratio endo/exo
CH_3	H	DL-Lactate	95	3.9
C_4H_9	H	DL-Lactate	90	3.8
CH_3	H	BF_4	96	3.7
CH_3	H	NTf_2	95	6.0
$CH_2OC_9H_{19}$	H	Salicylate	94	3.7
$CH_2OC_6H_{13}$	H	Salicylate	93	3.7

Table 1.5. Yields obtained for Diels-Alder reaction in ionic liquids.

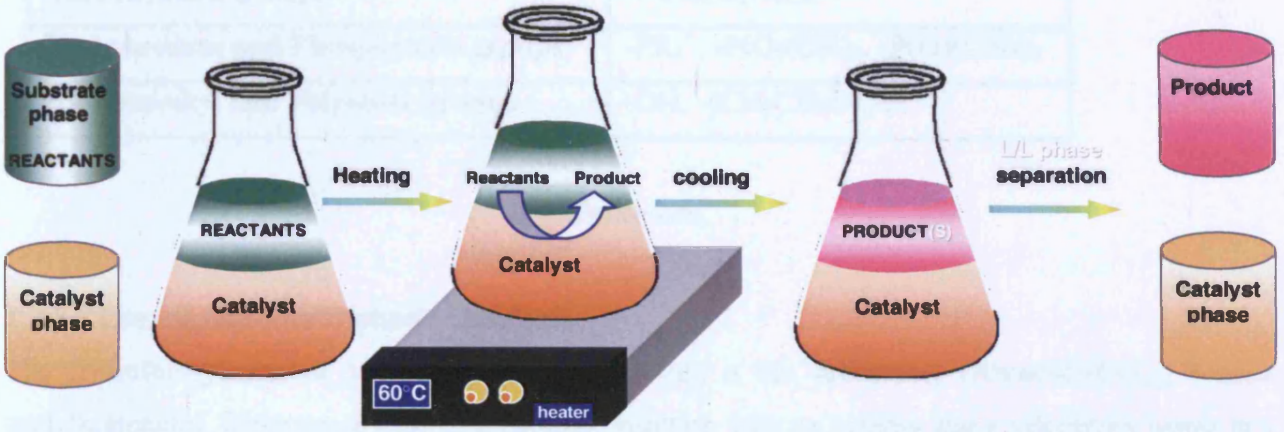
1.2.2.3 Ionic Liquids - Conclusions.

ILs present some advantages over $scCO_2$, the main ones being that the solvents are easier to handle and no special equipment is required. Also, there is no need to use surfactants or to modify the catalysts in order to make them soluble. ILs have, however, a main disadvantage, in that there is usually leaching of the organic catalyst in the organic phase and, also, the low solubility of many organic molecules in ionic liquids determines how useful ionic liquid catalysis can be. There is no data about the toxicity or ecological impact of them, but they are unlikely to be benign solvents, so their disposal could be problematic.

1.2.3. Biphasic catalysis.

Another way to separate homogeneous catalysts from product is the so-called biphasic catalysis. As **Scheme 1.5** shows, the system contains two phases; in one phase is the catalyst and in the other is the substrate. On heating,the reaction takes place and the product is formed. Afterwards, the

reaction is cooled down and the two phases are formed again, these two phases can then be separated by easy decantation and the catalyst is then reused. However, it is necessary to add solubilising groups on to the ligands in order to anchor the catalyst in the catalyst-containing phase and to minimise the effect of catalyst leaching into the product phase.



Scheme 1.5.

1.2.3.1 Aqueous Biphasic Catalysis.

Aqueous biphasic catalytic systems are used in some industrial processes. Examples are the hydroformylation of propene to *n*-butanal with Rh-TPPTS (tris(*m*-sulfonatophenyl)phosphine) or Rh-BISBIS (sodium salt of sulfonated 2,2'-bis (diphenylphosphinomethyl)-1,1'-biphenyl) as catalysts by Rhodia/Ruhrchemie, oligomerization of terminal alkynes with Rh/water-soluble phosphines by Hoechst-AG, carbonylation with $PdCl_2(PPh_3)_2$ by Boots/Hoechst-A and others.[20,21] As the examples above show, modified phosphines are essential ligands for these reactions (**Figure 1.4**, **Table 1.6**).

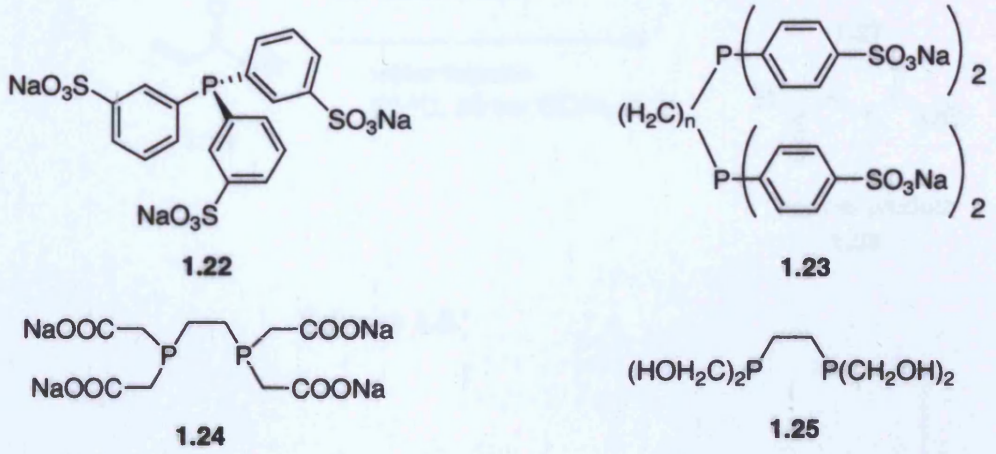


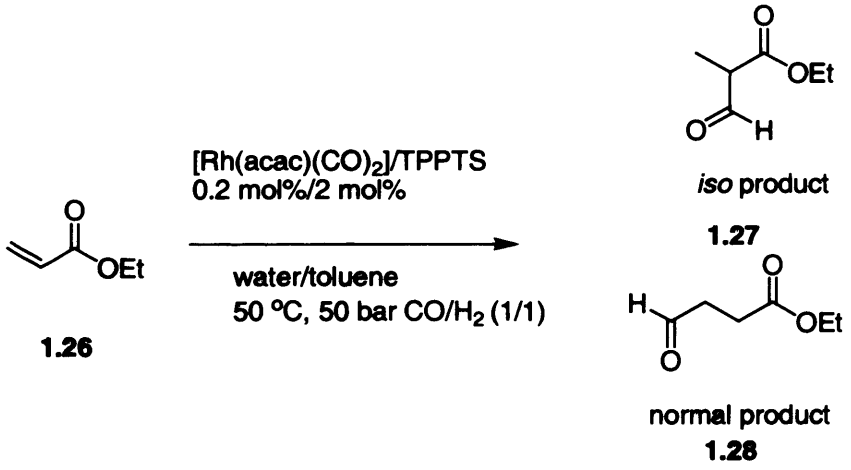
Figure 1.4.

Sulfonated Groups	$-SO_3H$, $-SO_3Na$
Ammonium groups	$-NR_4^+$, NR_3
Carboxylate groups	-COOH, COONa
Carbohydrate groups	$-C_5H_{9-n}O(OH)_n$
Phosphonium and Phosphonate groups	$-PR_4^+$, $-P(O)(OR)_2$, $-P(O)(ONa)_2$
Hydroxyalkyl and Polyether groups	$-OH$, $-(CH_2CH_2O)_n-H$

Table 1.6.

1.2.3.2 Uses of Aqueous Biphasic Catalysis.

The hydroformylation of various acrylic esters with a Rh precursor, $[Rh(acac)(CO)_2]$ (acac= acetylacetonate), illustrates a case of a catalytic reaction with an activity and a selectivity better in a two-phase system than in a monophasic one.[22] Of particular note is the hydroformylation of ethylacrylate (**Scheme 1.5**) that occurs in water/toluene in the presence of [Rh]/TPPTS with a higher catalytic activity and selectivity to the *iso* product than the normal product. As **Table 1.7** shows changing the alkyl group of the ester had a dramatic effect on the yield although selectivities were not affected. The by-product observed in the reaction was the hydrogenation product, and there was no evidence for the generation of the *n*-isomer.

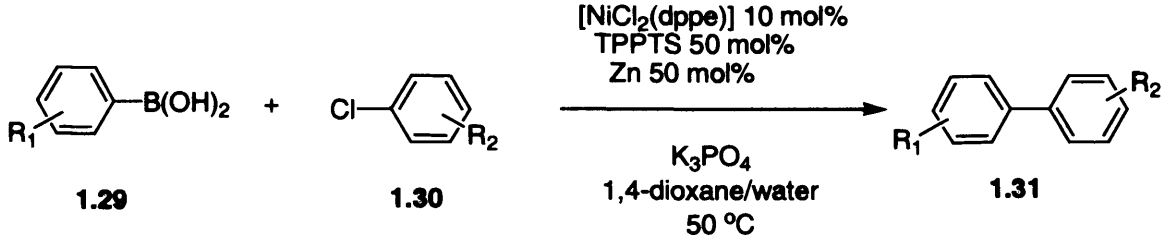


Scheme 1.5.

Substrate	Yield (%)	Selectivity (%)
Methyl acrylate	25	96.6
Ethyl acrylate	100	96.6
Butyl acrylate	40	98.2
2-Ethoxyethylacrylate	74	94.0
2-Ethylhexylacrylate	4	97.1

Table 1.7. Yields obtained for the hydroformilation of ethyl acrylate.

It is also possible to use a water-soluble Ni(0) catalyst, pre-formed from [$NiCl_2$(dppe)] and TPPTS, to perform cross-coupling reactions between arylboronic acids and aromatic chlorides in organo-aqueous media (**Scheme 1.6**).[23] Phenylboronic acid and aromatic chlorides substituted with electron withdrawing groups undergo cross coupling reactions catalysed by [$NiCl_2$(dppe)]/TPPTS/Zn (in the presence of K_2CO_3 in dioxane/water) in good yields.



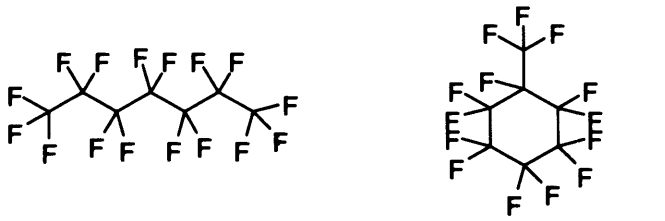
Scheme 1.6.

R_1	R_2	Yield(%)
H	4-$COCH_3$	79
H	4-CHO	81
H	4-COPh	70
4-MeO	4-Ac	81
4-F	4-Ac	86
3-NH_2	4-Ac	47
2,2-CH_3	4-Ac	94

Table 1.8. Yields of different substrates in Suzuki reaction

1.2.3.3 Fluorous Biphase Systems.

Fluorous Biphase Catalysis (FBC) is based on the utilization of liquid-liquid biphasic processes, in which perfluorocarbon solvents (**Figure 1.5**) deliver phase separation due to their extremely hydrophobic character and because they are not miscible with the majority of hydrocarbon solvents. However, unlike aqueous systems, some combinations of organic and fluorous solvents have increased miscibility at elevated temperatures and can even result in a homogeneous mixture. Perfluorinated solvents have high densities in comparison to water or organic solvents as well as low polarisability. The low polarisability of the electrons in a C-F Van der Waals bond means that intermolecular interactions are extremely weak. One consequence of which is the higher solubility of gases (e.g. O_2, CO_2) in perfluorocarbons than in conventional organic solvents.



Perfluorohexane Perfluoromethylcyclohexane

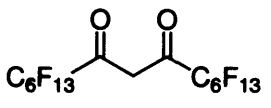
Figure 1.5.

To make a catalyst soluble in perfluorocarbon solvents it is necessary to attach fluoroponytails (long perfluoroalkyl chains attached to the ligand), which increase the fluorophilicity of the catalyst. The success of recycling the fluorous catalyst depends on the amount of fluorine that it contains. In general, to guarantee success in the separation of the catalyst from the organic product, it is necessary to examine the structure of the catalyst $M_x[L(R)_n(R_f)_m]_z$ (for example, $HRh(CO)_2\{P[CH_2\text{-}CH_2(CF_2)_5CF_3]_3\}_3$). It usually has a metallic centre coordinated by fluorous ligands $L(R)_n(R_f)_m$. The fluorinated ligand contains a hydrocarbon part $(R)_n$ and a fluorocarbon part $(R_f)_m$. The partition coefficient (P_{FBS}= $C_{fluorophilic\ solvent}$ / $C_{fluorophobic\ solvent}$) depends on the size and the type of the hydrocarbon and fluorocarbon parts.

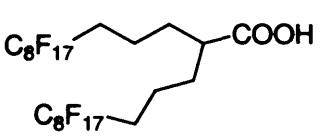
Then, the main question is how many fluorine atoms are necessary to anchor the catalyst into the fluorous phase? This question is not easily answered, but there are many rules that can help in the design of fluorous catalysts.

1) At least 60% of the weight of the compound must be fluorine, which can be obtained by attaching fluoroponytails, however increasing the molecular weight and costs of the resulting catalyst could limit the industrial applicability of this approach.
2) The size of the fluoroponytail. Very long perfluoroalkyl groups can increase the partition coefficient into the fluorous phase, but there will also be a decrease in absolute solubility in both fluorous and organic phases.
3) The number of fluoroponytails. An increase in the number of the fluoroponytails normally increases the partition coefficient.
4) Structure. The number of functional groups that can generate intermolecular interactions of attraction should be minimised.
5) The structure of the ponytail. There is no data on the effect of branched fluoroponytails or the addition of heteroatoms as segments e.g $-CF_2XCF_2-$ (X = O, S, N).

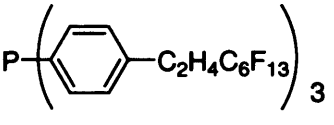
Another important behaviour of fluorous ponytails is the electron-withdrawing effect of perfluoroalkyl groups. These can weaken the electron donating ability of the heteroatom attached to the ponytail or modify the electronic properties of the ligand. To avoid this electron withdrawing effect spacer groups can be added between the heteroatom and the first CF_2 group. The most common spacer groups are methylenic groups,[24] $-(CH_2)_n-R_f$ (n = 3), and silyl groups,[25] $(-SiMe_{3-m}-(CH_2CH_2(R_f)_n)_m)$ (m= 1- 3), because of their stability. Some examples of these ligands are shown in **Figure 1.6** and have been used successfully for a wide range of reactions.[26,27,28]



1.34



1.35



1.36

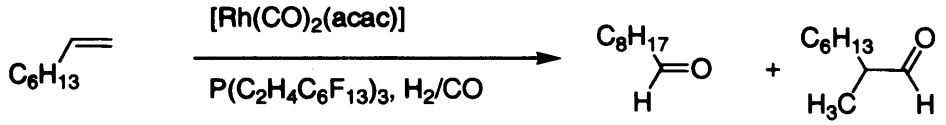
Figure 1.6.

1.2.3.4 Uses of Fluorous Biphase Systems.

Fluorous biphase catalysis has been used in a wide range of reactions such as oxidation of alcohols,[27] oxidation of sulfides,[30] Wacker oxidation, Suzuki[28] and Heck[29] reactions involving a wide variety of metals including Cu(II),[29] Pd(II),[30,31] and Mn(III)[32] which are active in monophasic and biphasic systems. In the same way the use of fluorinated carboxylates have proved to be

successful in the oxidation of a wide range of substrates (alcohols, alkenes) using biphasic catalysis.[26]

The initial work on fluorous biphase catalysis by Horváth and Rábai was focused on the hydroformylation of oct-1-ene and dec-1-ene.[33] The reactions were carried out in a perfluoromethylcyclohexane/ toluene biphase at 100 °C with a H_2/CO pressure of 10 bar. The Rh(I) catalyst could be recovered up to eight times and the selectivities were good but decreased slightly after a few runs.



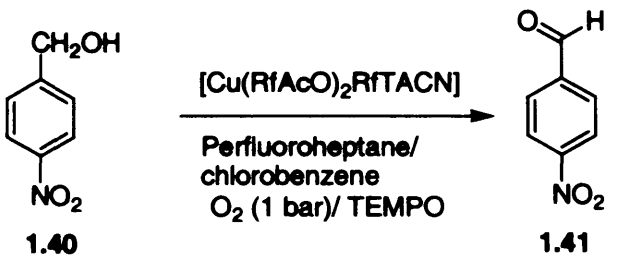
1.37 **1.38** **1.39**

Scheme 1.7.

Run	Rh in the reactor (μmol)	n- (%)	iso- (%)	Octane (%)
1	15.63	91.5	7.83	0.7
2	15.54	89.4	9.86	0.7
3	15.46	89.3	10.1	0.6
4	15.38	89.5	9.93	0.6
5	15.30	89.1	10.30	0.6
6	15.23	89.0	10.33	0.6
7	15.14	88.9	10.57	0.5
8	15.06	88.3	11.01	0.6
9	14.98	88.3	11.03	0.6

Table 1.9. Yields and selectivities obtained in hydroformilation.

Another good example of fluorous biphase catalysis is the oxidation of nitrobenzylalcohol to nitrobenzylaldehyde (**Scheme 1.8**),[25] using Cu(II) fluorous carboxylates with a fluorous tagged triazacyclononane in perfluoroheptane. This system was successfully used and allowed the catalyst to be recovered up to five times (**Table 1.10**). However, in the sixth run a drop in the yield occurred, and in the seventh run only 8 % conversion was obtained.



Scheme 1.8.

Run	Time (h)	Conversion(%)
1	8	96
2	8	94
3	8	92
4	8	90
5	8	92
6	8	51
7	8	8

Table 1.10. Oxidation of alcohols using Cu(II) fluorous catalysts.

1.2.3.5 Biphase Catalysis - Conclusions.

Biphase systems provide a simple method for separation of the catalyst from the product that has been successfully used in industrial catalysis (section 1.2.3.1). However, catalyst leaching into the organic phase can be a major problem for this separation technique. Aqueous biphases cannot be used with water-sensitive substrates, and the low solubility in water of lots of organic substrates limits the yields for reactions of such substrates. Fluorous biphase catalysis overcomes this problem by being miscible with organic phases at high temperatures and the problem of the water-sensitive substrates is also overcome for obvious reasons. However, fluorous solvents are very expensive which may prove prohibitive to their use in industry. Fluorous solvents are also persistent in the environment and for this technique to be used it is necessary for a high percentage of fluorine to be attached to the ligands (>60%). This last disadvantage is quite important because sometimes ligand modification can be difficult and affects rates/selectivities of the reactions. Even so, if leaching levels are low and the solvent is carefully recycled this technique could be interesting for certain systems.

1.2.4 Supported Catalysis Systems.

The use of supports in organic chemistry has been increasing since their first application in the sixties.[34] It was proposed that anchoring the ligand to an organic, inorganic or fluorous support, would enable the catalyst to be recycled by simple filtration and the reactivity and selectivity would be maintained. Two kinds of support have been researched, organic and inorganic, and will be discussed below.

1.2.4.1 Organic supports.

The use of organic supports in organic synthesis has become common practice, especially following the rapid development of combinatorial chemistry. The use of polymers in synthesis falls into two areas: the use of the polymer as a support for reactants and the use of the polymer as a support for reagents and catalysts during the reaction. Many different soluble polymers have been used as supports for catalyst immobilization (**Figure 1.7**). These supports have found many significant applications in the immobilization of classical solution-phase catalysts. A wide variety of catalysts have been tested in a wide range of reactions such as asymmetric addition of $ZnEt_2$ to benzaldehyde,[35] asymmetric hydrogenation,[36] oxidations and Michael addition.[37]

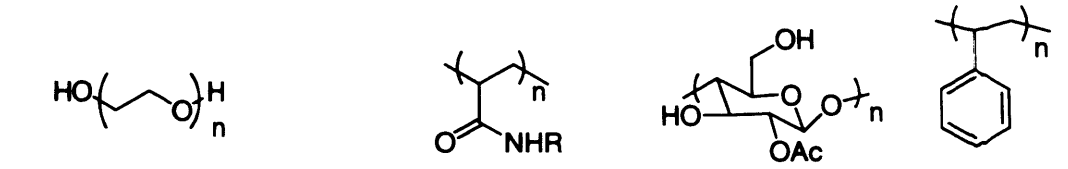
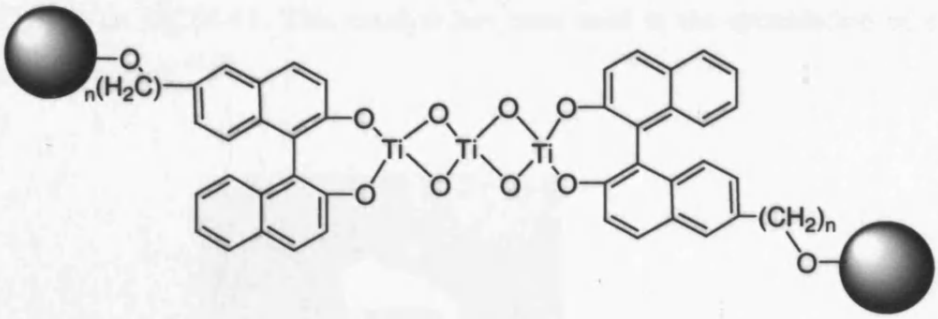


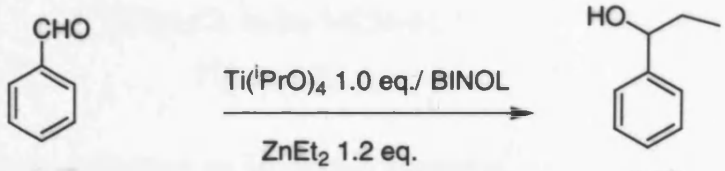
Figure 1.7.

One example of the use of such supports in catalysis is the asymmetric alkylation of benzaldehyde using a supported Ti(BINOL) system (**1.46**) (**Scheme 1.9**). Good yields and enantioselectivities (67% and 83% respectively) were obtained although these results are a bit lower than the ones observed in homogeneous Ti(BINOL) systems (see chapter 4). However, attempts to reuse the catalyst were less successful due to problems with precipitation of Zn-Ti compounds along with the catalyst, making the catalyst less effective upon reuse.



1.46

Figure 1.8.



1.47 **1.48**

Scheme 1.9.

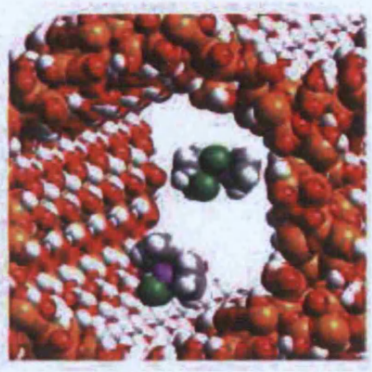
Solvent	Temperature (°C)	Time (h)	Yield (%)	ee (%)
Toluene	0	14	60	67
DCM	-20	22	56	87
DCM	0	17	42	79
DCM	20	7	61	83
DCM	0	18	44	72

Table 1.11. Yields obtained for the addition of dethylzinc to benzaldehyde.

1.2.4.2 Inorganic supports for catalysis.

Inorganic solids tend to give more robust supports that have higher thermal and solvent ageing stabilities than their organic counterparts.[38] The most popular inorganic support is silica (although there are others based on magnesia, titania, zirconia and vanadia),[39] which can be functionalised using chlorosilanes or alkoxysilanes to yield derivatised surfaces with Si-O-Si linkers. Though the advantages of silica for immobilizing various kinds of catalysts were recognised one century ago, it was not until the early seventies that Ballard and others began to study it for organometallic immobilization.[40] One example of these mesoporous Si derived structures is detailed below (**Figure**

1.9)[41] with $Ti(Cp)_2Cl_2$ in MCM-41. This catalyst has been used in the epoxidation of cyclohexene although results were modest.[42,43]



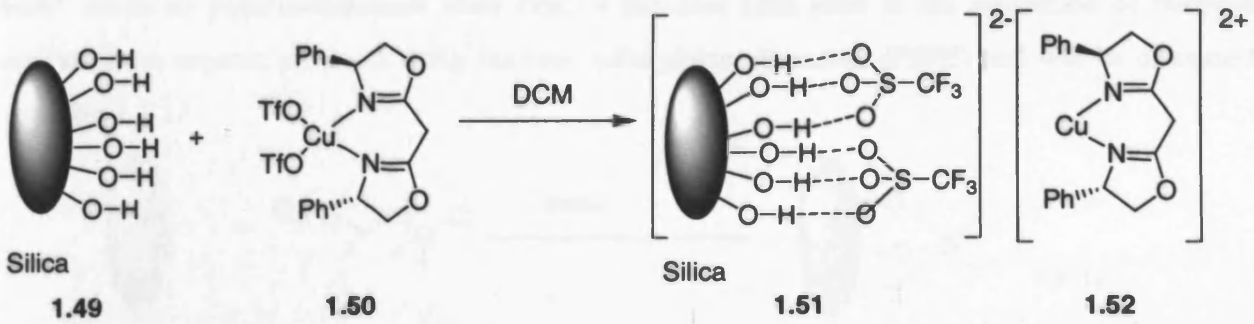
$Ti(Cp)_2Cl_2$ inside MCM-41.

Figure 1.9.

1.2.4.3 Electrostatic Immobilisation on Inorganic Supports.

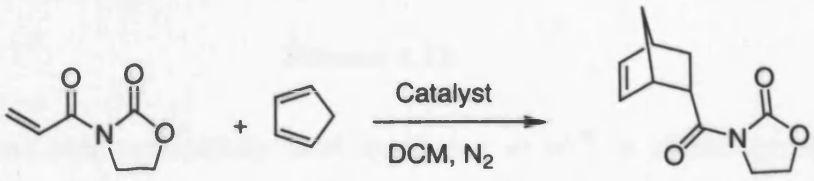
The ability to recycle expensive chiral catalysts is attractive at the research and application level and, as a result, research into immobilisation of catalytic species on supports is ongoing.[44] In recent years, the immobilization of a cationic chiral rhodium-phosphine hydrogenation catalyst was reported via hydrogen bonding of the triflate counter anion with the MCM-41 silica surface. The electrostatically-immobilised catalyst had similar activity to the catalyst in homogeneous phase with good recyclabilities and low levels of leaching.

In 2004, Gebbink *et al.*[45] reported the immobilisation of a Cu(II) bis(oxazoline) catalyst on silica gel and its use as a catalyst in the Diels-Alder reaction. Immobilisation of the catalyst was achieved by addition of a solution of the catalyst to silica gel and then drying the catalyst under vacuum at 70 °C for 2 h (**Scheme 1.10**). The Diels-Alder reaction was performed using acryloyloxazolidinone as a dienophile and cyclopentadiene as the diene and the supported Cu(II) catalyst. As **Table 1.12** shows the conversions and enantioselectivities are equivalent if not higher in the case where the supported catalyst was used compared to the homogeneous one. There was an inversion of configuration in the case of the phenyl substituted catalyst. When the reaction was performed homogeneously the major isomer obtained had an (*S*)-configuration, however, when the heterogeneous reaction was performed the (*R*)-isomer predominated.



1.49 **1.50** **1.51** **1.52**

Scheme 1.10.



1.53 **1.54** **1.55**

Scheme 1.11.

Catalyst (10 mol%)	R	Conversion (%)	ee(%)
Homogeneous	Ph	100	20 (S)
Heterogeneous	Ph	100	33 (R)
Homogeneous	^{t}Bu	50	59 (S)
Heterogeneous	^{t}Bu	43	57(S)

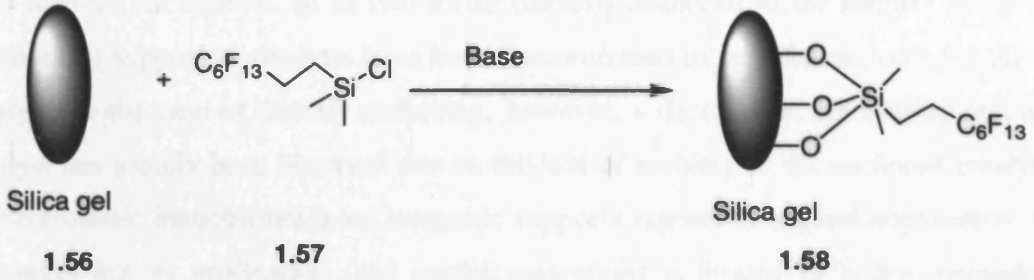
Table 1.12. Yields obtained for a Diels-Alder Reaction immobilised in SiO_2.

1.2.4.4 Electrostatic Immobilisation on Fluorous Supports.

Organic molecules bearing few fluorous tags (C_6F_{13}, C_8F_{17}) are called light fluorous molecules.[46] Fluorous derivatised catalysts (section 1.2.3.3), are of special interest since they induce the same reactions as their non-fluorous counterparts under the same conditions but are reliably removed from the crude products. Unlike the catalysts used in biphasic catalysis, these catalysts are usually not soluble in perfluorocarbon solvents, but can be separated, recycled and reused by supporting them on Fluorous Reverse Phase Silica Gel (FRPSG).

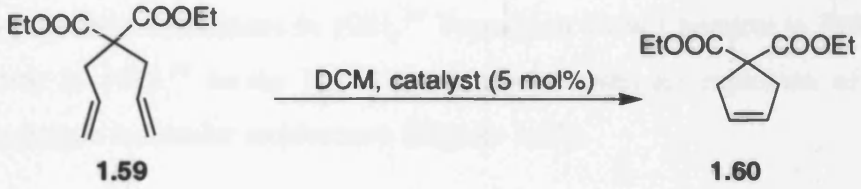
Fluorous Reverse Phase Silica Gel (FRPSG) can be prepared by mixing silica gel with $C_6F_{13}C_2H_4SiMe_2Cl$ (**Scheme 1.12**). This product has been known since the eighties[47] and it has been used chromatographically for the separation of polar/non-polar species. It works in a "reverse

phase" mode so polar compounds elute first. It has also been used in the separation of fluorous catalysts from organic products using fluorous solid phase extraction (FSPE) and will be discussed in section 1.3.1.



Scheme 1.12.

This method has been successfully used by Curran *et al.*[48] in alkene metathesis catalysed by a Grubbs-Hoveyda catalyst (**Figure 1.10**). The catalyst was immobilised by adding a solution of the catalyst to FRPSG and then drying it under vacuum. As **Table 1.13** shows good yields were obtained and the catalyst could be recycled three times although in the fourth run the reaction time was increased to 3 hours in order to achieve good yields. After the reaction was finished MeOH/water was added to the reaction to separate the immobilised catalyst from the product. The catalyst was then dried and used again.



Scheme 1.13.

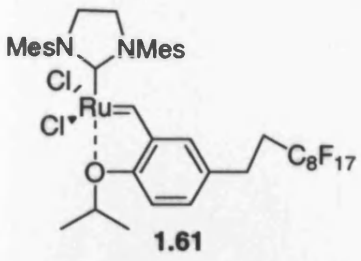


Figure 1.10.

Run	Time (h)	Yield (%)
1st	1	97
2nd	1	98
3rd	1	98
4th	3	94

Table 1.13. Yield obtained for different runs in a metathesis reaction.

1.2.4.5 Supported Catalysis - Conclusions.

Supporting the active catalyst on different organic, inorganic and fluorous supports is a well known tactic to recover the catalyst. In its two forms (directly anchored to the support or by electrostatic immobilisation) supported catalysts have been demonstrated to be efficient tools for the recovery of the catalyst. In the case of directly anchoring, however, a decrease in the activity and selectivity of the catalyst has usually been observed due to the loss of mobility of the anchored catalyst. The case of the electrostatic immobilisation on inorganic supports represents a good approach to the problem of separation but its application (and useful separation) is limited to a few examples. Fluorous Reverse Phase Silica Gel (FRPSG) represents a useful approach to the problem of the catalyst-product separation where the light fluorous catalysts can be easily retained on FRPSG based on fluorine-fluorine interactions allowing a better separation of the metal catalysts. However, as in the case of the electrostatic immobilisation on inorganic supports, there are not many examples of its successful application in the literature.

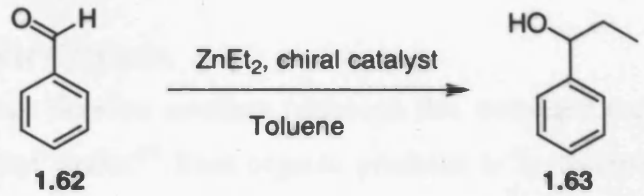
1.2.5 Dendrimers.

A dendrimer is a regularly branched fully synthetic polymer molecule which resembles the branches of a tree. The name comes from the Greek *dendron*, meaning "tree." The first dendrimers were described by Tomalia and co-workers in 1978,[49] Denkewalter and co-workers at Allied Corporation as polysilane dendrimers in 1981,[50] Tomalia at Dow Chemical in 1983[51] and in 1985,[52] and by Newkome in 1985.[53] In the 1990s dendrimers caused an explosion of scientific interest because of their unique molecular architecture (**Figure 1.11**).

Figure 1.11.

1.2.5.1 Uses of dendrimers.

One example of the use of dendrimers for catalysis is reported by Pu *et al.*[54] The catalytic reaction performed was the asymmetric addition of $ZnEt_2$ to benzaldehyde (**Scheme 1.14**) using an optically active chiral BINOL dendrimer (**Figure 1.12**). The dendritic BINOL catalyst behaved in a similar way to the free BINOL molecule. In the presence of $Ti(^iPrO)_4$ the dendritic catalyst gave a 100 % yield and 89 % enantiomeric excess. Similar results were reported by Chan *et al.*[55] (100 % yield, 90 % ee) when the homogeneous catalyst was used. The reaction of $Ti(^iPrO)_4$ with benzaldehyde may involve structurally similar catalytically active species when either the chiral dendrimer or the free ligand are used.



1.62 **1.63**

Scheme 1.14.

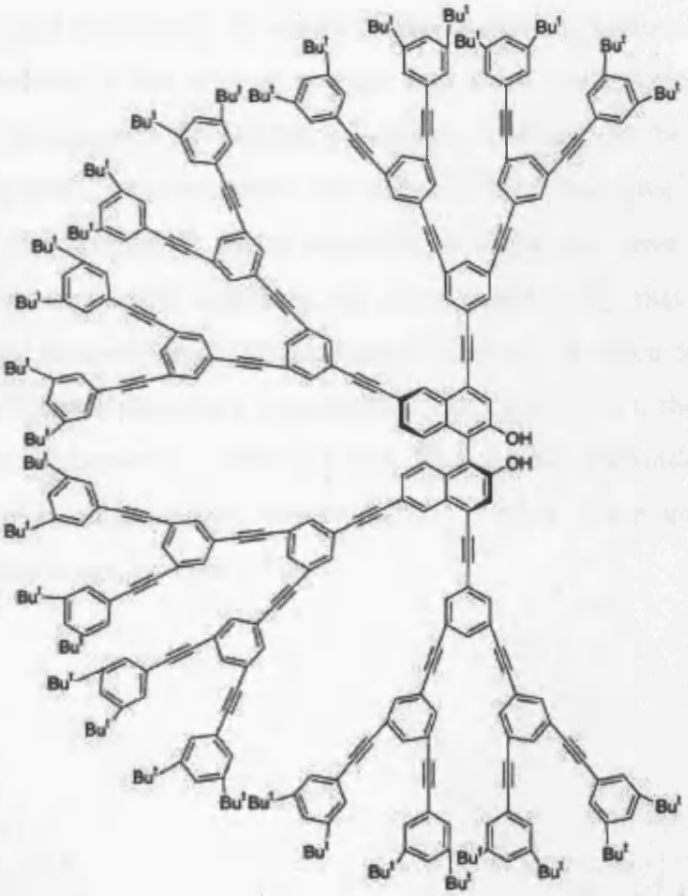


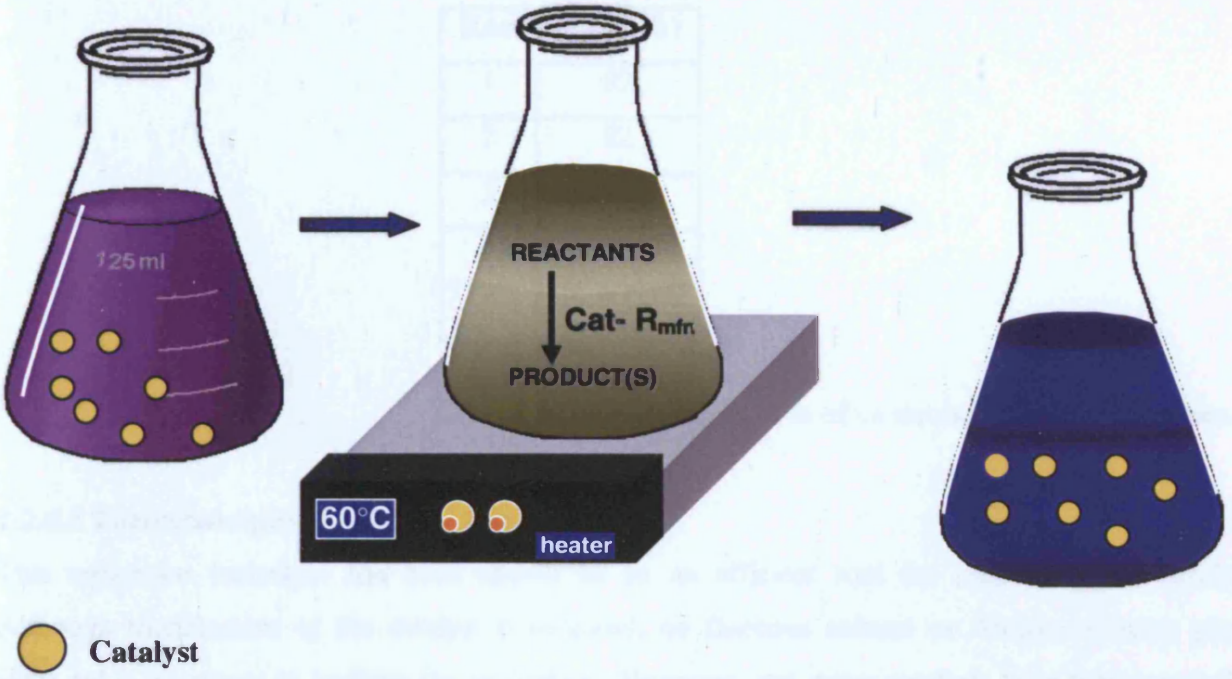
Figure 1.12.

1.2.5.2 Dendrimers - Conclusions.

In recent years, dendrimers have become a subject of intense research due to their unique structures and properties. Rigid dendritic molecules with well-defined structures and shapes are potentially useful in the fabrication of nanoscale optical and electronic devices for nano-technology.[56,57] However, there are only a few examples of successful testing, recovery and reuse of dendritic catalysts. For those systems where studies have been undertaken, the difficult synthesis and the difficulty in analysing the dendrimer spectroscopically are major obstacles for the development of this approach.

1.2.6 Thermomorphic Catalysis.

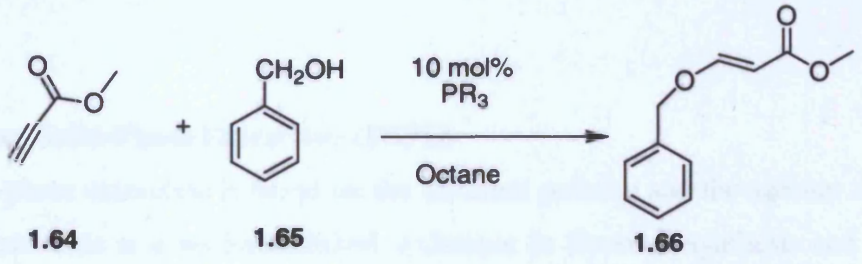
Another way to separate fluorous catalysts (although this technique can also be used with catalysts modified with long alkyl chains)[58] from organic products is by thermomorphic catalysis. Fluorous catalysts and ligands are often insoluble in organic solvents at room temperature. However, some of these catalysts/ligands are soluble in the same organic solvents at higher temperatures. This situation can be used to separate the catalyst. The reaction is performed at high temperature so that the catalyst is soluble in the organic solvent and when the reaction finishes and the reaction is cooled to room temperature the catalyst precipitates out and can be separated by simple filtration, then reused. Gladysz[58] reasoned that the same factors that give highly temperature-dependent organic(liquid)/ fluorous(liquid) phase miscibilities might also give highly temperature-dependent organic(liquid)/fluorous(solid) equilibria. In other words, fluorous molecules containing several long ponytails are normally insoluble in organic solvents at room temperature, but are soluble in organic solvents if the temperature is increased. The catalyst can, therefore, be easily recovered by filtration at room temperature (**Scheme 1.15**). This *modus operandi* has some advantages since it avoids the use of perfluorocarbon solvents, there is no leaching into the organic phase and high reaction temperatures can be used.



Scheme 1.15.

1.2.6.1 Uses of Thermomorphic Catalysis

The first example of the use of this technique was reported by Gladysz *et al.*[59] In this article, the addition of an alcohol to methyl propiolate at 65 °C (**Scheme 1.16**) was catalysed by fluorous trialkylphosphines. After the reaction had taken place, the solution was cooled down to -30 °C to precipitate out the catalyst which was recovered and reused in four cycles, with only a small loss in activity (**Table 1.14**).



Scheme 1.16.

Run	Yield(%)
1	82
2	82
3	80
4	81
5	75

Table 1.14. Yields obtained in of an alcohol to methyl propilate.

1.2.6.2 Thermomorphic Catalysis - Conclusions.

This separation technique has been shown to be an efficient tool for recovering the catalyst. Although modification of the catalyst is required, no fluorous solvent or fluorous reverse phase silica gel is necessary to perform the separation. However, not many catalysts have thermomorphic properties, which restricts its application as a separation technique.

1.3 Column Chromatography.

The above examples demonstrate that separation processes between catalyst and product are possible but quite often difficult and problematic, due to leaching into the organic phase, decomposition of the catalyst and loss of activity. In some other cases the problem is in the method and equipment used to perform the separation such as expensive and environmentally persistent solvents and expensive equipment.

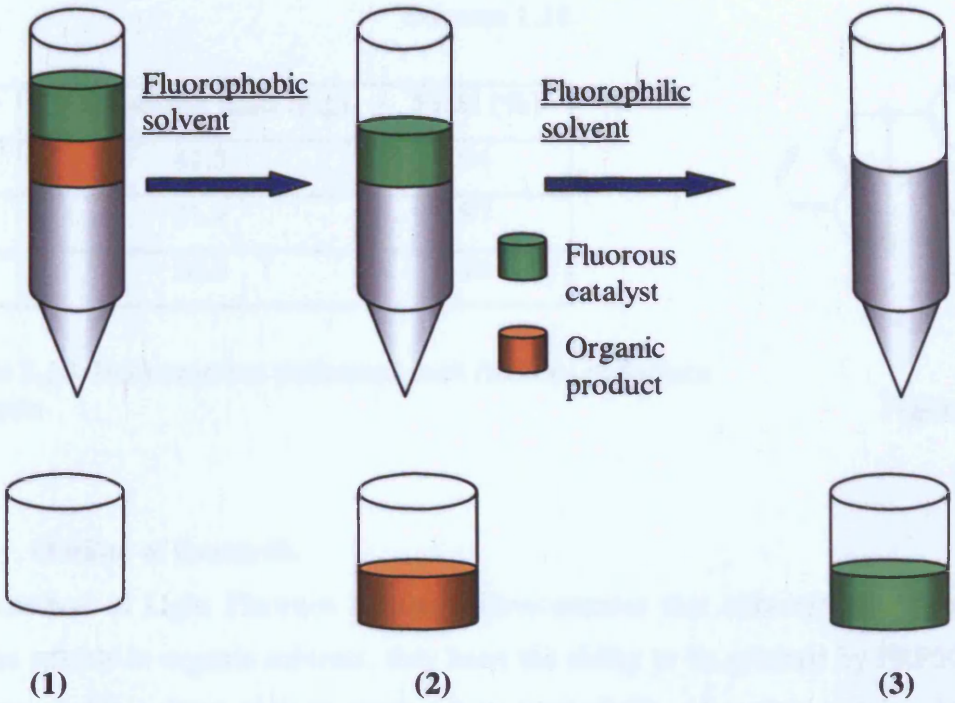
Separation using column chromatography requires a minor modification of the catalyst. However, the idea of using column chromatography to separate catalyst from products seems easy and efficient.

1.3.1 Fluorous Solid-Phase Extraction (FSPE)

Fluorous solid-phase extraction is based on the different polarity and the amount of fluorine that the catalyst contains. This is a well-established technique in fluorous synthesis and has been applied successfully many times.[60] The reaction is carried out in a homogenous organic phase and afterwards, the resulting crude mixture undergoes separation on fluorous reverse phase silica gel (**Scheme 1.17**). The separation is carried out in two steps. First, a fluorophobic solvent is used to elute only the product while the fluorous catalyst is retained by the column. After that, a fluorophilic solvent is added in order to recover the catalyst (**Scheme 1.17**).

The method has some advantages:

1) The catalyst can be recycled and reused.
2) Avoids the use of perfluorocarbon solvents.
3) The fluorous reverse phase silica gel can be recycled and reused.



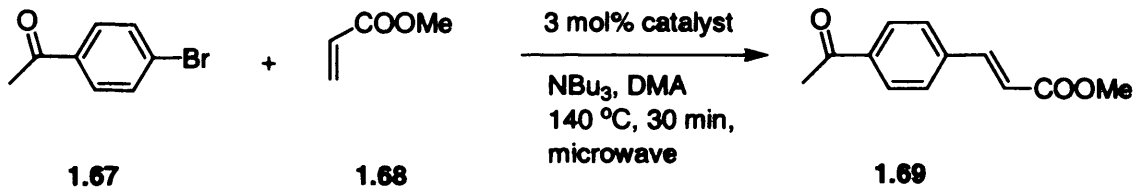
Fluorophobic solvents: MeOH, MeOH/H_2O, acetonitrile.

Fluorophilic solvents: THF, Et_2O, AcOEt

Scheme 1.17.

1.3.1.2 Uses of Fluorous Solid Phase Extraction (FSPE).

Column chromatography has been a useful tool for the separation of organic products for decades. With the same purpose Fluorous Reverse Phase Silica Gel (FRPSG) was synthesised in the eighties[46] (section 1.2.4.4). One example of the use of FRPSG as a useful tool to separate fluorous catalysts from products was reported by Curran *et al.*[61] A Heck reaction was reported using palladium fluorous pincer ligands (**Scheme 1.18, Figure 1.13**). As **Table 1.15** shows, good yields were obtained over three runs, however, the decomposition of the catalyst was quite high. Recent work suggested that such palladacycles might be precursors for trace quantities of soluble or nanoparticulate palladium metal.

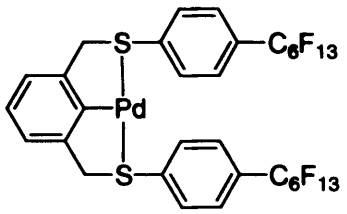


1.67 1.68 1.69

Scheme 1.18.

Run	Wt. catalyst used (mg)	Yield (%)
1st	41.5	94
2nd	31.4	97
3rd	26.0	98

Table 1.15. Heck reaction performed with fluorous palladium catalysts



1.70

Figure 1.13.

1.4 Outline of Research.

The method of Light Fluorous Synthesis demonstrates that although the "light/fluorous" catalyst can be soluble in organic solvents, they have the ability to be retained by FRPSG when eluted with a fluorophobic solvent such as methanol or acetonitrile. After that a fluorophilic solvent such as Et_2O or THF should be added in order to recover the catalyst so that it can be reused.

This system has been successfully used at the University of Leicester using fluorous derivatives of acetylacetonate like $[Ni(C_6F_{13}COCHCOC_6F_{13})_2]$, which catalysed successfully the synthesis of enaminodiones and could be recovered 3 times. However, a drop in the yield on the fourth run suggested decomposition of the catalyst (see chapter 3). It was thought that by using a tetradentate ligand, such as a salen ligand, this problem could be avoided because such ligands will not fully dissociate from the metal centre.

The work presented in this thesis describes research into a number of different catalytic systems. For each system the following aims are discussed:

- The synthesis of achiral and chiral salen ligands and their metal complexes which offer a broad range of catalytic applications and full characterisation.
- The ability to separate catalysts from organic products using separation techniques.
- The effect on reactivity and / or selectivity of catalysts as a consequence of the powerful electron withdrawing effect of the fluorine containing catalysts.

- An investigation in the field of Lewis acid catalysis for new metal catalysts able to perform known and new asymmetric reactions.

1.5 References

1 L. Oro, E. Sola, *Fundamentos y aplicaciones de la catalisis homogenea*, 2000, CYTED, Zaragoza.

2 C. C. de LaTour, *Ann. Chim. Phys.*, 1822, **21**, 127.

3 V. Ipatiev, O. Rutala, *Ber.*, 1913, **46**, 1748.

4 P. G. Jessop, T. Ikariya, R. Noyori, *Science*, 1995, **269**, 1065.

5 K. Wittmann, W. Wisniewski, R. Mynott, W. Leitner, C. L. Kranemanm, T. Rische, P. Eilbracht, S. Kluwer, J. M. Ernsting, *Chem. Eur. J.*, 2001, **7**, 4584.

6 D. Wynne, P. G. Jessop, *Angew. Chem. Int. Ed.*, 1999, **38**, 1143.

7 P. G. Jessop, W. Leitner, *Chemical Synthesis using supercritical fluids*, 1999, 1, Wiley, New York.

8 T. Sako, M. Sato, S. Yamane, *J. Chem. Eng. Jpn.*, 1990, **23**, 770.

9 J. W. Rathke, R. J. Klingler, T. R. Krause, *Organometallics*, 1991, **10**, 1350.

10 K. E. Laintz, C. M. Wai, C. R. Yonker, R. D. Smith, *J. Supercritical Fluids*, 1991, **4**, 194.

11 I. Bach, D. J. Cole-Hamilton, *Chem. Commun.*, 1998, 1463.

12 Y. Kayaki, T. Suzuki, Y. Noguchi, S. Sakurai, M. Imanari, T. Ikariya, *Chem. Lett.*, 2002, 424.

13 K. D. Wagenr, N. Dahmen, E. Dinjus. *J. Chem. Eng. Data*, 2000, **45**, 672.

14 S. Kainz, D. Koch, W. Baumann, W. Leitner, *Angew. Chem. Int. Ed.*, 1997, **36**, 1628.

15 P. G. Jessop, *J. Supercritical Fluids*, 2006, **38**, 211.

16 I. Komoto, S. Kobayashi, *J. Org. Chem.*, 2004, **69**, 680.

17 R. D. Rogers, K. R. Seddon, *Ionic Liquids: Industrial Applications to Green Chemistry*, 2002, Kluvert, Netherlands.

18 T. Ollevier, V. Desyroy, B. Debailleul, S. Vaur, *Eur. J. Org. Chem.*, 2005, 4971.

19 J. M. Martin P. B. McCorman, K. R. Seddon, Green Chemistry, 1999, **1**, 23.

20 B. Cornils, W. A. Herrmann. *Applied Homogeneous Catalysis with Organometallic Compounds*, 1996, Wiley, New York.

21 R. V. Chaudhari, A. Bhattacharya, B. M. Bhanage. *Catal. Today*, 1995, **24**, 123.

22 G. Fremy, E. Monflier, J. F. Carpentier, Y. Castenet, A. Mortreux. *J. Mol. Cat. A*, 1998, **129**, 35.

23 J. C. Galland, M. Savignac, J. P. Genêt. *Tetrahedron Lett.*, 1999, **40**, 2323.

24 M. Vincent, A. Rabion, V. K. Yachandra, R. H. Fish, *J. Fluorine Chem.*, 2001, **108**, 195.

25 E. de Wolf, P. Ruelle, J. van den Broeke, B. J. Deelman, G. van Koten, *J. Phys. Chem. B*, 2004, **108**, 1458.

26 B. Croxtall, E. G. Hope, A. M. Stuart, *Chem Commun.*, 2003, 2430.

27 M. Contel, C. Izuel, M. Laguna, P. R. Villuendas, P. J. Alonso, R. H. Fish, *Chem. Eur. J.*, 2003, **9**, 4168.

28 E. G. Hope, A. M. Stuart, *J. Fluorine Chem.*, 1999, **100**, 75.

29 G. Ragagnin, B. Betzemeier, S. Quici, P. Knochel, *Tetrahedron*, 2002, **58**, 3985.

30 B. Betzemeier, F. Lhermitte, P. Knochel, *Tetrahedron Lett.*, 1998, **39**, 6667.

31 M. Moreno Cañas, R. Pleixats, S. Villaroya, *Organomet.*, 2001, **20**, 4524.

32 G. Pozzi, M. Cavazzini, F. Cinato, F. Montanari, S. Quici, *Eur. J. Org. Chem.*, 1999, 1947.

33 I. T. Horváth, J. Rabái. *Science*, 1994, **266**, 72.

34 F. Hartley, *Supported metal complexes: a new generation of catalysts*, 1985, 4, Reidel, Dordrecht.

35 D. Jayaprakash, H. Sasai, *Tetrahedron Asymm.*, 2001, **12**, 2589.

36 S. Doherty, E. G. Robins, I. Pál, C. R. Newman, C. Hardcare, D. Rooney, D. A. Mooney *Tetrahedron Asymm.*, 2003, **14**, 1517. .

37 M. I. Burguete, J. M. Fraile, J. I. Garcia, E. V. Garcia, S. V. Luis, J. A. Mayoral, *Org. Lett.*, 2000, **2**, 3905.

38 R. Grubbs, L. Kroll, E. Stuart. *J. Makromol. Sci. Chem.*, 1973, **7**, 1047.

39 J. M. Thomas, R. Raja, *J. Organomet. Chem.*, 2004, **689**, 4110.

40 D. G. H. Ballard, *Adv. Catal.*, 1973, **23**, 263.

41 T. Mashmeyer, F. Rey, G. Sankar, J. M. Thomas, *Nature*, 1998, **378**, 159.

42 J. Jarupatrakorn, T. D. Tidley, *J. Am. Chem. Soc.*, 2002, **124**, 8380

43 S. T. Nguyen, L. K. Johnson, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.*, 1994, **114**, 3974.

44 C. E. Song, S.-G. Lee, *Chem. Rev.*, 2002, **102**, 3495.

45 P. O'Leary, N. P. Krosveld, K. P. DeJong, G. van Koten, R. J. M. Klein Gebbink, *Tetrahedron Lett.*, 2004, **45**, 3177.

46 D. P. Curran, Z. Luo, *J. Am. Chem. Soc.*, 1999, **121**, 9069.

47 P. Varighese, M. E. Gongoda, R. K. Gilpin, *J. Chrom. Sci.*, 1988, **26**, 401.

48 M. Matsugi, D. P. Curran, *J. Org. Chem.*, 2005, **70**, 1636.

49 E. Buhleier, W. Wehner, F. Vögtle. *Synth.*, 1978, 155.

50 A. Denkewalter,U.S Patent 4.289.872, 1981.

51 D. A. Tomalia, J. R. Dewald, U.S. Patent 4.507.466, 1978.

52 D. A. Tomalia, H. Baker, J. Dewald, M. Hall, G. Kallos, S. Martin, J. Roeck, J. Ryder, P. Smith. *Polymer J.*, 1985, **17**, 117.

53 G. R. Newkome, Z. Yao, G. R. Baker, V. K. Gupta. *J. Org. Chem.*, 1985, **50(11)**, 2003.

54 Q.-S. Hu, V. Pugh, M. Sabat, L. Pu. *J. Org. Chem.*, 1999, **64**, 7528.

55 F.-Y. Zhang, C. W. Yip, R. Cao, A. S. C. Chan, *Tetrahedron: Asymm.*, 1997, **8**, 585.

56 J. S. Moore, *Acc. Chem. Res.*, 1997, **30**, 402.

57 T. Butz, H. Sellner, *Top. Curr. Chem.*, 1998, **197**, 125.

58 G. Barre, D. Taton, D. Lastecoueres, J. M. Vincent, *J. Am. Chem. Soc.*, 2004, **126**, 7764.

59 M. Wende, R. Meier, J. A. Gladysz, *J. Am. Chem Soc.*, 2001, **123**, 11491.

60 M. Matsugi, D. P. Curran, *Org. Lett.*, 2004, **6**, 2717.

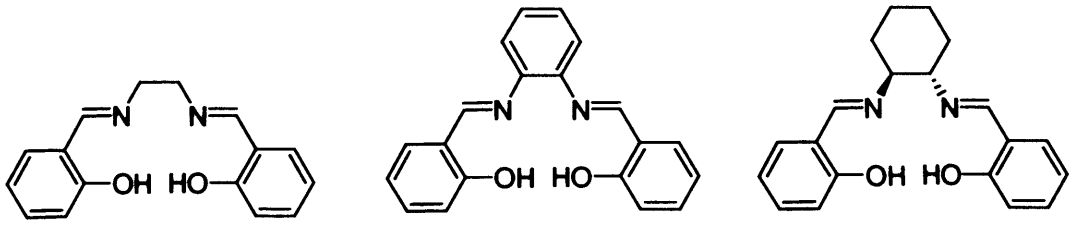
61 D. P. Curran, K. Fischer, G. Moura-Letts, *Synlett*, 2004, **8**, 1379.

2 Synthesis and coordination chemistry of H_2salen-type ligands

2.1 Introduction

2.1.1 Synthesis of H_2salen-type ligands

Hugo Schiff described the condensation between an aldehyde and an amine leading to a Schiff base in 1864.[1] Schiff base ligands coordinate to metals through an imine nitrogen and another group, usually linked via the aldehyde. Schiff bases are still being applied today as useful tools in catalysis. One particular class that are obtained by condensation of two equivalents of salicylaldehyde with a diamine, are the so called salen ligands. Salen complexes with their four coordinating sites and two axial sites open to ancillary ligands are very much like porphyrins, but are more easily prepared. Although the term salen was used only to describe the tetradentate Schiff bases derived from ethylenediamine, the more general term Salen-type is used in the literature to describe the tetradentate [O,N,N,O] class of bis-Schiff base ligands (**Figure 2.1**).

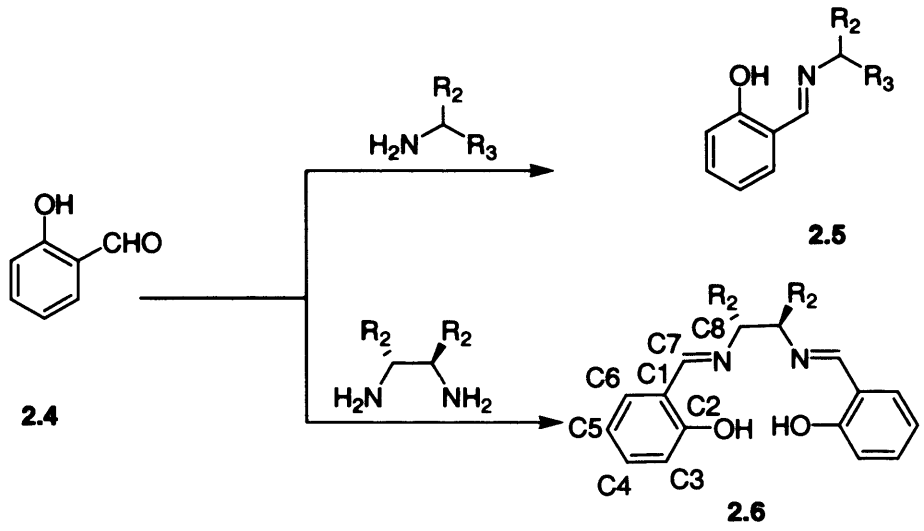


2.1 **2.2** **2.3**

Figure 2.1.

Condensation of salicylaldehydes with 1,2-diamines leads to salen-type ligands (**2.6**), while the condensation of salicylaldehydes and amines lead to bidentate phenol derivatives (**2.5**) (**Scheme 2.1**). There are many methods available for the successful condensation of a salicylaldehyde with an amine. Water is produced in the reaction and can be a problem, resulting in low yields. This problem can be solved in many ways:

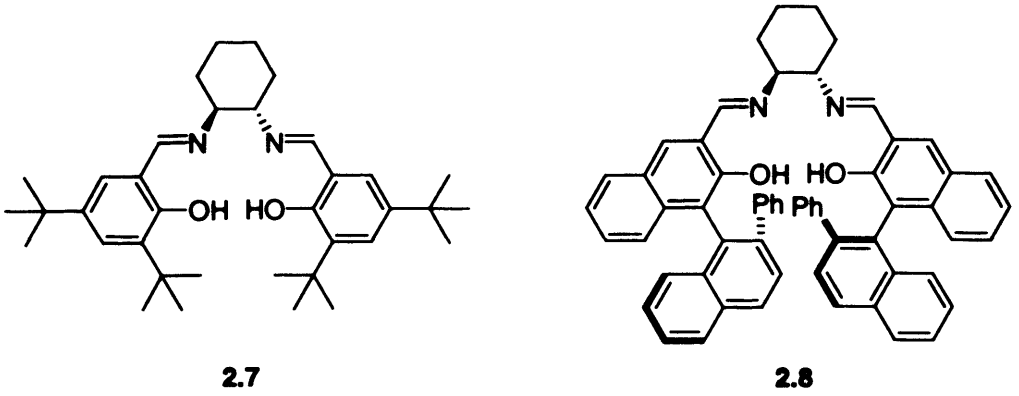
1) Using dried solvents and dehydrating agents such as $MgSO_4$;
2) Using a Dean Stark apparatus to remove the water if the reaction is performed in toluene.



Scheme 2.1.

Ethanol is also a valuable solvent for the preparation of Schiff bases and can be used at room temperature or under refluxing conditions. The use of silica gel to purify the product can lead to decomposition of the salen ligand, and recrystallisation is a much better purification method. In general, Schiff bases are air stable and can be stored without precautions.

In chiral salen-type ligands bulky groups are often introduced on the aromatic part in order to regulate the orientation of the incoming substrates and to determine a high diastereofacial preference. When different elements of chirality are present in the same ligand, the conformational effects are more pronounced. This is the case of the salen described by Katsuki[2] (**2.8**). When different chiral elements are not combined the ligand is said to belong to the first generation (**2.7**) and when different chiral elements are combined it belongs to the second generation (**2.8**). The ligand conformation in **Figure 2.2**, right, where a naphthyl unit is combined with a diamine containing stereogenic centres, is dictated by at least two factors. The combination of stereogenic elements controls the folding and the binaphthyl ligands bring an aryl group close to the metal centre.



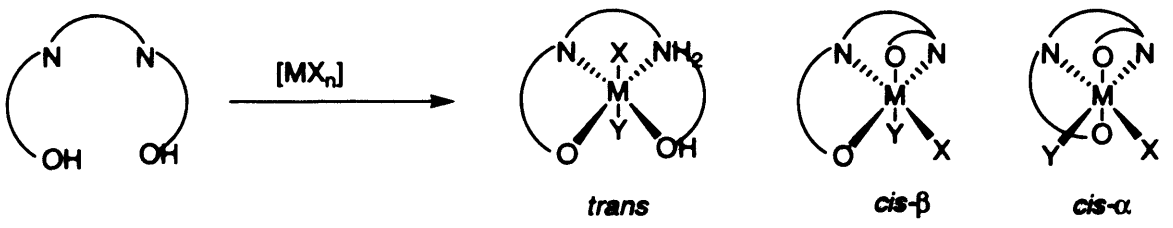
2.7 **2.8**

Figure 2.2

2.1.2 Synthesis and structure of salen coordination compounds

A wide variety of metal-salen complexes have been synthesised and a number of chiral and achiral salen derivatives are commercially available. These complexes adopt mainly square planar or octahedral configurations and can carry two ancillary ligands (Figure 2.3). Tetradentate salen-type ligands are dianionic and ancillary ligands may be anionic or neutral, depending on the valency of the central metal ion. When the complex bears a non-coordinating anion such as PF_6^- or ClO_4^-, a neutral ligand such as water or solvent can be coordinated to the metal. The geometry of the metallosalen complex depends on the ancillary ligand as well as the central metal ion.

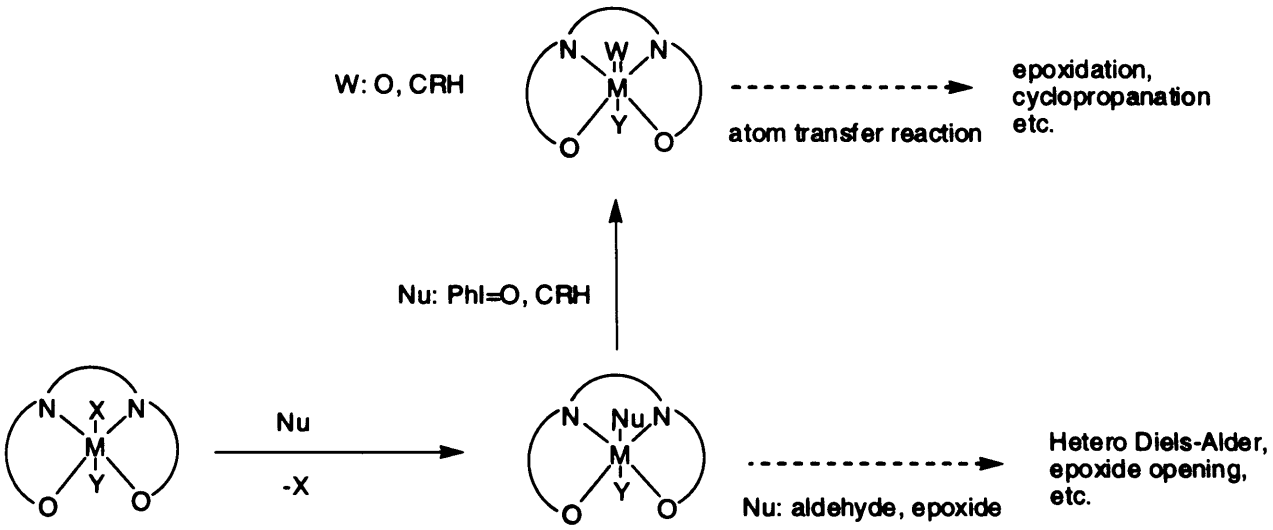
The importance of metallosalen complexes with metals such as chromium,[3] cobalt,[4,5] vanadium[6] and manganese[7] in catalysis have been demonstrated. Due to the presence of two sp^3 carbons at the diamine unit, metallosalen complexes can present different stereoisomers (configurational and conformational). Metallosalen complexes can adopt three different configurations (*trans*, *cis*-β and *cis*-α) (**Figure 2.3**): two ancillary ligands occupy the apical positions in *trans* isomer, one apical and one equatorial in the *cis*-β and two equatorial in the *cis*-α.



trans *cis*-β *cis*-α

Figure 2.3.

Ancillary ligands can be substituted by a nucleophilic reagent or the substrate in a catalytic reaction. The metallosalen complex shown below (**Scheme 2.2**), adopts a *trans* configuration. The coordinated nucleophile is activated by the Lewis acidic metal ion and can be further transformed into the active species, depending on the nature of the nucleophile. For example, treatment of the metallosalen complex with nucleophiles such as iodosylbenzene and diazoester, generates an active oxene- (W: O) and a carbene-metal complex (W: CRH), respectively, via the corresponding addition of compounds. These active species can undergo oxygen- or carbon-atom transfer to a variety of substrates.[8,9] On the other hand, when the coordinated nucleophile is an aldehyde or an epoxide, it undergoes a hetero Diels-Alder reaction or an epoxide ring-opening reaction. If the salen ligand is chiral, then the reactions proceed in an enantioselective manner.



Scheme 2.2.

Due to the rotational freedom of the ethylenediamine unit, a *trans*-metallosalen complex can adopt different conformations as shown in **Figure 2.4**. Typical conformations are stepped or umbrella and the conformation of the complex depends on the conformation of the five membered chelate ring formed between the metal and the ethylenediamine unit. The chelate ring can adopt either a half chair, envelope, or their distorted conformers (**Figure 2.4**). The chelate rings of *trans*-metallosalen complexes that adopt the stepped conformation generally exist in the half chair conformation whereas the complexes adopting the symmetrical umbrella conformation exist as the envelope conformer.[10,11] It is worth observing that most of the metallosalen complexes substituted at C8 and C8' adopt the stepped conformation, because the half chair conformer would allow both substituents to adopt quasi-equatorial orientations (conformer A). Not only does the chirality of C8 and C8' affect the asymmetric induction of the metallosalen

complexes but also the conformation, as shown in **Scheme 2.3**. An achiral stepped metallosalen complex exists as an equilibrated mixture of enantiomeric conformers (A and B). The enantiomeric conformers become diastereomeric when the apical ligand (L) is replaced by a chiral ligand and the equilibrium shifts to one side. Thus, an achiral metallosalen complex functions asymmetrically by adding a chiral ligand.[10] Except for a few examples, chiral metallosalen complexes used for asymmetric catalysis have common structural features:

1) The presence of substituents at C8 and C8';
2) The presence of bulky or/and chiral substituents at C3 and C3';
3) The C_2-symmetric structure.

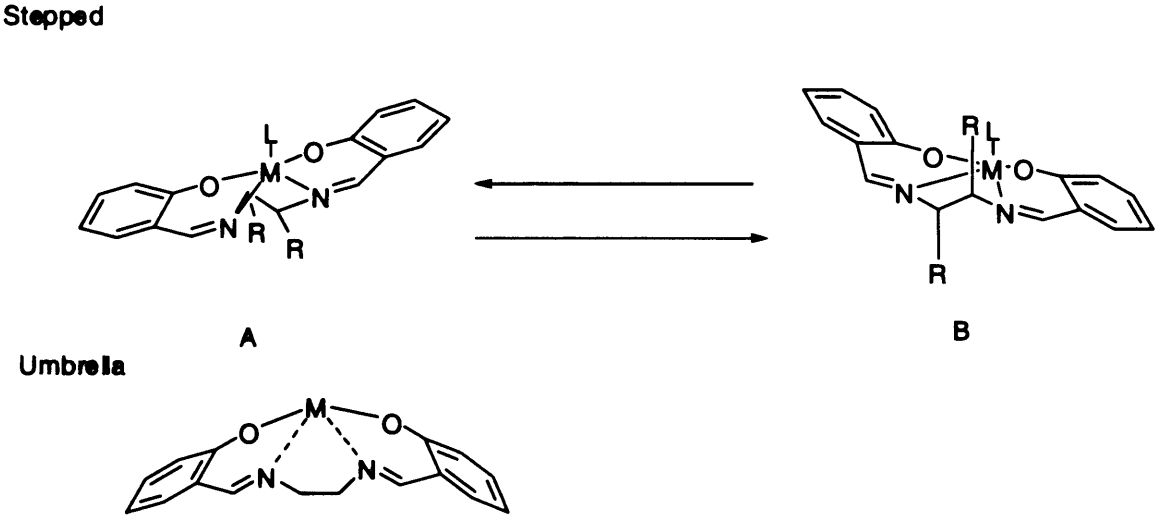
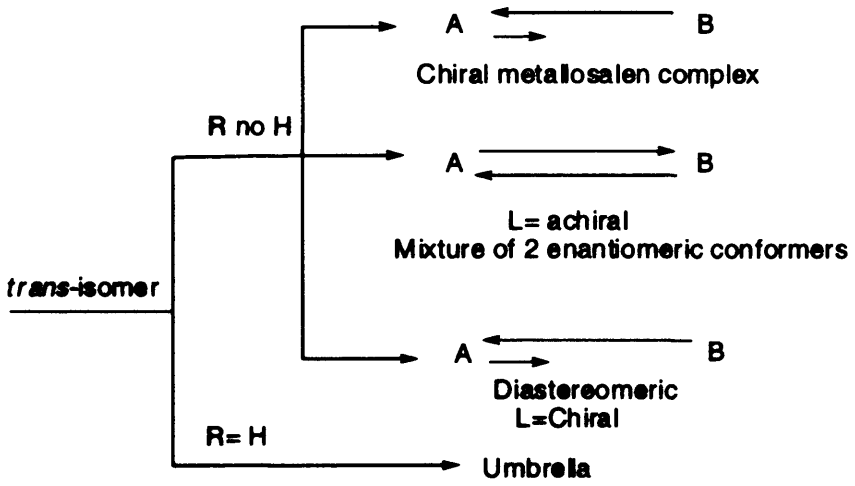
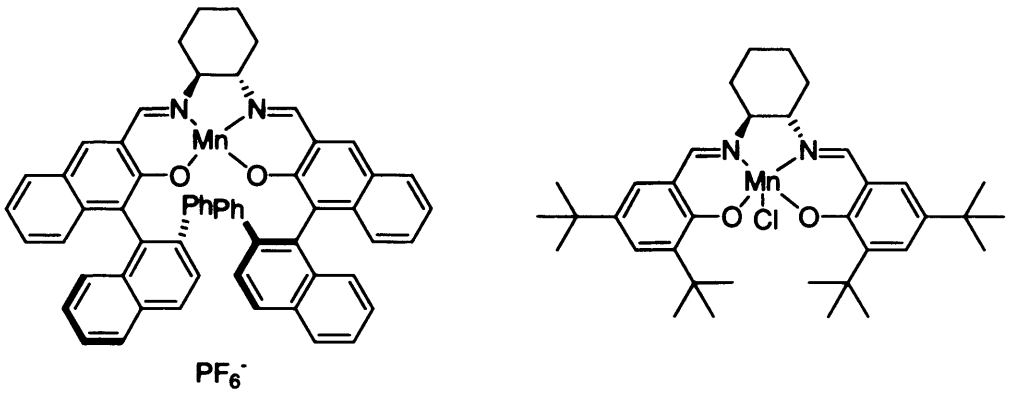


Figure 2.4.



Scheme 2.3.

A *trans*-metallosalen complex provides an available coordination site(s) for a monodentate reagent or substrate, but it is not necessarily a suitable catalyst, when a reagent or substrate is multidentate. Some typical examples of *trans*-metallosalen compounds are those of manganese salen complexes (**Figure 2.5**)[8] but also those of cobalt,[11] nickel,[12] ruthenium and aluminium.[13] The use of these compounds as catalysts will be discussed in the next section.



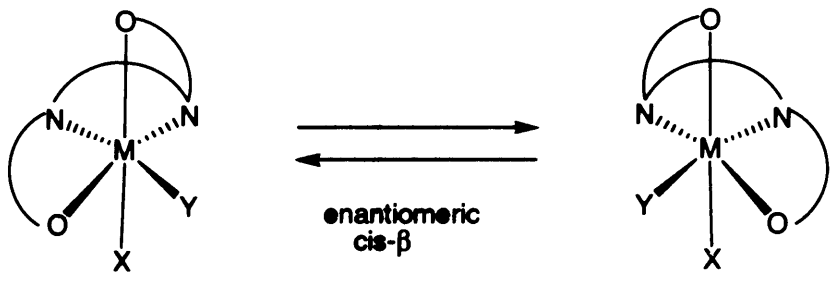
2.9 **2.10**

Figure 2.5.

A metallosalen complex can adopt an octahedral *cis*-β configuration, in which the two ancillary ligands are *cis* to each other. The *cis*-β complex can be a good catalyst for the reaction with bidentate (X-Y) ancillary ligands (**Scheme 2.4**). Some metallosalen complexes can adopt this configuration without a bidentate ancillary ligand, examples are:

1) Complexes of the second and third row transition metals such as zirconium, hafnium[14] and ruthenium.

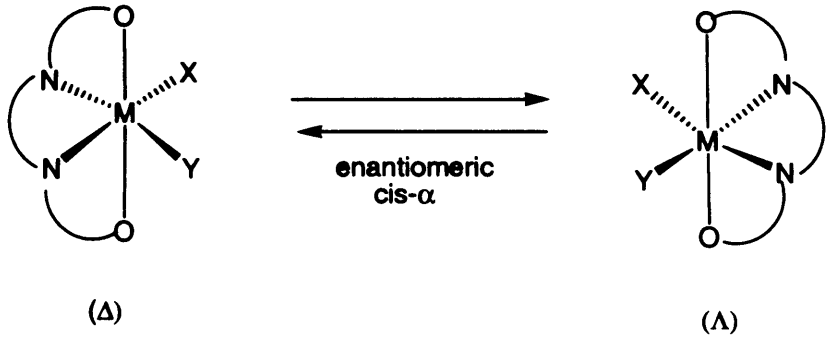
2) Chiral metallosalen complexes having a substituent at C7 and C7' adopt the *cis*-β configuration to avoid repulsion between substituent on C7 and C8 (and C7' and C8').



(Δ) (Λ)

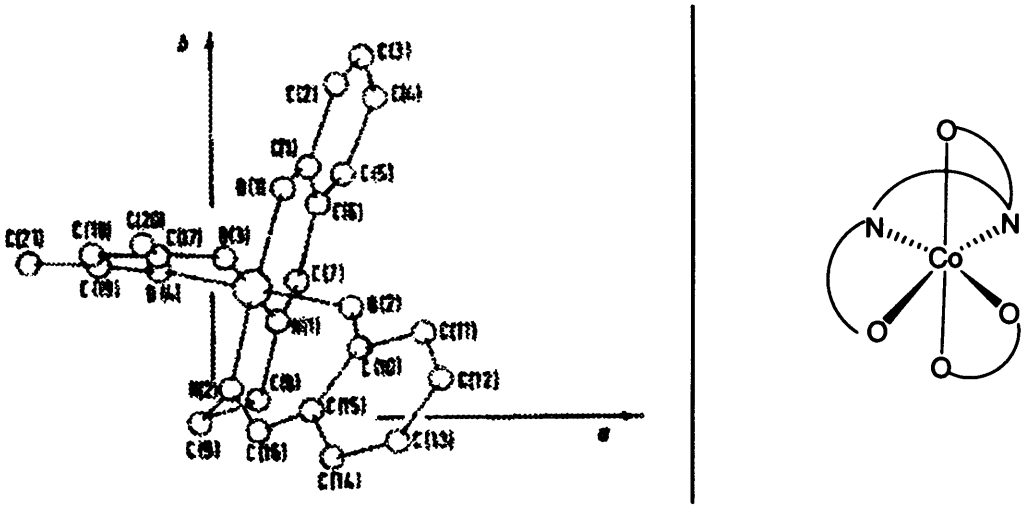
Scheme 2.4.

The last configuration a salen complex can adopt is *cis*-α. In this configuration, the nitrogens are situated *cis* in the equatorial position and the oxygens are situated in the axial positions (**Scheme 2.5**). This configuration has two isomers Λ and Δ and has C_2 symmetry, unlike *cis*-β which has C_1 symmetry.



Scheme 2.5.

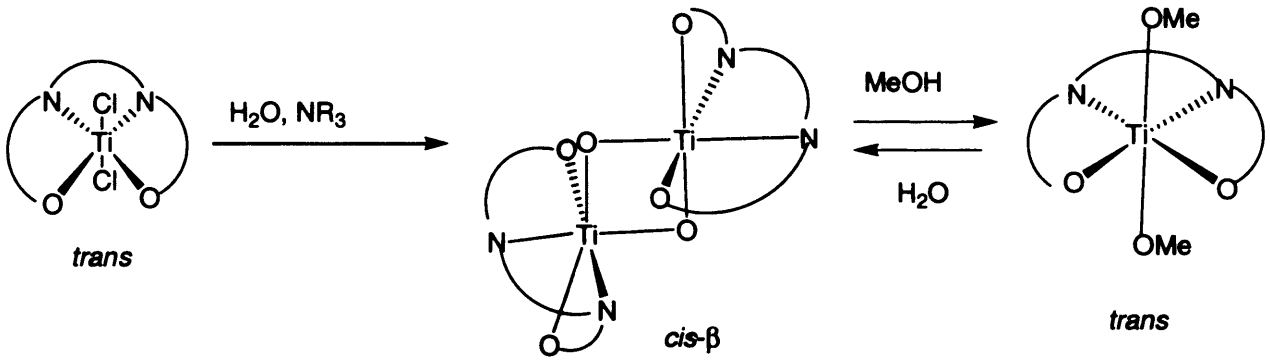
Simple achiral Co(salen) complexes adopt the *trans* configuration with stepped or umbrella ligand conformation.[2] Co(salen) complexes, however, can also take *cis*-β configurations, when they are treated with a bidentate ligand such as acetylacetonate (acac) or oxalate (ox). For example, [Co(III)(salen)(acac)] has been determined to have an approximately octahedral configuration and the salen ligand adopts the *cis*-β configuration as shown by X-ray structural analysis (**Figure 2.6**).[15] It is noteworthy that even if a *trans*-metallosalen complex is achiral, the resulting *cis*-β is chiral. Okawa *et al.* have reported that a Co(III)(salen) complex gives Λ-*cis*-β-Co(III)(salen)(*l*-moba) in preference to Δ-*cis*-β-Co(III)(salen)(*l*-moba), when the ligand H(*l*-moba) is added in methanol (*l*-moba= l-methyloxy-3-benzoyl-acetone).[16]



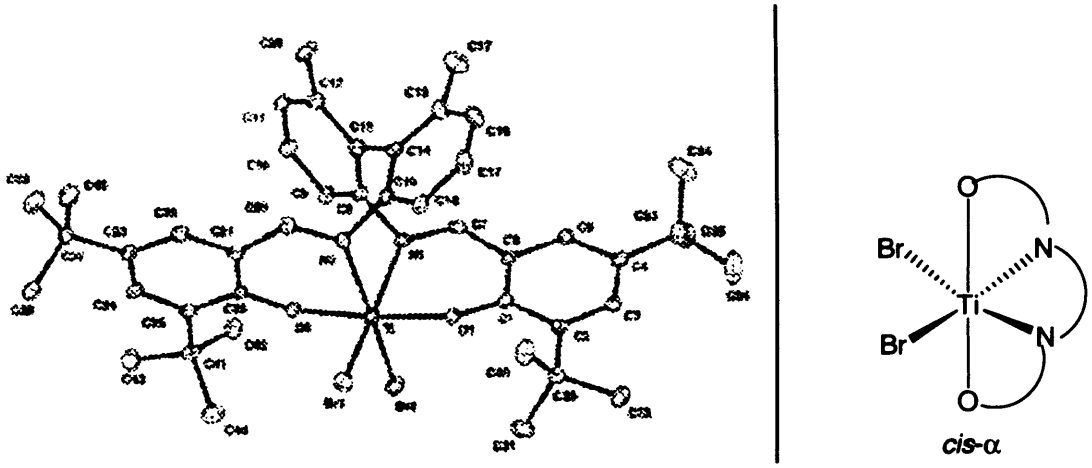
2.11

Figure 2.6.

Other interesting species are [Ti(salen)X_2] complexes (X: Cl, OR, alkyl), which usually adopt *trans*-configurations. However, the [Ti(salen)Cl_2] complex can be converted into the corresponding di-μ-oxo Ti(salen) complex in which a bridging di-μ-oxo moiety serves as a bidentate ligand. The salen adopts *cis*-β geometry upon treatment with water in the presence of an amine (**Scheme 2.6**).[17] On the other hand, the di-μ-oxo-Ti complex can be converted into a *trans*-Ti(salen)$(OMe)_2$ complex by dissolving it in methanol.[18] This suggests that the configuration of the salen can be tuned by changing the solvent. By tuning the diamine backbone it is also possible to obtain the *cis*-α derivative (**Figure 2.7**).[19]



Scheme 2.6.

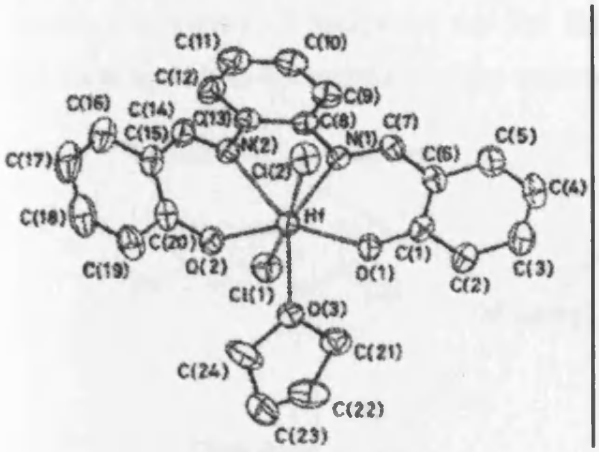


2.12

Figure 2.7.

In contrast to the first row metals, Zr(salen) and Hf(salen) complexes adopt a seven-coordinate pentagonal bipyramidal configuration (**Figure 2.8**).[20] One solvent molecule, such as tetrahydrofuran, is coordinated to the metal in an equatorial position. However, if the complex is

refluxed in toluene the THF is lost and the conformation is *cis*-β. This indicates that *cis*-β Zr and Hf complexes are more stable than the corresponding *trans*-complexes.



2.13

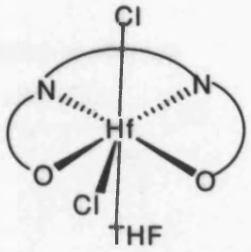
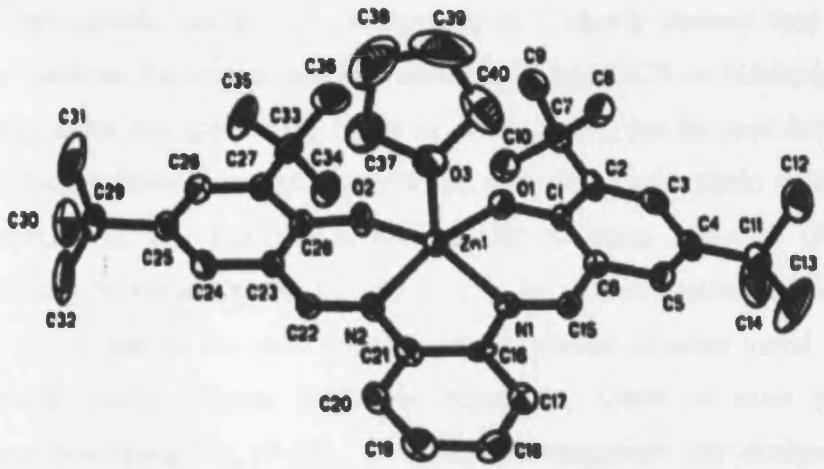


Figure 2.8.

Several reports have described the synthesis of Zn salen complexes from either $[Zn(OAc)_2]$ or $ZnCl_2/NEt_3$. However, these routes can create some difficulties in isolating the pure product.[21] In some cases a mixture between the complex and the free H_2salen is isolated. A more direct route is the treatment of these H_2salen-type ligands with $ZnEt_2$. This strategy is successful because of the higher reactivity of $ZnEt_2$. Isolation of the Zn(II) salen complex and its characterisation by X-ray analysis can be facilitated by adding THF (**Figure 2.9**). In this case, THF is placed in an axial position of a square based pyramid.

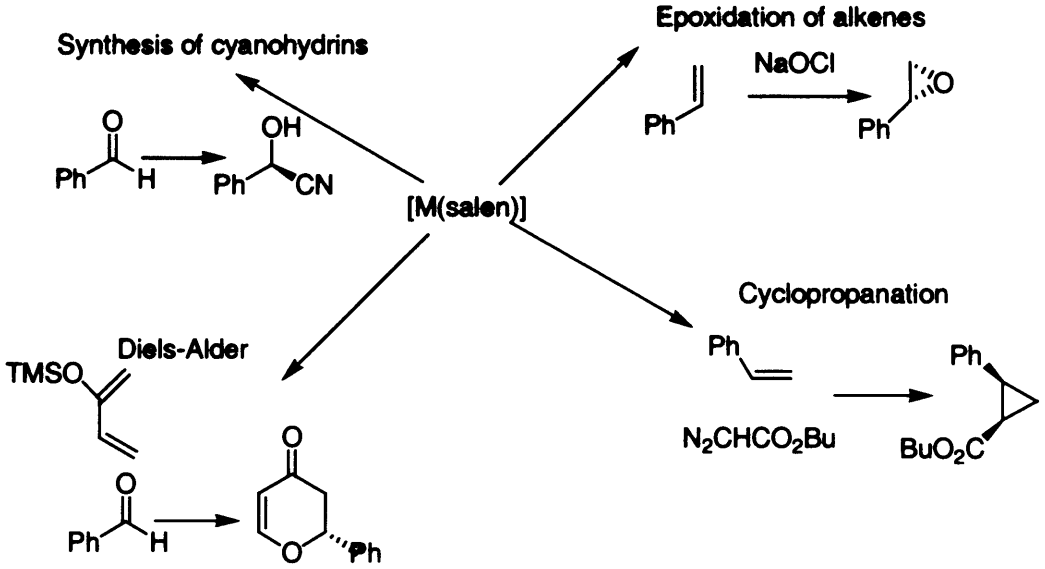


2.14

Figure 2.9.

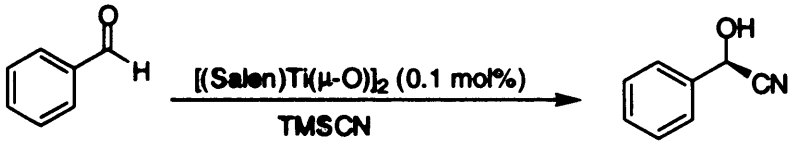
2.1.3 Lewis acid catalysis using salen metal complexes

There are plenty of examples of catalysis using metallosalen complexes (**Scheme 2.7**). The facile synthesis, the variety of backbones and the high number of conformations and configurations make these ligands an exceptional tool for asymmetric catalysis.

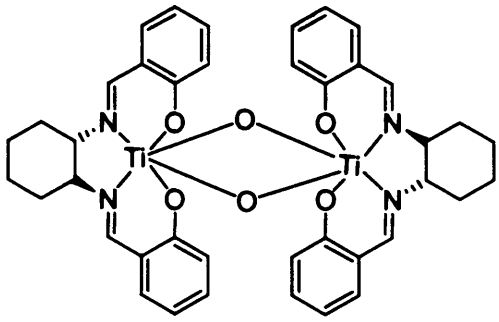


Scheme 2.7.

In general, Schiff bases possess many interesting characteristics. They are moderate electron donors, with a chelating structure and a low electron counting number. In addition, a large library of Schiff bases can be easily generated with structural diversity. Schiff base complexes of early transition metals are active catalysts in Lewis acid catalysis and polymerisation. In the case of [Ti(salen)] complexes different species are formed by the reaction of [Ti(^{i}PrO)$_4$] and chiral H_2salen-type ligands (section 4.3.2). North *et al.*[22] clearly showed that oxo-titanium species are effective catalysts for enantioselective addition of Me_3SiCN to aldehydes and ketones (**Scheme 2.8**). Metal salen oxo species are stable to moisture and can be used for catalytic reactions under environmentally friendly catalytic conditions. Detailed mechanistic studies have shown that the active species in this reaction is a bimetallic titanium complex (**Figure 2.11**). Also, the corresponding VO(salen)X (X: Cl^-, Br^-,....) is an effective catalyst for the same reaction. The reaction shows one of the most peculiar characteristics of salen metal complexes, the ability to work cooperatively (**Figure 2.10**)This behaviour, which is more pronounced in M(salen) complexes containing Cr or Co, is highly advantageous for designing processes in which activation of both nucleophile and electrophile is necessary.



Scheme 2.8.



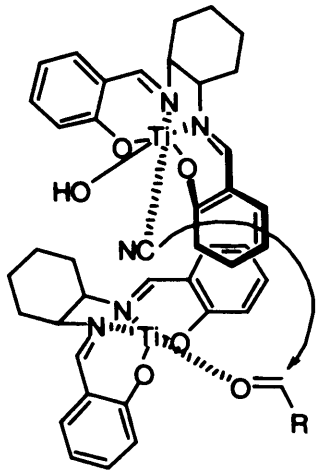


Figure 2.10.

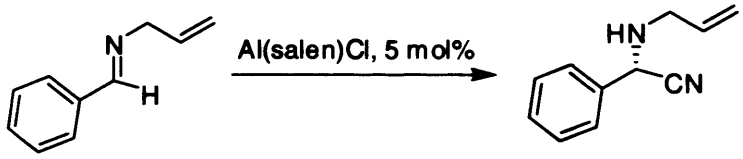
Figure 2.11

Mol % catalyst	Substrate	Conversion (%)	Ee (%)
12	Ph	100	66
3	Ph	100	68
1	Ph	100	78
0.5	Ph	100	82
0.1	Ph	100	86
0.01	Ph	80	86
0.1	4-$CF_3C_6H_4$	100	50
0.1	3-MeC_6H_4	100	74

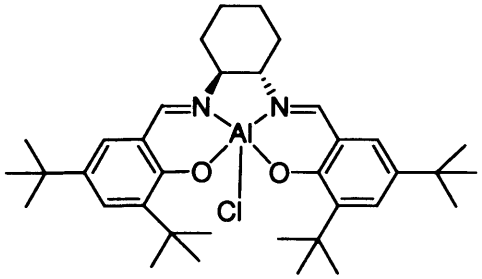
Table 2.1. Yield for different substrates in the synthesis of cyanohydrins using salen complexes.

Another example of Lewis acid catalysis using metal salen derivatives uses [Al(salen)X] (X= Cl, Br, I) that are usually prepared from the alkyl reagents R_2AlX (X = Cl, Br, I). Difficulties in the isolation and characterisation of the complexes are derived from their low solubility. The introduction of ^{t}Bu groups in 3,3'- and 5,5'-positions helps to solubilise the compounds in hydrocarbon solvents. The characterisation shows five coordinate compounds that can be trigonal bipyramidal or square pyramidal,[14] depending on the diamine backbone used. Alkyl and chloride aluminium salen complexes are quite robust and can be handled in open air without decomposition. The complete displacement of the monodentate ligand from the Schiff base complex causes the formation of the cationic compound. For example, in the presence of water or methanol or aprotic ligands (L = THF, HMPA), the hexacoordinate complex [Al(salen)L_2] is

formed. The rapid formation of pentacoordinate compounds combined with their Lewis acidic properties, make Al(salen) complexes good candidates for asymmetric catalysis. Some reactions using [Al(salen)Cl] are the Friedel-Crafts reaction, the Diels Alder reaction and the phosphoaldol reaction. Another interesting reaction with this metal is the addition of HCN to imines (**Scheme 2.9**).[23] The reaction probably takes place via a double activation process in which one molecule of Al(salen) delivers the nucleophile while another activates the substrate. This double activation is a general feature of Al(salen) chemistry. The Michael catalysed addition of CN^-, $CNCH_2COOR$ and N_3^- to amides also takes place in this way with enantioselectivities up to 90%.[23]



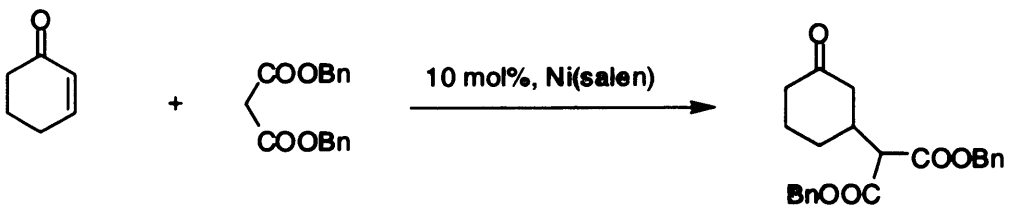
Scheme 2.9.



2.15

Figure 2.12.

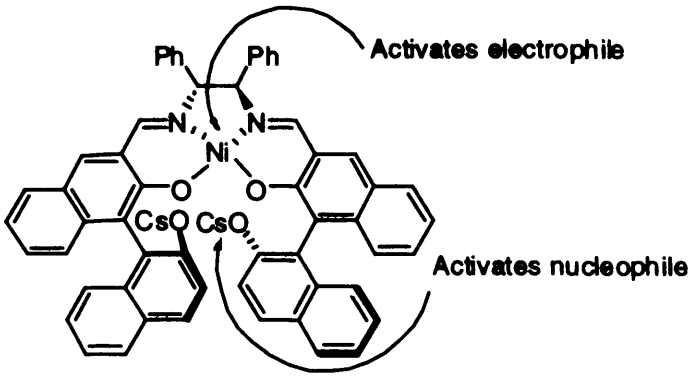
Although Ni(salen) complexes have not found many applications as catalysts some interesting examples can be found in the literature. Ni(salen) complexes bearing other alkaline metals can behave as bifunctional catalysts, as described by Kozlowski *et al.*[24] (**Scheme 2.10**). Different metals were tested in the BINOL part (Cs, K, Na) resulting in a higher enantioselectvity for Cs derivatives (**Table 2.2**). Cu (II) derivatives of this ligand were found to be almost as active catalysts as Ni(II) derivatives and good yields but lower enantioselectivities were found when Pd(II) was used instead.



Scheme 2.10.

M	conversion (%)	ee (%)
Cs	79	71
K	70	10
Na	56	13

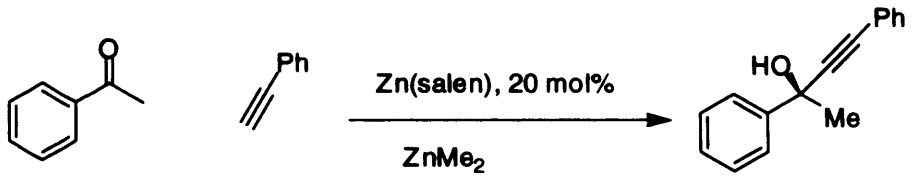
Table 2.2.



2.16

Figure 2.13.

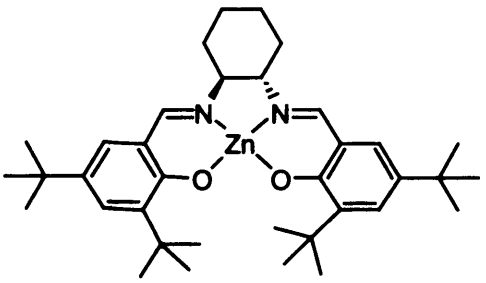
One of the most common application of Zn(salen) complexes such as compound **2.17** is the addition of diethylzinc to benzaldehyde. This reaction will be studied in detail in Chapter 4. Compound **2.17** has the ability to promote the reaction of other organometallics as well. Alkynylation has attracted considerable interest in recent years, as propargylic alcohols are valuable synthetic precursors. The addition of alkynyl zinc reagents to ketones can be realised using this complex as a catalyst,[25] leading to new perspectives in the formation of quaternary stereocentres.



Scheme 2.11.

Catalyst (mol%)	Conversion (%)	ee (%)
10	40	62
20	72	61
20 (50 °C)	85	31

Table 2.3



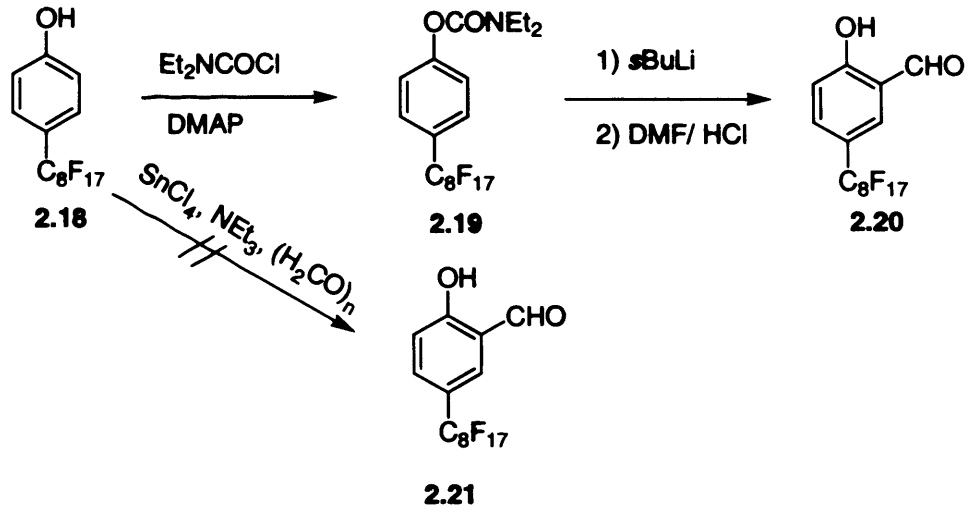
2.17

Figure 2.14.

2.1.4 Synthesis and catalysis using fluorous salen coordination compounds

The first attempts to synthesise fluorous salen metal complexes were published in the late nineties by Pozzi *et al.*[26] Fluorous ponytails were added to the H_2salen ligand in order to enable

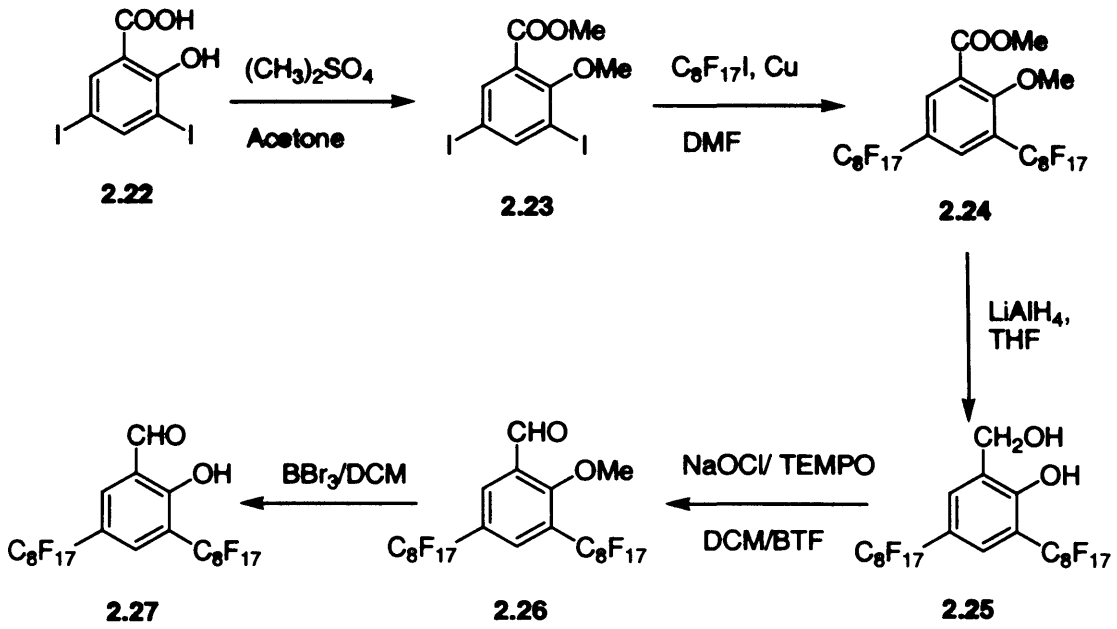
the catalyst to be recycled using fluorous techniques. Here, fluorous ponytails were directly attached to the salicylaldehyde through C-C bond forming reactions. The first salicylaldehyde to be synthesised was 4-perfluorooctylsalicylaldehyde. The first attempts to synthesise this using Casiraghi's method,[27] gave none of the desired product. However, a two step synthesis was developed in order to afford the product in good overall yields (63%) (**Scheme 2.12**).



Scheme 2.12.

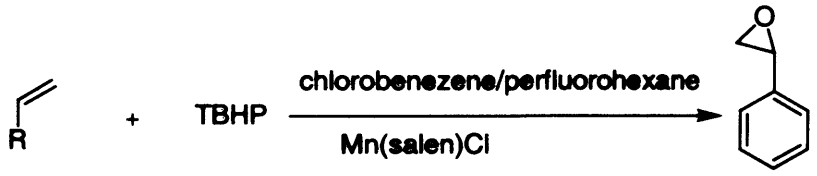
2,4-*Bis*-(perfluorooctyl)salicylaldehyde was then synthesised via the five step procedure shown in **Scheme 2.13**:[26]

1) Protection of the carboxylic acid and phenol with CH_3;
2) C-C coupling of the fluorous ponytails to the aromatic ring;
3) Reduction of the ester by $LiAlH_4$ to yield the benzyl alcohol;
4) Oxidation of the alcohol to yield a salicylaldehyde;
5) Deprotection of the methoxy group with BBr_3 to yield the desired salicylaldehyde



Scheme 2.13.

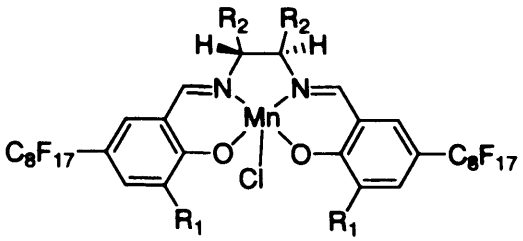
The functionalised H_2salen-type ligands were easily synthesised by condensation of the perfluoroalkylated salicylaldehyde with the corresponding diamine. The resulting ligands were then reacted with $[Mn(AcO)_2.4H_2O]$ to yield catalysts that could then be used for the epoxidation of alkenes (**Scheme 2.14**).[26] Using these fluorous catalysts good yields and enantioselectivities were obtained, although only for certain substrates. The experiments were normally carried out in fluorous biphasic systems in order to recycle the catalyst and *tert*-butyl hydroperoxide (TBHP) was used as an oxidant (see Chapter 1). Enantioselectivity values were the same if the experiments were carried out in biphasic systems or in monophasic systems. Although there was a decrease in yield in the second run, no major changes in enantioselectivity were observed. **(Table 2.4)**



Scheme 2.14.

Catalyst	Substrate	Yield (%)	Ee (%)
2.28	Indene	77	81
2.29	Indene	83	92
2.30	Indene	77	90
2.30 (Run 2)	Indene	73	89
2.31	Styrene	86	<5
2.31	3-Nitrostyrene	36	<5

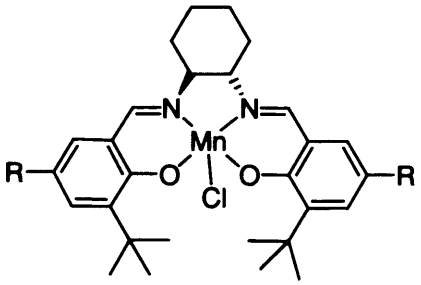
Table 2.4. Asymmetric epoxidation using Mn(Salen).



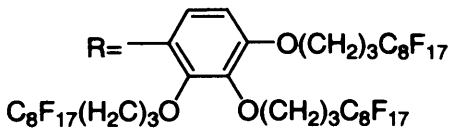
2.28 R_1=H R_2=$-(CH_2)_4-$
2.29 R_1=H R_2=Ph
2.30 R_1=C_8F_{17} R_2=$-(CH_2)_4-$
2.31 R_1=C_8F_{17} R_2=Ph

Figure 2.15.

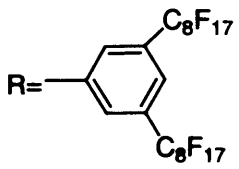
A new generation of metallosalen derivatives were synthesised with ^{t}Bu ponytails in the 3,3'-positions in order to enhance enantioselectivity. A wide number of new catalysts were synthesised with a wide range of fluorine content (**Figure 2.16**). These catalysts were then tested in a fluorous biphasic system and, as **Table 2.5** indicates, yields were high to moderate depending on the catalyst used. The enantioselectivities were found to be moderate for 1,2-dihydronaphthalene, but, when triphenylethylene was used, good yields and good enantioselectivities were obtained. **2.32** was recycled 3 times by decantation with a negligible loss in yield or enantioselectivity.



R= C_8F_{17} 49 %F **2.32**



55 %F **2.33**



56 %F **2.34**

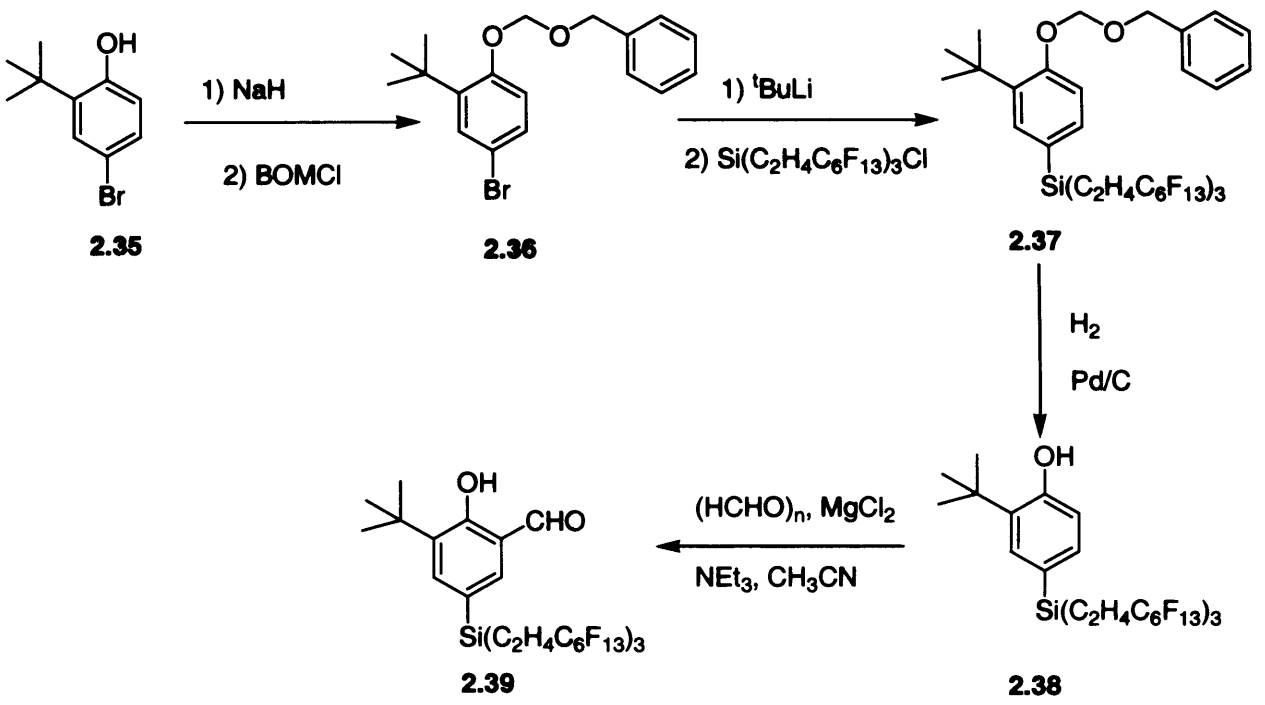
Figure 2.16.

Catalyst	Substrate	Yield (%)	Ee (%)
2.32	1,2-dihydronaphthalene	84	47
2.33	1,2-dihydronaphthalene	65	64
2.34	1,2-dihydronaphthalene	73	63
2.32 (Run 1)	Triphenylethylene	98	87
2.32(Run 2)	Triphenylethylene	96	85
2.32 (Run 3)	Triphenylethylene	92	83

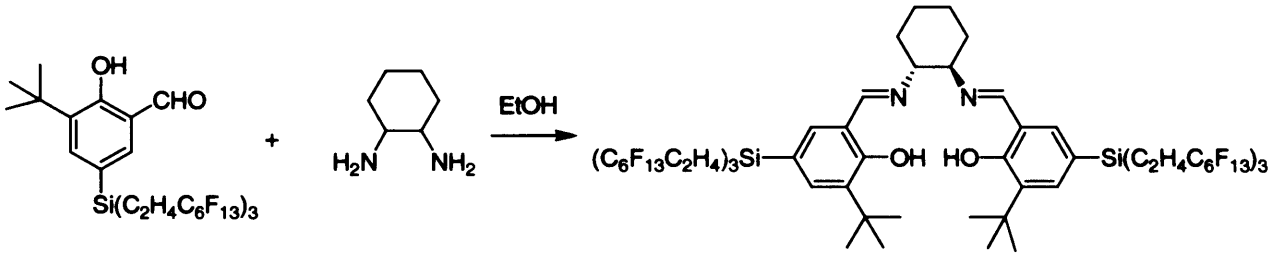
Table 2.5. Asymmetric epoxidation of alkenes using Mn(salen).

The most recent report of fluorous H_2salen ligands was by Bannwarth *et al.*[28] In this case, fluorous silyl ponytails were introduced in the 5,5'-positions to yield the fluorous H_2salen ligand. These fluorous ponytails have been used before in ligands like fluorous BINOL which had been used for the asymmetric alkylation of benzaldehyde.[29] After the H_2salen ligand had been synthesised experiments were carried out in order to determine the ability of the ligand to be retained by a FRPSG column on HPLC. It was concluded that there was a strong interaction between the fluorous column and the fluorous catalyst, hence the high retention times. The synthesis of the H_2salen-type ligand was performed in five steps: (**Scheme 2.15** and **2.16**)

1) OH protection with BOMCl;
2) Introduction of the silyl fluorous ponytails onto the aromatic ring;
3) Deprotection using H_2 and Pd/C;
4) Ortho-formylation;
5) Condensation with a diamine to yield the H_2salen ligand.



Scheme 2.15.



Scheme 2.16.

2.2 Results and discussion

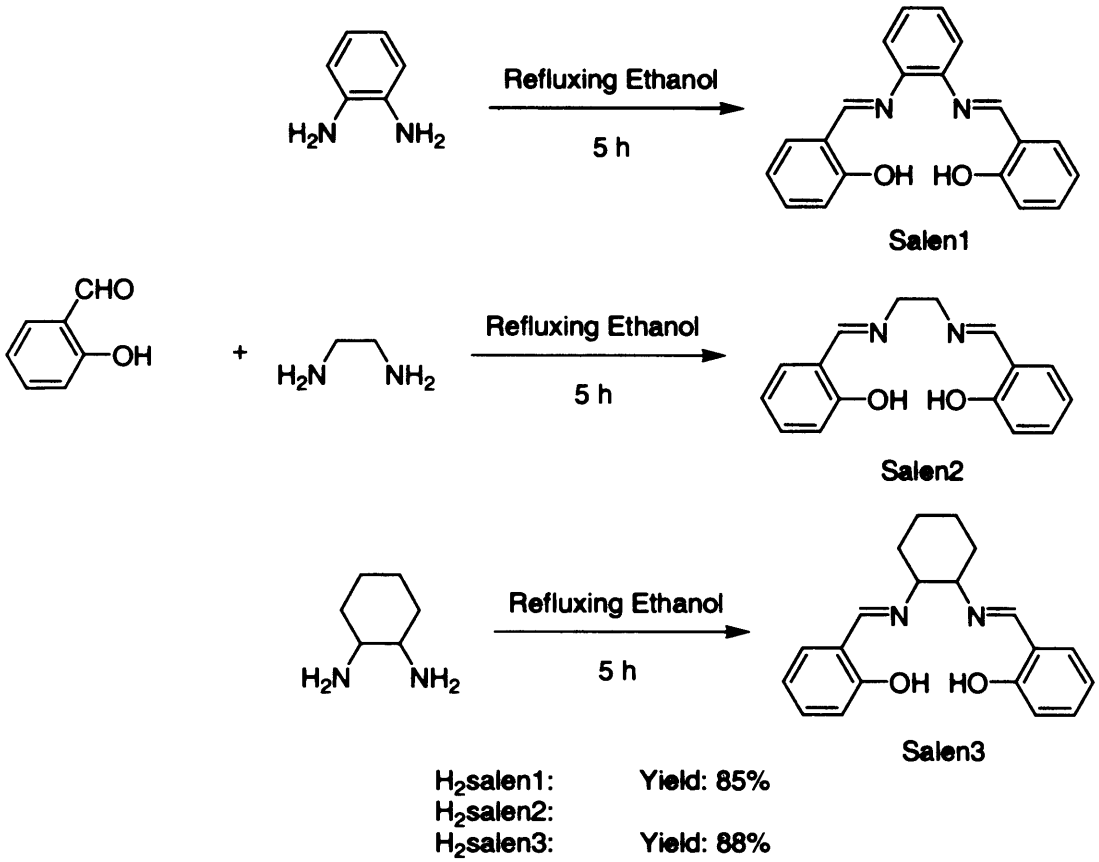
Metallosalen complexes are useful catalysts in a wide range of reactions and M(salen) catalysts from aluminium, titanium, zinc and nickel have demonstrated their ability to perform a number of Lewis acid catalysed reactions.[24,25] In this section, a number of fluorous and non-fluorous salen-type ligands will be synthesised and their coordination chemistry to nickel, zinc and copper will be investigated.

2.2.1 Synthesis of salen-type ligands

The IR spectra of the salen ligands showed distinctive bands in CO and CN regions (1800-1500 cm^{-1}). ^1H NMR spectra showed characteristic singlets in the region δ 8.00 and 8.50 ppm due to

the imine protons and the melting points varied from 132 °C to 140 °C, which are consistent with literature values.

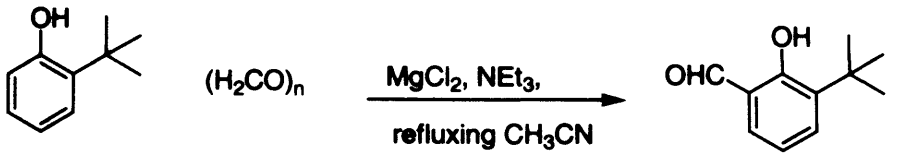
Initially, two H_2salen ligands were prepared by the condensation of salicylaldehyde with either 1,2-ethylenediamine or 1,2-cyclohexyldiamine in refluxing ethanol to give the products as yellow solids in 85% and 58% yields respectively (**Scheme 2.17**). H_2Salen2 is available commercially but can also be easily synthesised. The spectroscopic data (mp, IR, ^{1}H NMR, ^{13}C NMR) of both products were the same as reported in the literature.[30]



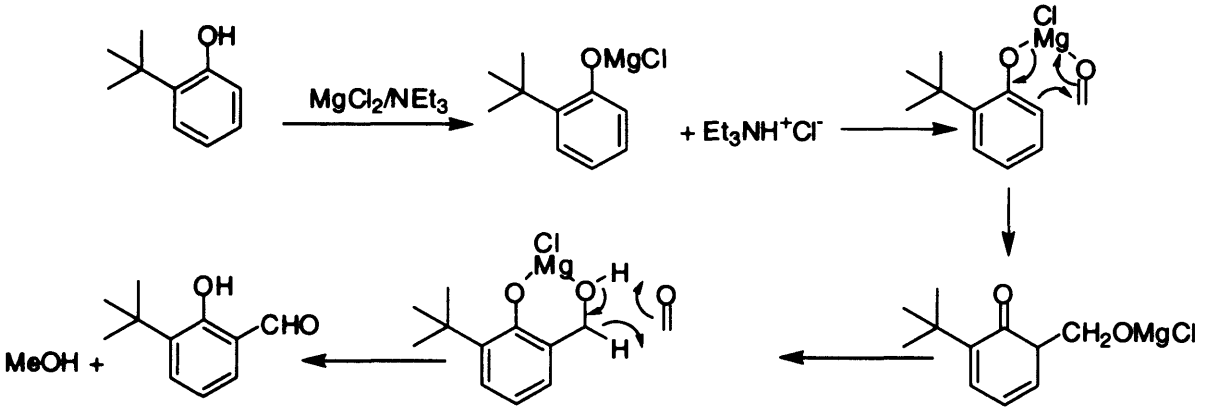
Scheme 2.17.

H_2salen-type ligands containing a *tert*-butyl group in the 3,3'-positions were synthesised next. The salicylaldehyde from which these H_2salen-type ligands were derived was 2-*tert*-butyl-salicylaldehyde, which can be easily prepared by the addition of paraformaldehyde to 2-*tert*-butylphenol in the presence of a Lewis acid catalyst ($MgCl_2$) and NEt_3 (**Scheme 2.18**).[31] This reaction is quite similar to the reaction described by Casiraghi *et al.* (Scheme 2.12).[27] The mechanism is also quite similar (**Scheme 2.19**). The base and the magnesium chloride react with the phenol to give the phenoxymagnesium chloride. This intermediate reacts with formaldehyde, through a cyclohexadienone, to yield the magnesium salt of the salicylic alcohol. This intermediate takes part in a redox reaction with formaldehyde in which the salicylaldehyde is formed together with methanol. It is necessary to add 2 equivalents of paraformaldehyde for each

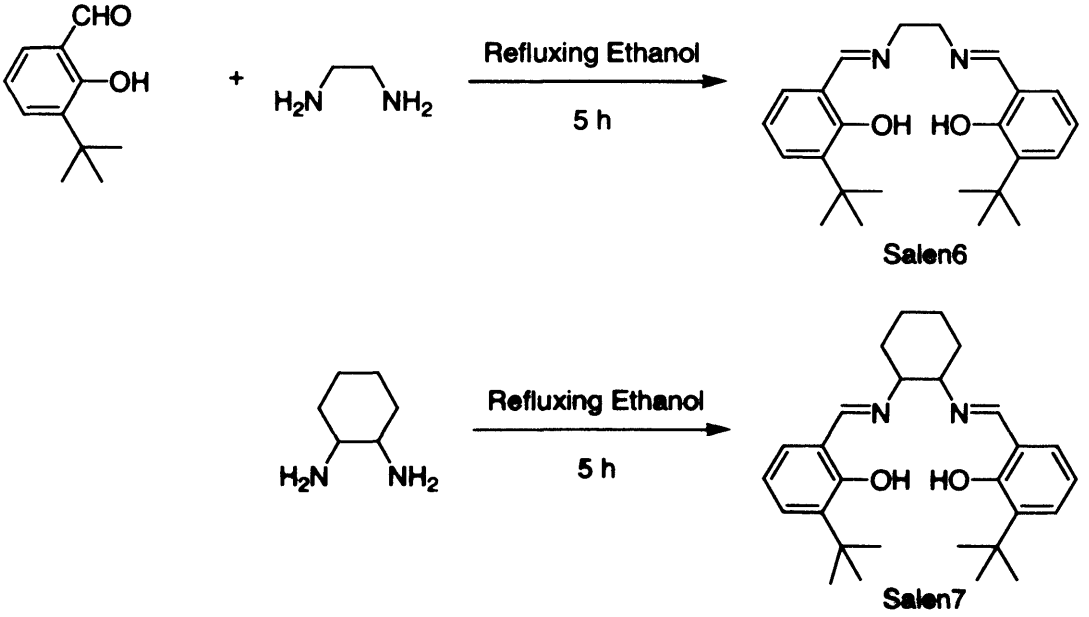
equivalent of phenol. After preparing 2-tert-butyl-salicyladehyde, the H_2salen-type ligands were obtained by the straightforward reaction with the corresponding diamines (**Scheme 2.20**).



Scheme 2.18.



Scheme 2.19.



Scheme 2.20

2.2.2 Coordination chemistry of H_2salen-type ligands

The coordination chemistry of the H_2salen-type ligands were investigated with nickel, zinc and copper. The Ni (II) derivatives were first synthesised from $NiCl_2.6H_2O$ in hot ethanol.[33] The ^1H NMR spectrum did not show water for the *N,N'*-bis(salicylene)-1,2-phenylenediamine (salen1) derivative but for the *N,N'*-bis(salicylene)-1,2-ethylenediamine (salen2) derivative large amounts of water were observed. The N,N'-bis(salicylene)-1,2-cyclohexyl diamine derivative was synthesised from [Ni(acetate)$_2$.4H_2O] in hot ethanol.[34] The water in these two compounds was removed using a cold finger. These three compounds were all square planar (as shown by the X-ray structure of [Ni(salen3)] obtained by Wang *et al.*, **Figure 2.17**)[35] and their colours (from orange to red) are typical for square planar Ni(II) conformations. One interesting point in the ^1H NMR spectra is that the chemical shift of the H-C=N signal moves to a higher field on coordination to nickel.

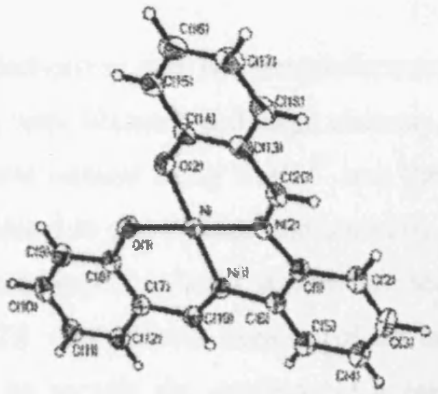
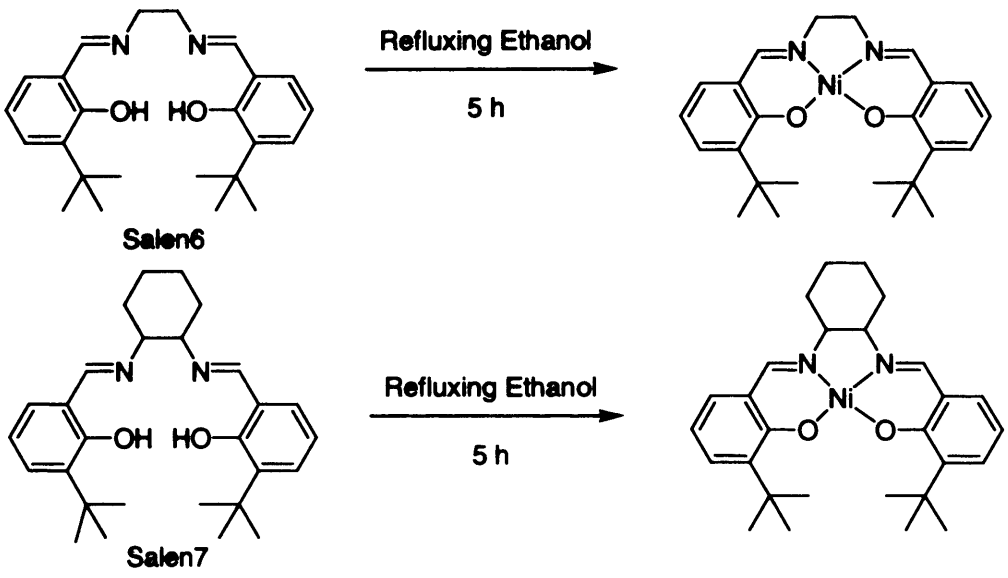


Figure 2.17

[Ni(salen6)] and [Ni(salen7)] were also synthesised by reacting Ni(acetate)$_2$.4H_2O and the relevant H_2salen ligand in ethanol (**Scheme 2.21**). These compounds are also square planar and were characterised by ^1H NMR, mass spectrometry, and solid-state IR. No X-ray crystal structures have been reported or obtained.



Scheme 2.21.

The synthesis of the Zn(II) derivatives was not straightforward. At first they were synthesized from [$ZnCl_2$],[36] but low yields were obtained and large amounts of water were coordinated to the metal complexes. An alternative method using $ZnEt_2$[37] was then used and had two advantages. Firstly, the compound was isolated in good yields and secondly, there was no water coordinated, because anhydrous solvents and reagents ($ZnEt_2$ is moisture sensitive) were used. However, the characterization of [Zn(salen2)] was difficult because of its low solubility in organic solvents. This behaviour will be used to recycle the catalyst by a simple filtration in Chapter 3. The addition of Hacac to a suspension of [Zn(salen2)] in deuterated DCM allowed the coordination compound to dissolve and it was then characterised by ^1H NMR spectroscopy. A survey of the Cambridge X-ray database revealed that some [Zn(salen)] complexes tend not to be four coordinate in the solid state. Instead trigonal bipyradimal, five-coordinate complexes are formed by intermolecular association involving the salen oxygen atoms (**Figure 2.18**).[38] Polymerisation of [Zn(salen2)] in this way would explain the low solubility of this compound. [Zn(salen1)] and [Zn(salen3)] were slightly soluble in deuterated solvents therefore their characterisation was not so problematic.

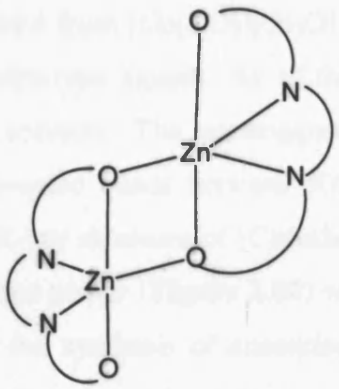


Figure 2.18.

[Zn(salen6)] was synthesised in dry THF to yield the desired compound as a yellow powder in 48% yield. In contrast to [Zn(salen2)] and as has been stated before (section 2.1.2), some [Zn(salen)] derivatives are five coordinate with a molecule of solvent in the axial position (in a square base pyramid structure). One of the special characteristics of some salen complexes is their fluorescence. Almost all of the Zn derivatives, fluorous or non fluorous, present this characteristic. In the case of [Zn(salen6)] there is also another interesting property; the compound is a dimer in its anhydrous state (**Figure 2.19**).[39] This special structure (reported by S. Mizukami *et al.*) is accompanied by intramolecular π-π interactions which also determine their colour (blue crystals for the mononuclear and green for the dimer).[40] [Zn(salen7)] was also synthesised in dry THF under nitrogen from $ZnEt_2$ and the corresponding H_2salen-type ligand. The pure compound, isolated in 78% yield, was soluble in most organic solvents and was used in asymmetric catalysis (Chapter 4).

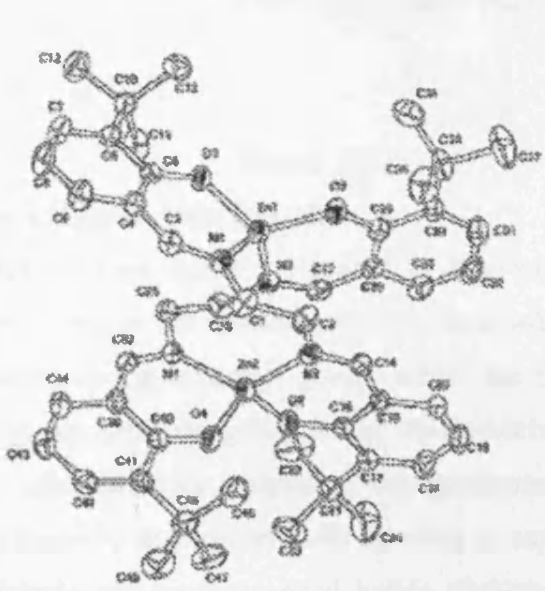


Figure 2.19.

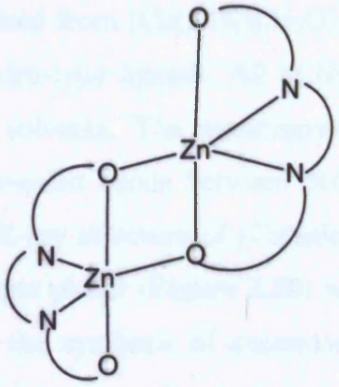


Figure 2.18.

[Zn(salen6)] was synthesised in dry THF to yield the desired compound as a yellow powder in 48% yield. In contrast to [Zn(salen2)] and as has been stated before (section 2.1.2), some [Zn(salen)] derivatives are five coordinate with a molecule of solvent in the axial position (in a square base pyramid structure). One of the special characteristics of some salen complexes is their fluorescence. Almost all of the Zn derivatives, fluorous or non fluorous, present this characteristic. In the case of [Zn(salen6)] there is also another interesting property; the compound is a dimer in its anhydrous state (**Figure 2.19**).[39] This special structure (reported by S. Mizukami *et al.*) is accompanied by intramolecular π-π interactions which also determine their colour (blue crystals for the mononuclear and green for the dimer).[40] [Zn(salen7)] was also synthesised in dry THF under nitrogen from $ZnEt_2$ and the corresponding H_2salen-type ligand. The pure compound, isolated in 78% yield, was soluble in most organic solvents and was used in asymmetric catalysis (Chapter 4).

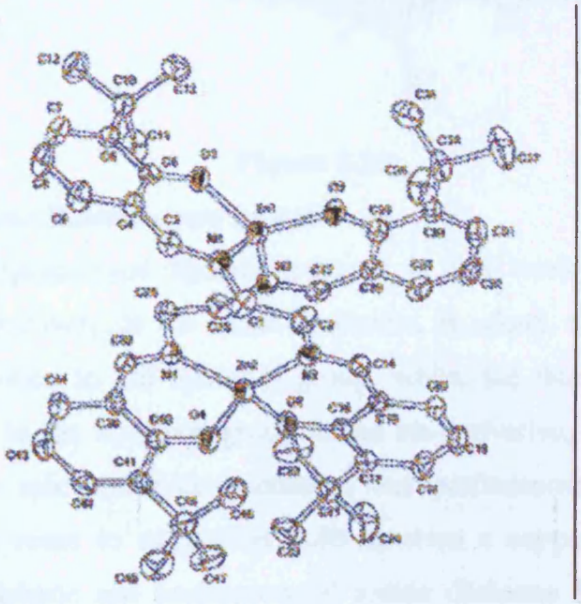


Figure 2.19.

The Cu(II) derivatives were synthesized from $[Cu(NO_3)_2.H_2O]$ in hot ethanol,[41] using NaOH to remove the hydrogen from the H_2salen-type ligands. All of the compounds were dark violet in colour and are soluble in organic solvents. The paramagnetism of Cu(II) salts made NMR spectrauninformative, but UV/vis revealed bands between 500 and 900 nm which is a typical value for Cu(II) compounds.[42] The X-ray structure of [Cu(salen3)] is reported in the literature[43] and revealed that the structure is square planar (**Figure 2.20**) with *trans* conformation. However, due to the low yields obtained for the synthesis of enaminodiones catalysed by the Cu salen complexes (see Chapter 4), the copper complexes were not studied further. [Cu(salen1)], [Cu(salen2)] and [Cu(salen3)] were obtained in good yields (73%, 83% and 49%).

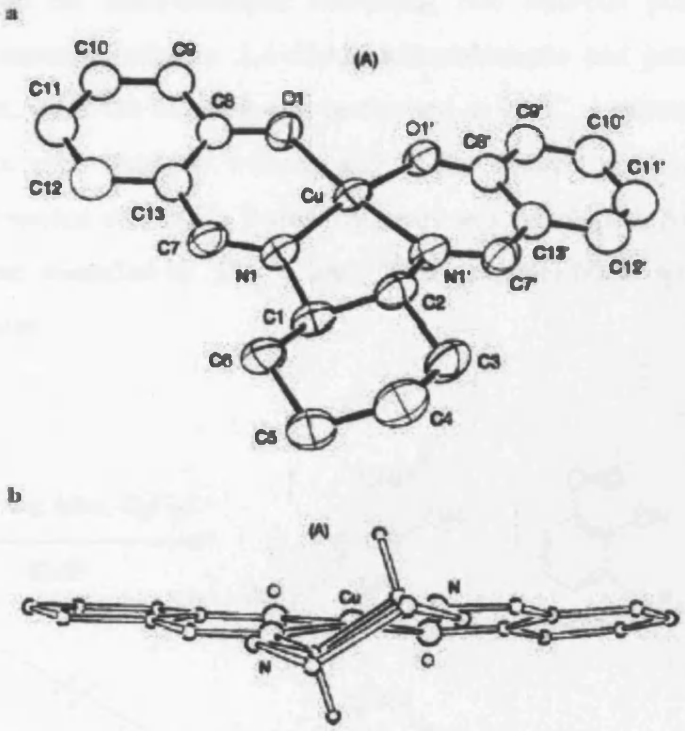
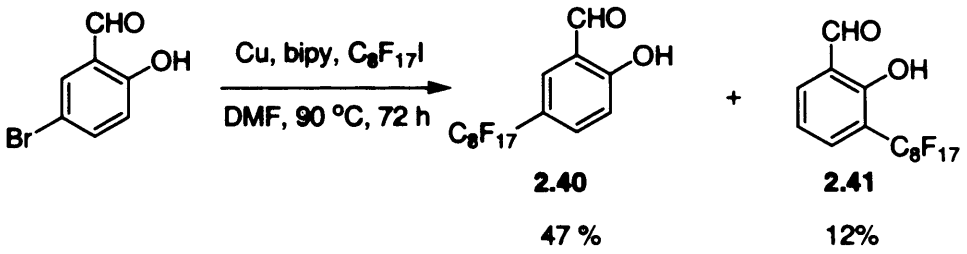


Figure 2.20

2.2.3 Synthesis of fluorous H_2salen-type ligands

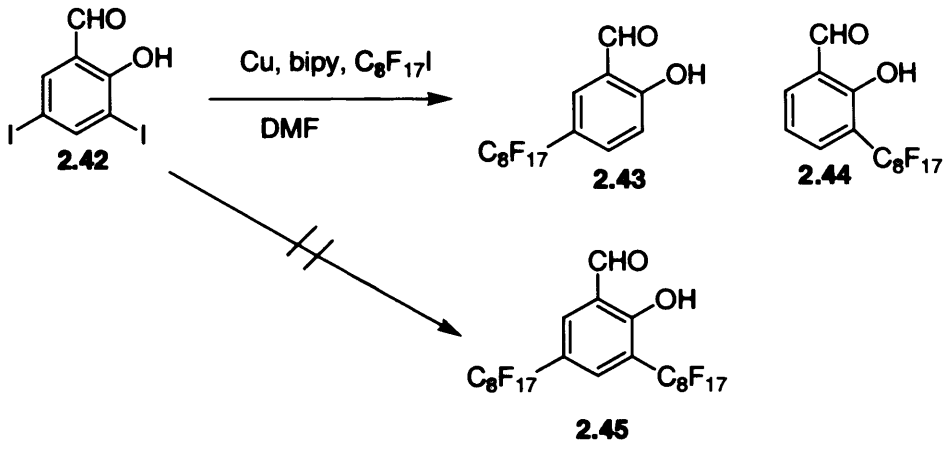
The first two fluorous H_2salen-type ligands prepared in this work contained one and two perfluorooctyl groups respectively. In the mono-derivative, H_2salen8, the perfluoroalkyl group is contained in the *para*-position to the hydroxyl group, whilst the fluorous ponytails are in the *ortho*- and *para*-positions to the hydroxyl group in the bis-derivative, H_2salen5 (**Scheme 2.29**). Pozzi had synthesised the salicylaldehyde containing one perfluorooctyl group *via* a two step synthesis.[32] An alternative route to compound **2.40** involves a copper-catalysed C-C coupling between 4-bromosalicylaldehyde and perfluorooctyl iodide (**Scheme 2.21**). The crude product

was obtained as a mixture of the 2- and 4-monosubstituted products and the desired product was obtained pure in 47 % yield after column chromatography.



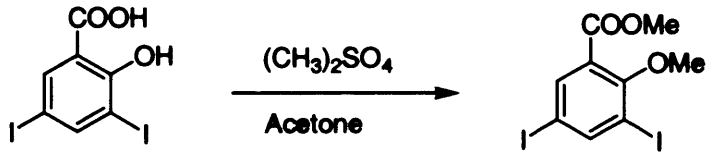
Scheme 2.21.

In the first attempt to synthesise the salicylaldehyde containing two fluorous ponytails, the copper-catalysed C-C coupling reaction between 2,4-diiodo-salicylaldehyde and perfluorooctyl iodide was investigated. However, when the reaction was performed at 90 °C, a mixture of the 2- and 4-mono-substituted products were obtained without any of the desired product (**Scheme 2.22**). Consequently, a modified version of Pozzi's 5-step synthesis was developed. At each step, the intermediates were isolated and identified by ^{1}H (^{13}C and ^{19}F, if possible) NMR spectroscopy, mass spectrometry and melting point.



Scheme 2.22.

In the first step both the carboxylic acid and the phenol are protected with a methyl group. This was because, in contrast with diiodophenols, methyl ethers are active for C-C coupling on the aromatic ring.[44] Dimethylsulphate was used as the methylating reagent and gave the pure product in 65% yield (**Scheme 2.23**).

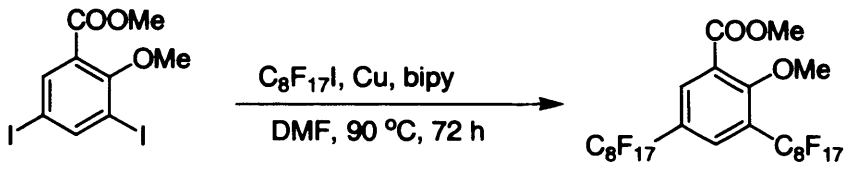


2.46

65%

Scheme 2.23.

The Cu coupling reaction, developed by McLoughlin and Thrower, was used to attach the perfluoroalkyl groups directly to the aromatic ring. Initially, the reaction was carried out at 120 °C using the same conditions as Pozzi, but a wide range of products were obtained, which were extremely difficult to separate by column chromatography.[45] When the temperature of the reaction was lowered to 90 °C and a catalytic amount of 2,2'- bipyridine (~ 5 mol%) was added, the desired product (**2.47**) was obtained in a good yield (**Scheme 2.24**). The product was purified by column chromatography in order to remove the mono-perfluoroalkylated byproducts.

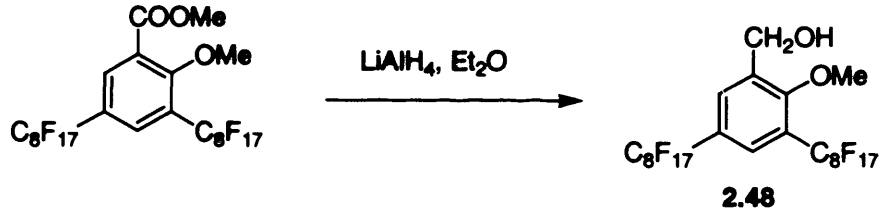


2.47

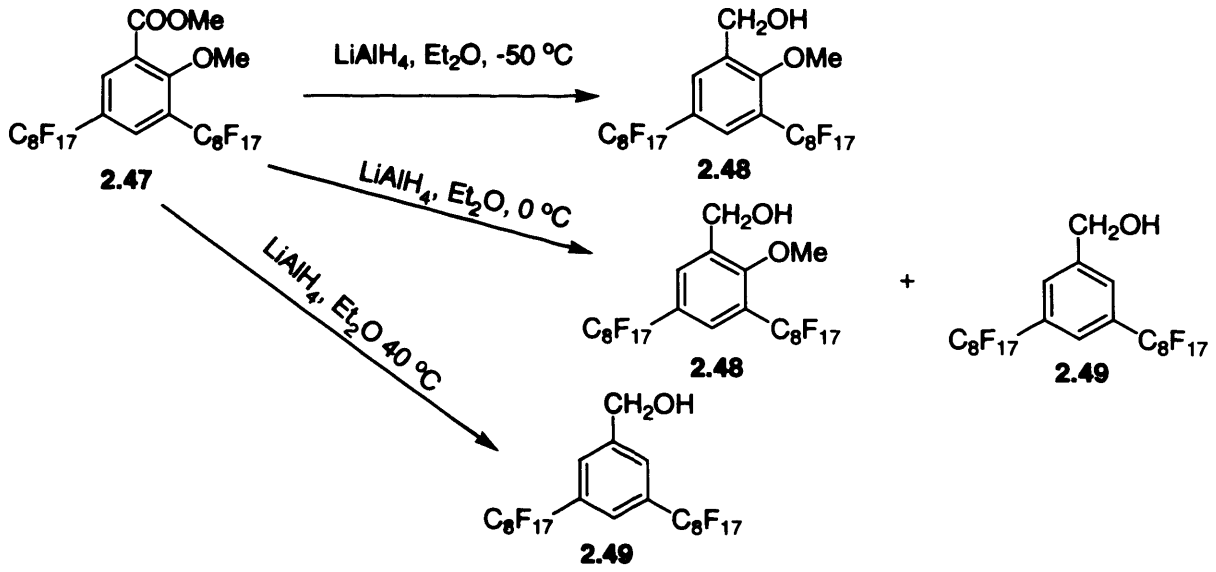
62%

Scheme 2.24.

The next step was the reduction of the ester to the alcohol, but this was more difficult. Previous work had shown that it was not possible to synthesise the aldehyde directly by using the reducing agents, diisopropylbutylaluminium hydride or tributyltin hydride. Hence, the reaction was carried out under nitrogen with $LiAlH_4$ at 0 °C following the reaction conditions developed by Pozzi (**Scheme 2.25**).[44] However, a mixture of two products were formed that were extremely difficult to separate (**Scheme 2.26**). By increasing the temperature to 40 °C, only the byproduct was formed and it has been characterised fully in the literature.[46] The problem was solved by carrying out the reaction at –50 °C for 8 h to give the pure product in 75 % yield (**Scheme 2.26**).

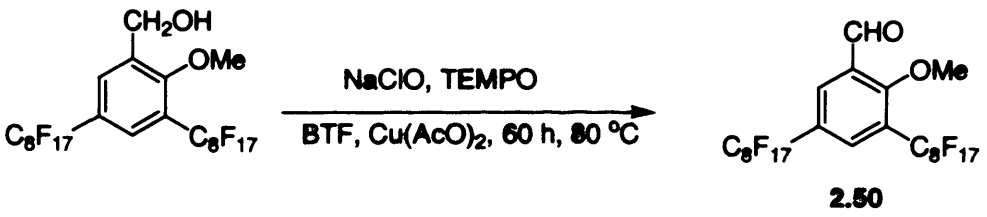


Scheme 2.25.



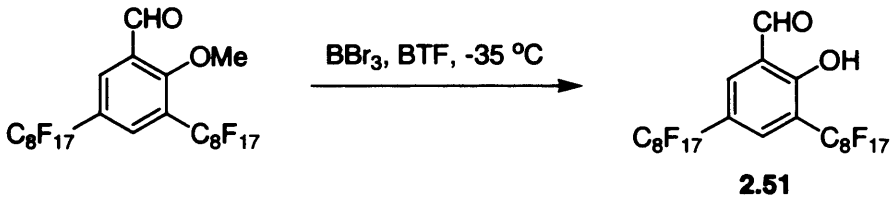
Scheme 2.26.

The oxidation of the benzylalcohol to the benzaldehyde was also troublesome due to the low solubility of the fluorous substrate in halogenated organic solvents. This problem was solved by using benzotrifluoride instead of CH_2Cl_2.[47] When Pozzi used MnO_2 he initially obtained a 50% yield, but the reaction was improved by carrying it out in a biphasic system (water/benzotrifluoride) using NaOCl as the oxidant and radical TEMPO (2,2,6,6-tetramethyl-1-piperydinyloxy) as the co-oxidant at 0 °C. This method was optimized by the addition of a catalytic amount (5 mol%) of $Cu(AcO)_2$, since the $Cu(AcO)_2$/ TEMPO system has been studied before in biphasic systems.[48] The temperature was also raised to 80 °C in order to enhance mixing and the product was obtained in 79% yield.



Scheme 2.27.

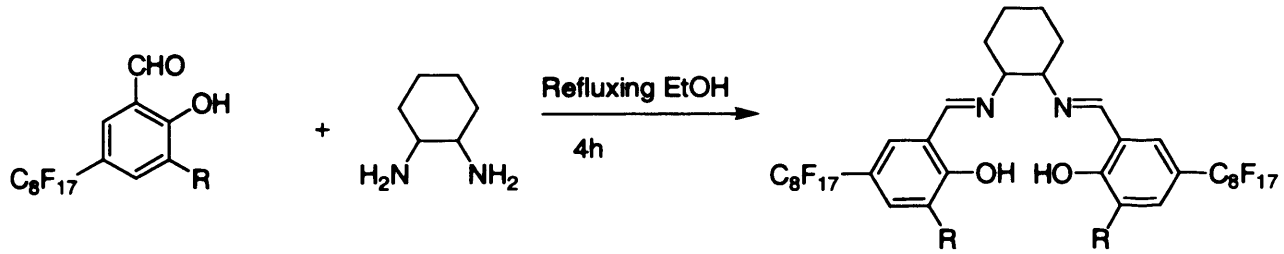
The deprotection of aryl methoxy groups with BBr_3 has been widely studied.[49] These reactions do not occur in donor solvents, such as THF or diethylether, and the reaction is slowed down by electron withdrawing substituents. Pozzi reported that benzotrifluoride was used as the solvent for this reaction at –78 °C, but at this temperature benzotrifluoride is a solid. Hence, DCM was used as the solvent but a strange mixture of products that were too difficult to separate was obtained. Finally, the problem was solved by carrying out the reaction at –35 °C in benzotrifluoride, allowing the reaction mixture to warm to room temperature and stirring at that temperature for eight hours. Although, the electron withdrawing substituents, the fluorous ponytails, made the reaction slower, the product could still be isolated in good purity after column chromatography in 75% yield (**Scheme 2.28**).



2.51

Scheme 2.28.

Finally, the fluorous-derivatised H_2salen ligands were synthesised by the conventional procedure. The perfluoroalkylated salicylaldehydes were dissolved in hot ethanol and the diamine was added drop-wise. After removal of the solvent, the crude product was recrystallised from hexane to give a yellow powder (**Scheme 2.29**). Good yields were obtained for H_2salen8 (73%), while lower yields were obtained for H_2salen5 (48%).

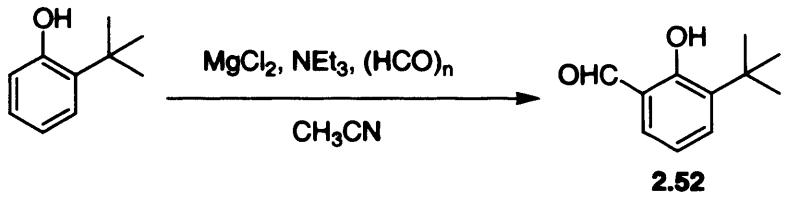


R: H H_2Salen8
R: C_8F_{17} H_2Salen5

Scheme 2.29.

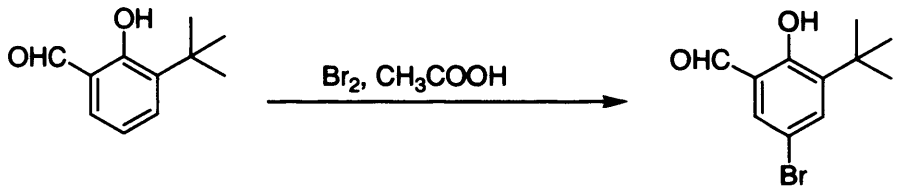
H_2salen9 (**Scheme 2.33**) was synthesised from 2-*tert*-butylphenol and contains one perfluorooctyl group in the para-position to the hydroxyl group. Although Pozzi[44] performed an

ortho-formylation using Cassiraghi's method ($SnCl_4$) here Hoffsløkken's method was used to obtain the pure product without any purification steps. 4-Bromo-2-*tert*-butyl-salicylaldehyde was prepared using bromine in acetic acid giving the pure product in 78% yield with no evidence for starting material or any byproducts (**Scheme 2.31**).



2.52

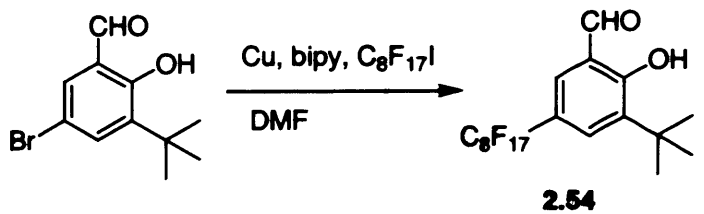
Scheme 2.30.



2.53

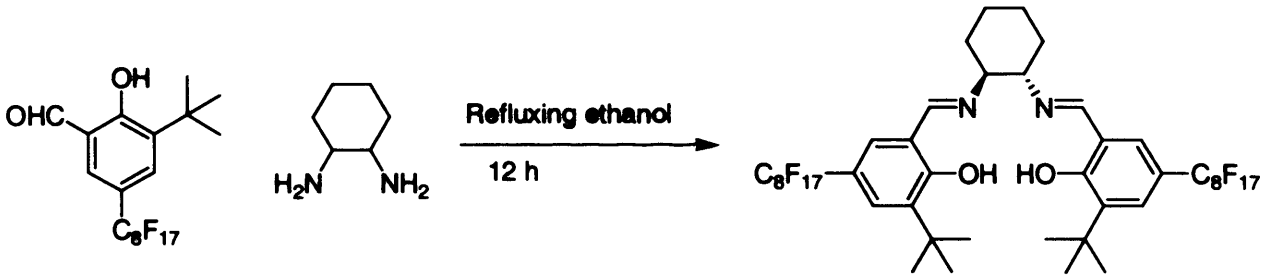
Scheme 2.31.

The penultimate step was the copper-catalysed C-C coupling reaction. Although Pozzi maintains that the reaction temperature should be 125 °C, none of the product was observed if the reaction was performed at this temperature and instead a large number of byproducts were obtained. When the reaction was performed at 90 °C, the product was obtained in 65 % yield after purification by column chromatography (**Scheme 2.32**). Finally, H_2salen9 was synthesised by refluxing the perfluoroalkylated salicylaldehyde and the diamine together in ethanol to give the pure product (**Scheme 2.33**).



2.54

Scheme 2.32.



Scheme 2.33.

Due to the moderate enantioselectivity that was obtained (chapter 4) with [Zn(salen9)] in the asymmetric addition of $ZnEt_2$ to benzaldehyde, it was decided to incorporate an additional spacer group between the fluorous ponytail and the aromatic ring. The first spacer group that was investigated was $-CH_2CH_2-$ (**Scheme 2.34**). The attempted synthesis involved a Pd-catalysed Heck[50] reaction of a perfluoroalkylated alkene with the functionalised aryl bromide (**2.55**). The Heck reaction was investigated with Herrmann's catalyst in DMF at 120 °C[51] and with $[Pd(OAc)_2]$ in DMF at 90 °C,[52] but the product was not formed in either of the reactions.

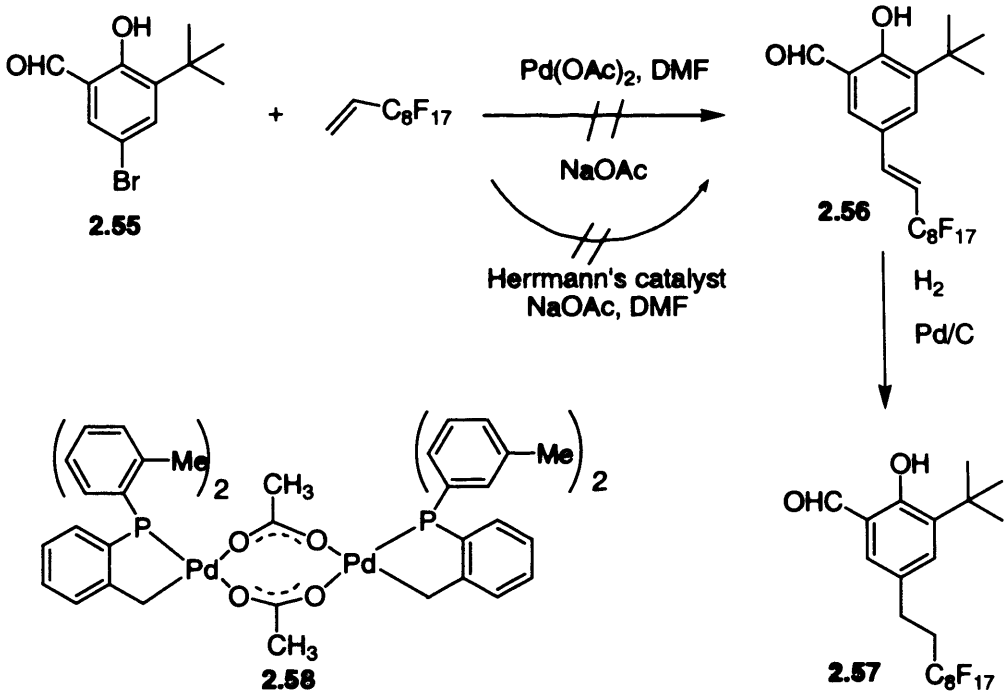


Figure 2.21 **Scheme 2.34.**

The second spacer group that was investigated was $SiMe_2C_2H_4C_6F_{13}$ (**Figure 2.22**) and is similar to the H_2salen-type ligand that was prepared by Bannwarth (H_2salen11, Section 2.1.4), but it contains only 2 perfluorohexyl units in order to offer catalysts with better solubilities in conventional organic media.

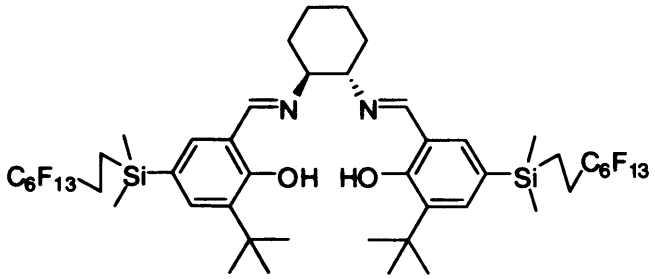
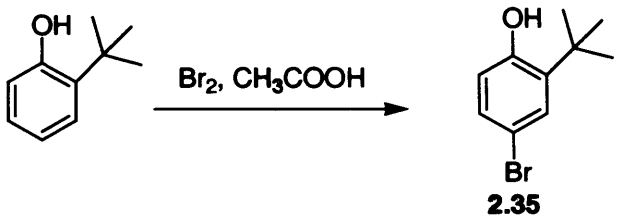


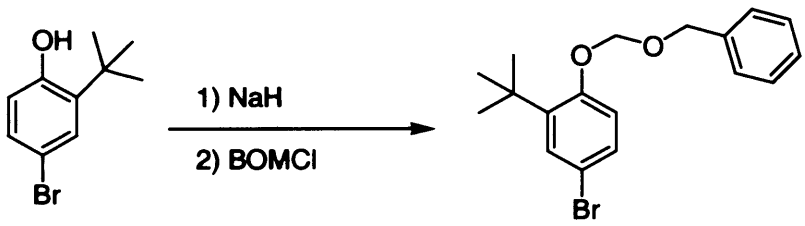
Figure 2.22.

Bromination of 2-*tert*-butylphenol under standard reaction conditions in acetic acid gave only the pure *para*- product, with no traces of the *ortho*- or *meta*- derivatised products. The phenol group was first protected with benzyloxymethoxychloride (BOMCl) as used by Bannwarth *et al.*[28] (**Scheme 2.15**). The hydroxy group was deprotonated with NaH at 0 °C for 5 h, after which BOMCl was added with stirring. At room temperature lower yields and an impure product was obtained; however, when the reaction temperature was increased to reflux, the pure product was obtained and easily recrystallised from hexane.



2.35

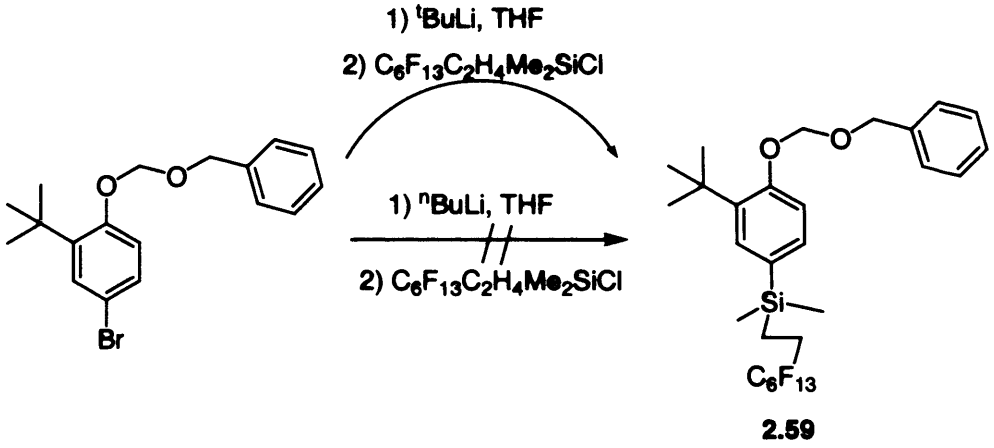
Scheme 2.35.



2.36

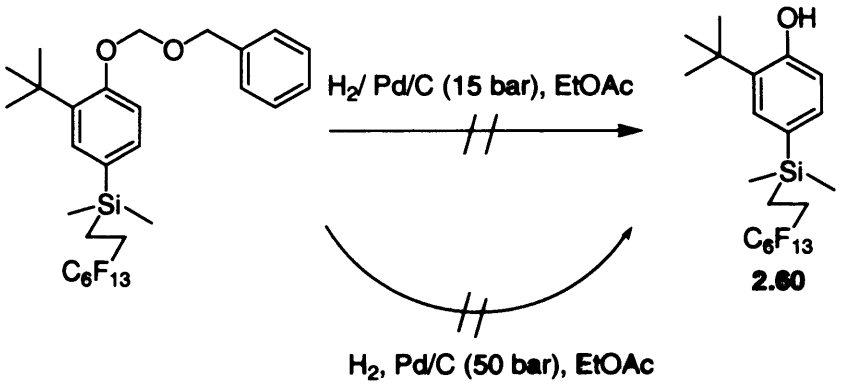
Scheme 2.36.

After lithiating the aryl bromide with ^{n}BuLi in THF at -78 °C, the fluorous silyl chloride was added to introduce the fluorous ponytail. Unfortunately, none of the desired product was obtained and only **2.36** was isolated. However, when the lithiation was performed with ^{t}BuLi, the results were much better and the product (**2.59**) was easily isolated by recrystallisation from petroleum ether.



Scheme 2.37.

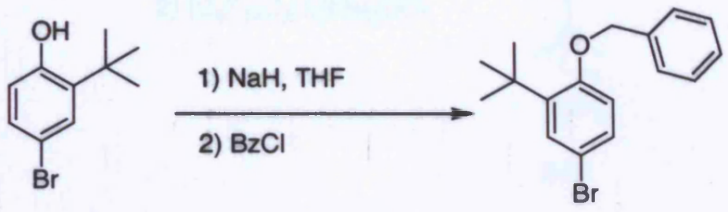
In the deprotection step, a Pd-catalysed hydrogenation was carried out to yield the phenol (**2.60**). The reaction was first performed following Bannwarth's method for the tris(perfluoroalkylated) derivative, using Et_2O, AcOEt and AcOH as solvents. When this solvent system was used with 15 bar of pressure there was cleavage of the C-Si bond to yield 2-*tert*-butylphenol, presumably because of the acetic acid. The reaction was then performed at 15 bar of pressure but using just AcOEt as the solvent, but no reaction was observed. With this solvent system a higher pressure was also tested (50 bar), but unfortunately, at this pressure the compound decomposed to 2-*tert*-butylphenol.



Scheme 2.38.

Due to these problems with the deprotection step, an alternative protecting group, benzyl, was investigated. First, the hydroxy group was deprotonated by reacting with NaH at 0 °C for 5 h, followed by the addition of benzyl chloride. After refluxing the reaction mixture, the pure product was obtained and easily recrystallised from hexane. Some of the crystals obtained were

suitable for X-ray diffraction and the structure is shown in **Figure 2.23**. Crystallographic parameters and structural data for (**2.61**) are given in Appendix I.



2.61

Scheme 2.39

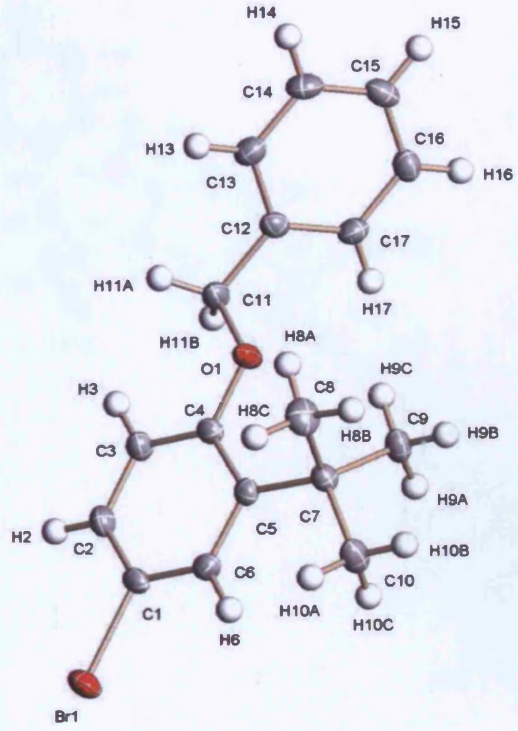
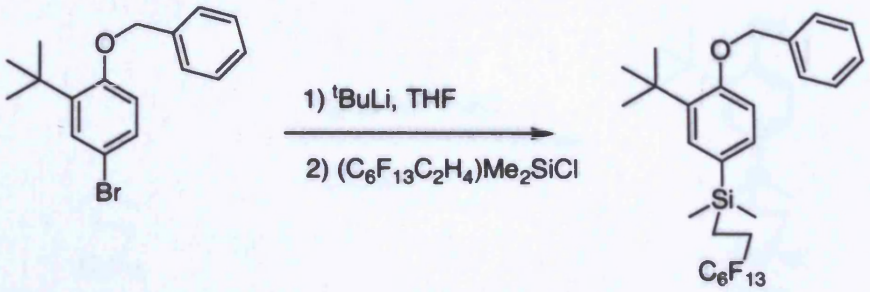


Figure 2.23.

The next step was, to attach the silyl fluorous ponytail. Again ^{n}BuLi did not work in this reaction, but when ^{t}BuLi was used good yields were obtained and the product was recrystallised from petroleum ether. Some of the crystals were suitable for X-ray analysis (**Figure 2.24**). Crystallographic parameters and structural data are available in Appendix II.



2.62

Scheme 2.40.

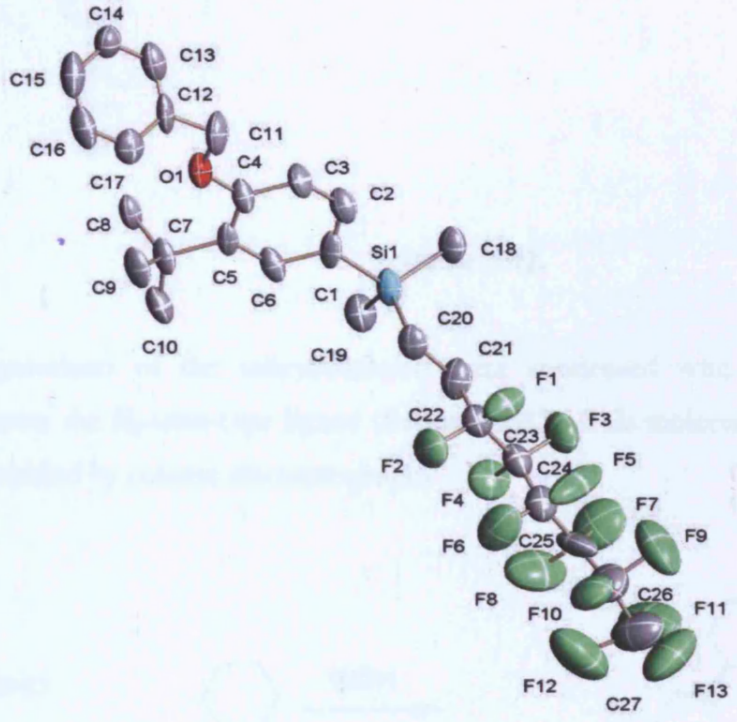
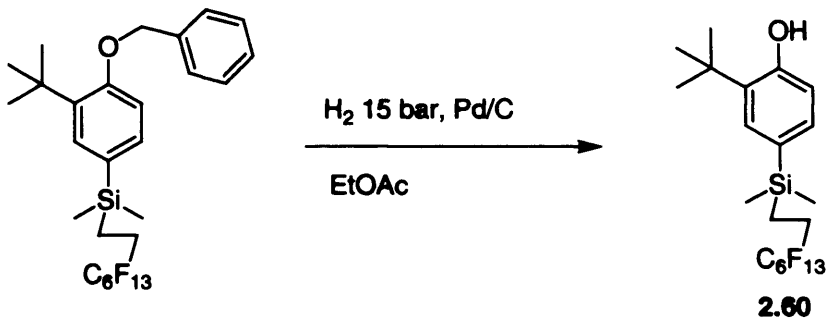


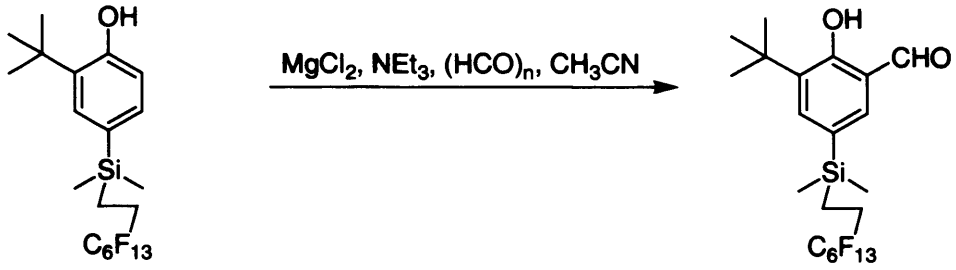
Figure 2.24.

The deprotection step was performed in EtOAc at room temperature for 72 hours under 15 bar of H_2 pressure. Total conversion was obtained and the desired product was obtained in 93 % yield without any need for recrystallisation. In the last step to obtain the salicylaldehyde, the *ortho*-formylation of the fluorous phenol derivative was performed in acetonitrile, which is a fluorophobic solvent, however no solubility problems were observed. A neutral aqueous work up was used instead of the conventional acidic work up in order to avoid C-Si cleavage. The product was then purified by column chromatography.



2.60

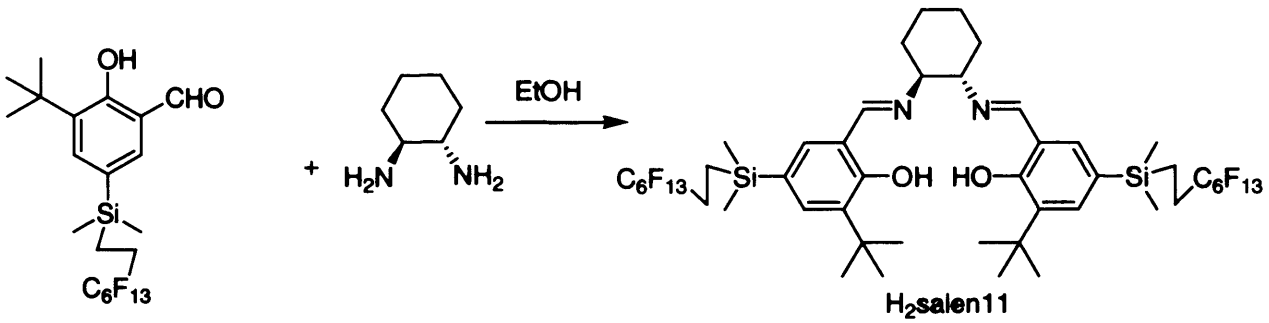
Scheme 2.41.



2.63

Scheme 2.42.

Finally, two equivalents of the salicylaldehyde were condensed with one equivalent of the diamine to generate the H_2salen-type ligand (**Scheme 2.43**). This molecule was obtained impure, but was easily purified by column chromatography.



H_2salen11

Scheme 2.43.

In conclusion, four different fluorous H_2salen-type ligands have been synthesised. The fluorine contents vary from 40 to 65 % (**Table 2.5**) and the different structures will define the properties of the different catalysts (e.g. solubility). These properties will be shown to be important for their catalytic applications.

Salen	R_1	R_2	Fluorine (%)
Salen5	$-C_8F_{17}$	$-C_8F_{17}$	65
Salen8	$-C_8F_{17}$	-H	56
Salen9	$-C_8F_{17}$	$-^tBu$	51
Salen11	$C_6F_{13}C_2H_4Me_2Si-$	$-^tBu$	40

Table 2.5.

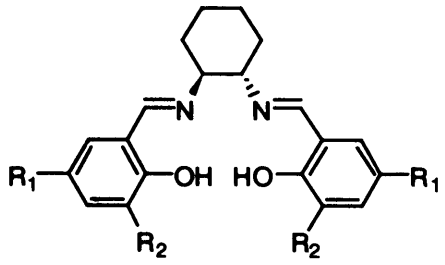


Figure 2.25.

2.2.4 Synthesis of fluorous salen coordination compounds

A small series of Zn(II) and Ni(II) complexes were synthesised from the fluorous H_2salen-type ligands. Following the general method for the synthesis of Zn(II) salen derivatives from $ZnEt_2$, the new perfluoroalkylated [Zn(salen5)] was prepared successfully. The product was obtained dry without any further purification (**Figure 2.26**). Although the percentage of fluorine in the molecule is 62%, [Zn(salen5)] is insoluble in fluorous solvents such as perfluoroalkanes (perfluorohexane and perfluoro-1,3-dimethylcyclohexane (PP3)) or partially fluorinated solvents such as benzotrifluoride, $CF_2ClCFCl_2$, trifluoroethanol as well as organic solvents. This strange property could possibly be due to the close proximity of the fluoroponytails and the metallic centre.

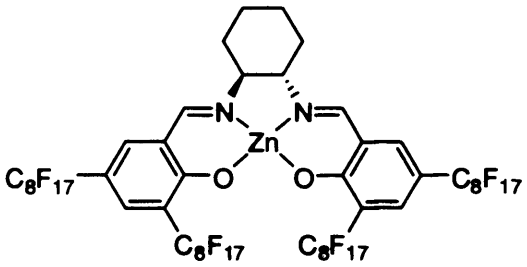
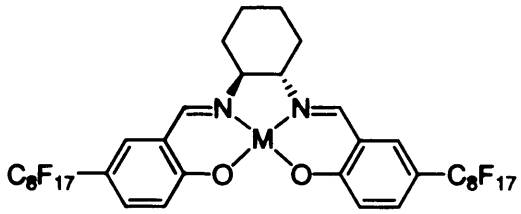


Figure 2.26.

[Zn(salen8)] was synthesised in dry THF under nitrogen. The product was then washed with ethanol, and resulted in a pale yellow powder. This powder was also insoluble in any organic solvents, fluorous solvents such as perfluoroalkanes and partially fluorinated solvents. The Ni(II) (**Figure 2.27**) derivative was synthesised from [Ni(acetate)$_2$.4H$_2$O] and H_2salen8 in ethanol, but was more soluble than the Zn(II) derivative, making the characterisation of the Zn(II) derivative

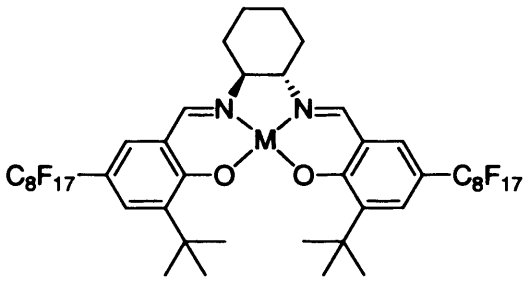
more difficult. [Ni(salen8)] could be characterised by ^{1}H, ^{19}F NMR, mass and IR, however, no NMR or mass spectra could be obtained of [Zn(salen8)] due to its low solubility.



M= Ni, Zn

Figure 2.27.

The synthesis of [Zn(salen9)] was also performed in dry THF under nitrogen. After refluxing the mixture for 16 hours the solvent was removed and the product was recrystallised from hexane to yield a pale yellow powder. However, this time the product was soluble in some organic solvents like ethanol (and partially soluble in other organic solvents like ether, $CHCl_3$, CH_2Cl_2 and hexane). The Ni(II) derivative was again synthesised from [Ni(acetate)$_2$.4H$_2$O] and the corresponding H_2salen9 in refluxing ethanol to yield the pure product as an orange powder. This product was soluble in most organic solvents and some of its crystals were suitable for X-ray diffraction (**Figure 2.29**). Crystallographic parameters and structural data are available in Appendix II.



M= Ni, Zn

Figure 2.28.

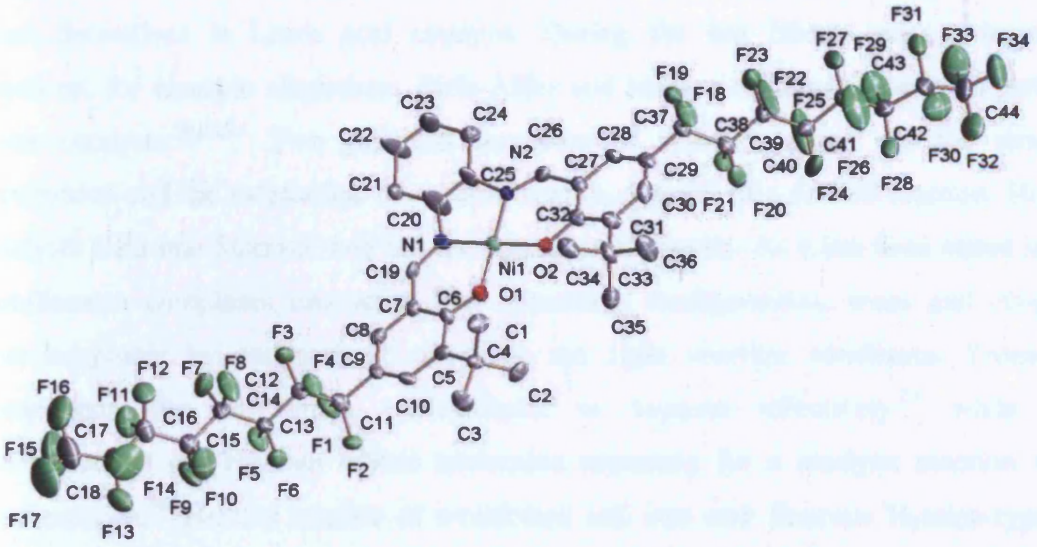


Figure 2.29.

Finally, Ni(II) and Zn(II) complexes were synthesised from H_2salen11. For the Zn(II) complex the reaction was performed in dry THF under nitrogen. After removing the solvent the result was a pale yellow powder which was recrystallised from chloroform. This product was partially soluble in chloroform, THF, and ether and insoluble in other organic solvents. The Ni(II) derivative was also synthesised, using [Ni(acetate)$_2$.4H_2O] as described previously. The product obtained was recrystallised from acetonitrile to yield an orange powder which was soluble in most organic solvents. These complexes were characterised by ^{1}H and ^{19}F NMR, mass and IR (see chapter 6).

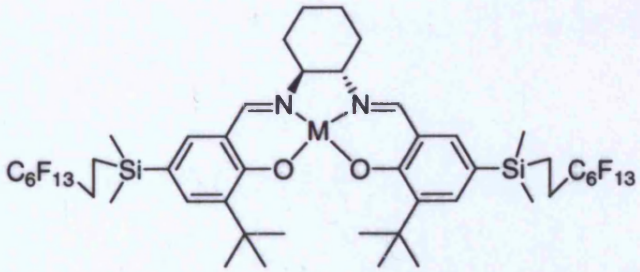


Figure 2.30.

2.3 Conclusions

In this chapter, the concept of Schiff bases and H_2salen-type ligands have been described. These ligands are versatile and their applications in catalysis grow every year. This adaptability is based on the multiple conformations and configurations that a metallosalen complex can adopt. Metal

complexes of almost every group has been studied. Particularly interesting is the use of metal salen derivatives in Lewis acid catalysis. During the last fifteen years a large number of reactions, for example alkylations, Diels-Alder and Michael additions have been performed using these catalysts.[16,23,24] Two principal functions of chiral catalysts are the strict molecular recognition and the satisfaction of stereoelectronic demand of a desired reaction. However, most catalysts fulfil one function well but the other less efficiently. As it has been stated in this chapter metallosalen complexes can adopt two interesting configurations, *trans* and *cis*-β, which are interchangeable by appropriately choosing the right reaction conditions. *Trans*-metallosalen compounds can distinguish enantio-faces or toposes effectively,[23] while some *cis*-β configurations can regulate orbital interaction necessary for a catalytic reaction with different configuration.[16] Here, a number of established and one new fluorous H_2salen-type ligand have been synthesised, along with a range of fluorous and non-fluorous Lewis acid salen coordination complexes. In this area old and new fluorous salen derivatives have an important role to play as recyclable asymmetric catalysts, as has already been demonstrated since the first work of Pozzi in 1999.[26] The applications of both the fluorous and non-fluorous metallosalen complexes as Lewis acid catalysts will be the issue of the next chapters.

2.3 References

1 H. Schiff, *Ann. Suppl.*, 1864, **3**, 343.

2 T. Katsuki, *Synlett,* 2003, 281.

3 E. G. Samsel, K. Srinivasan, J. K. Kochi, *J. Am. Chem. Soc.*, 1985, **107**, 7606.

4 T. Tsumaki, *Bull. Chem. Soc. Jpn.*, 1938, **13**, 252.

5 A. Nakamura, A. Konishi, Y. Tatsuno, S. Otsuka. *J. Am. Chem. Soc.*, 1978, **100**, 3443.

6 K. Nakajima, M. Kojima, J. Fujita, *Chem Lett.*, 1986, 1483.

7 K. Srinivasan, P. Michaud, J. K. Kochi, *J. Am. Chem. Soc.*, 1986, **108**, 2309.

8 E. N. Jacobsen, *Catalytic Asymm. Synth.*, 1993, 159.

9 T. Katsuki, *Coord. Chem. Rev.*, 1995, **140**, 189.

10 M. Calligaris, G. Nardin, L. Randanaccio, *Coord. Chem. Rev.*, 1972, **7**, 385.

11 T. Katsuki, *Adv. Synth. Catal.*, 2002, **344**, 131.

12 W-H Leung, E. Y. Y. Chan, E. K. F. Chow, I. D. Williams, S-M Peng, *J. Chem. Soc., Dalton Trans.*, 1996, 1229.

13 Y. Shimazaki, F. Tani, K. Fukui, Y. Narauta, O. Yamauchi, *J. Am. Chem. Soc.*, 2003, **125**, 10512.

14 E. N. Jacobsen , *Acc. Chem. Res.*, 2000, **33**, 421.

15 M. Calligahris, G. Manzini, G. Nardin, L. Randaccio, *J. Chem. Soc., Dalton Trans.*, 1972, 543.

16 M. Nakamura, H. Okawa, T. Inazu, S. Kida. *Bull. Chem. Soc. Jpn.*, 1982, **55**, 2400.

17 Y. N. Belokon, B. Green, N. S. Ikonnikov, V. S. Larichev, B. V. Lokshin, M. A. Moskalenko, M. North, C. Orizu, A. S. Peregudov, G. I. Timofeeva, *Eur. J. Org. Chem.*, 2002, 2655.

18 B. Saito, T. Katsuki, *Tetrahedron Lett.*, 2001, **42**, 8333.

19 P. R. Woodman, N. W. Alcock, I. J. Munslow, C. J. Sanders, P. Scott, *J. Chem. Soc., Dalton Trans.*, 2000, 3340.

20 F. Corazza, E. Solari, C. Floriani, A. Chiesi-Villa, C. Guastini, *J. Chem. Soc., Dalton Trans.*, 1996, 1335.

21 A. L. Singer, D. A. Atwood, *Inorg. Chim. Acta.* 1998, **277**, 157.

22 Y. N. Belokon, S. Caveda-Cepas, B. Green, N. S. Ikonnikov, V. N. Khrustalev, V. S. Laritchev, M. Tassinazzo, G. I. Timofeeva, L. V. Yashkina, *J. Am. Chem. Soc.*, 1999, **121**, 3968.

23 M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.*, 1998, **120**, 5315.

24 E. F. DiMauro, M. C. Kozlowski, *Organometallics*, 2002, **21**, 1454.

25 P. G. Cozzi, *Angew. Chem., Int. Ed.*, 2003, **42**, 2895.

26 G. Pozzi, M. Cavazzini, F. Cinato, F. Montanari, S. Quici, *Eur. J. Org. Chem.*, 1999, 1947.

27 G. Casiraghi, G. Casnati, M. Cornia, A. Pochini, G. Puglia, G. Sartori, R. Ungaro, *J. Chem. Soc., Perkin Trans.*, 1978, 318.

28 V. Andrushko, D. Schwim, C. C. Tzschuske, F. Michalek, J. Horn, C. Mössner, W. Bannwarth, *Helv. Chim. Acta*, 2005, **88**, 936.

29 Y. Nakamura, S. Takeuchi, Y. Ohgo, D. P. Curran, *Tetrahedron Lett.*, 2000, **41**, 57.

29 E. T. G. Cavalheiro, F. C. D. Lemos, J. Z. Schpector, E. R. Dockal. *Thermochim. Acta.* 2001, **370**, 129.

31 N. U. Hofsløkken, Lars Skkatebøl, *Acta Chem. Scandinavica*, 1999, **53**, 258.

32 G. Casiraghi, G. Casnati, M. Cornia, A. Pochini, G. Puglia, G. Sartori, R. Ungaro, *J. Chem. Soc., Perkin Trans.*, 1978, 318.

33 S. Gambarotta, F. Ursom, C. Floriani, A. Chiesi, C. Guastini, *Inorg. Chem.* 1983, **22**, 3966.

34 W. W. Fee, J. D. Pulsford, P. D. Vowles, *Aust. J. Chem.* 1973, **26**, 675.

35 J. Wang, F-L Bei, X-Y. Xu, X-J. Janj, X. Wang, *J. Chem Crystallography*, 2003, **33**, 845.

36 A. L. Singer, D. A. Atwood, *Inorg. Chim. Acta.* 1998, **277**, 157.

37 P. G. Cozzi, *Angew. Chem. Int. Ed.*, 2003, **42**, 2895.

38 L. Sacconi, M. Ciampolini, G. P. Speroni, *J. Am. Chem. Soc.*, 1965, **87**, 3102.

39 S. Mizukami, H. Houjou, Y. Nagawa, M. Kanesato, *Chem. Commun.*, 2003, 1148.

40 S. Mizukami, H. Houjou, K. Sugaya, E. Koyama, H. Tokuhisa, T. Sasaki, M. Kanesato, *Chem. Mater.*, **17**, 50.

41 S. Bunce, R. J. Cross, L. J. Farrugia, *Polyhedron*, 1998, **17**, 4179.

42 F. A. Cotton, G. Wilkinson, *Advanced Inorganic Chemistry*, Fifth Ed., 1988, 770.

43 K. Bernard., S. Leppard, A. Robert, G. Commenges, F. Dahan, B. Meunier, Inorg. Chem., 1996, **35**, 387.

44 G. Pozzi, I. Colombani, M. Miglioli, F. Montanari, S. Quici, *J. Chem.* Soc., *Chem. Comm.*, 1997, 69.

45 V. C. R. McLoughlin, J. Thrower, *Tetrahedron*, 1969, **25**, 5921.

46 S. Colonna, N. Gaggero, F. Montanari, G. Pozzi, S. Quici, *Eur. J. Org. Chem.*, 2001, 181.

47 A. Ogawa, D. P. Curran, *J. Org. Chem.*, 1983, **48**, 1935.

48 M. Contel, C. Izuel, M. Laguna, P. R. Villuendas, P. J. Alonso, R. H. Fish, *Chem. A Eur. J.*, 2003, **9**, 4168.

49 S. Punna, S. Meuner, M. G. Finn, *Org. Lett.*, 2004, **6**, 2779.

50 W. Chen, L. Xu, J. Xiao, *Tetrahedron Lett.*, 2001, **42**, 4275.

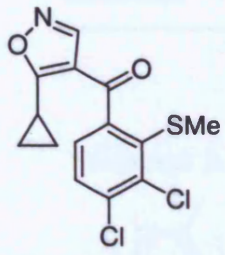
51 W. A. Herrmann, C. Brossmer, K. Öfele, C-P Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem. Int. Ed.*, 1995, **34**, 1844.

3 Synthesis of enaminodiones

3.1 Introduction

3.1.1 Non fluorous catalysts

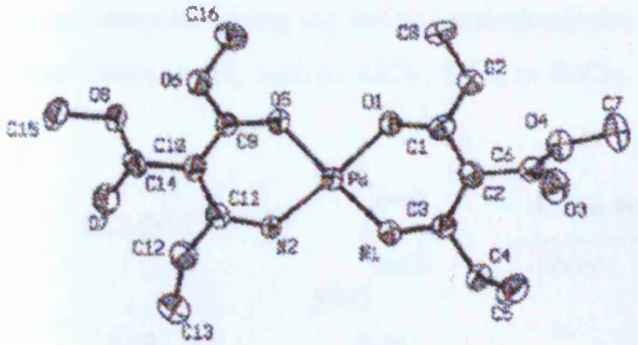
Many biologically interesting compounds originated either from nature or synthesis containing a substructure derived from unsaturated α-amino acids or cyanoformates. For instance, the herbicide derived from benzoylisoxazole (Figure 3.1),[1] contains such structural moieties. The reaction of nitriles with active methylene compounds, such as diketones and α-thioesters, has been studied; Tsuchihashi *et al.*[2] investigated the reaction of nitriles and methylthiomethyl sulfoxide in order to develop the synthesis of α-amino acids, α-keto thioesters and α-keto amides by modification of the enaminosulfoxide moiety. However, such a C-C bond forming reaction is limited to nitriles such as acetonitrile or benzonitrile.



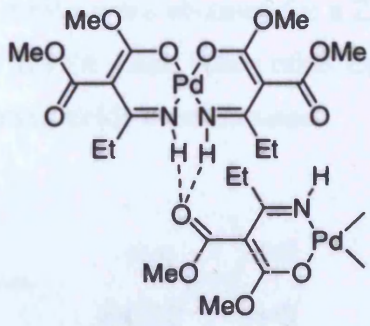
3.1

Figure 3.1.

Enaminodiones are not only useful as versatile intermediates for the synthesis of heterocycles but they also can be used as ligands for a range of metals.[3] Ni(II), Pd(II) and Cu(II) derivatives have been synthesised from their acetates. All of the structures are square planar and the metal is coordinated to a N and an O. There are also hydrogen-bonding interactions between the oxygen of the ester of one molecule and the hydrogen of the amine of another (**3.3**).



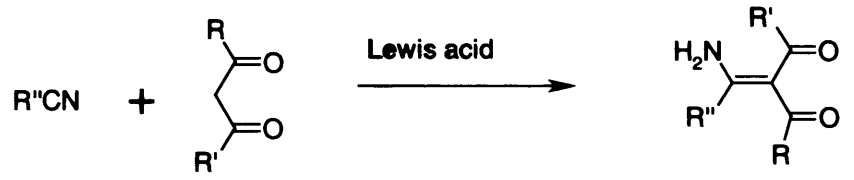
3.2



3.3

Figure 3.2.

The metal catalysed C-C bond forming reaction between a 1,3-dicarbonyl compound and a nitrile species is somewhat unique. The mechanism involves coordination of both species to the metal centre generating both the nucleophile and enhancing the electrophilicity of the nitrile. The reaction (**Scheme 3.1**) is very adaptable, tolerating a wide range of functionalities in both substrates. The unsaturated products are useful intermediates for the synthesis of aminoacids and heterocycles. Prior to the advent of a metal catalysed approach in the late seventies, the addition of protonated nucleophiles, such as 2,4-pentanedione, to Michael type electrophiles and nitriles was kinetically disfavoured. Although the reactions could be promoted by the addition of base, the chemoselectivity was quite poor.[4] However, upon coordination of the carbonyl substrate to a Lewis acidic metal centre, the nucleophilicity of the metallo–organic ring can be exploited (**Figure 3.3**).



Scheme 3.1.

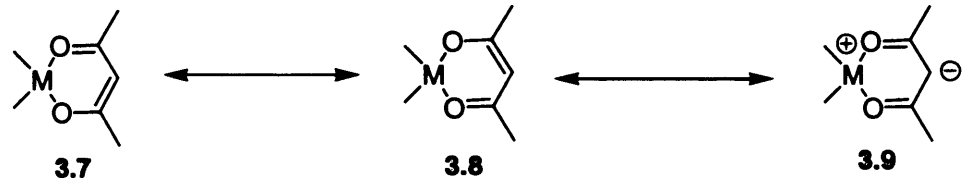
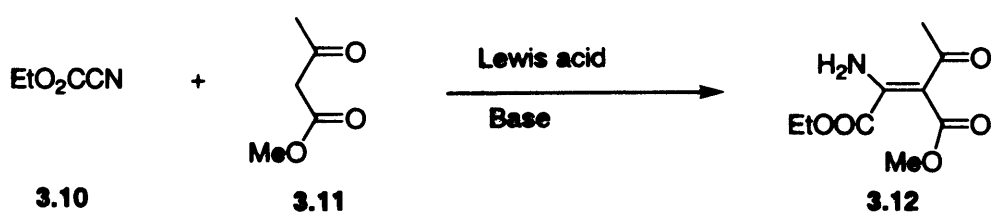


Figure 3.3.

One of the first approaches to the synthesis of enaminodiones involved the reaction of methylacetoacetate with ethylcyanoformate in the presence of a Lewis acid catalyst and a tertiary amine to yield the corresponding enaminodione (**Scheme 3.2**).[5] The use of this combination is based on the idea of activating the methylene group with a Lewis acid catalyst through chelation and generating a carbanion with a tertiary amine. The best results were obtained for a $ZnCl_2$ and NEt_3 combination giving the desired enaminodione product in 92% yield. When other Lewis acid catalysts were tested, such as $AlCl_3$, $TiCl_4$ or $SnCl_4$, much lower yields were obtained.

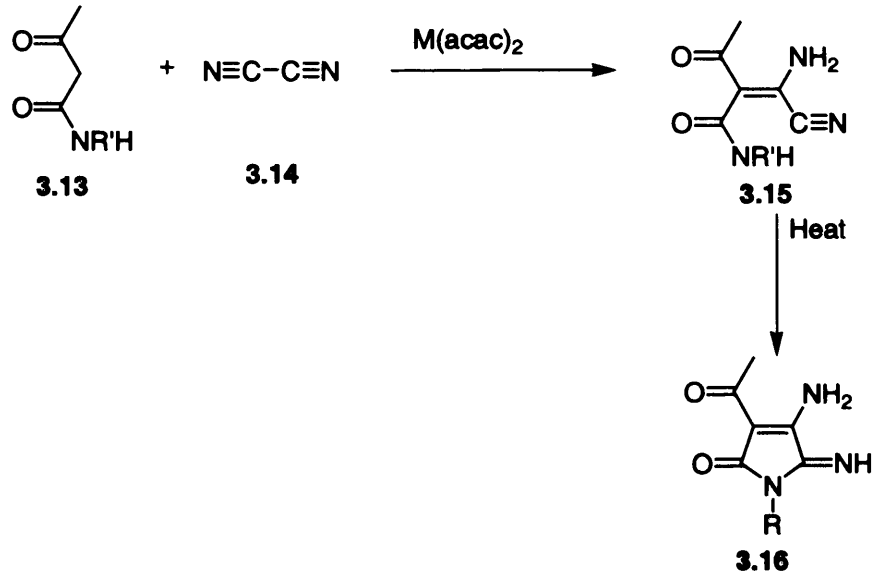


Scheme 3.2.

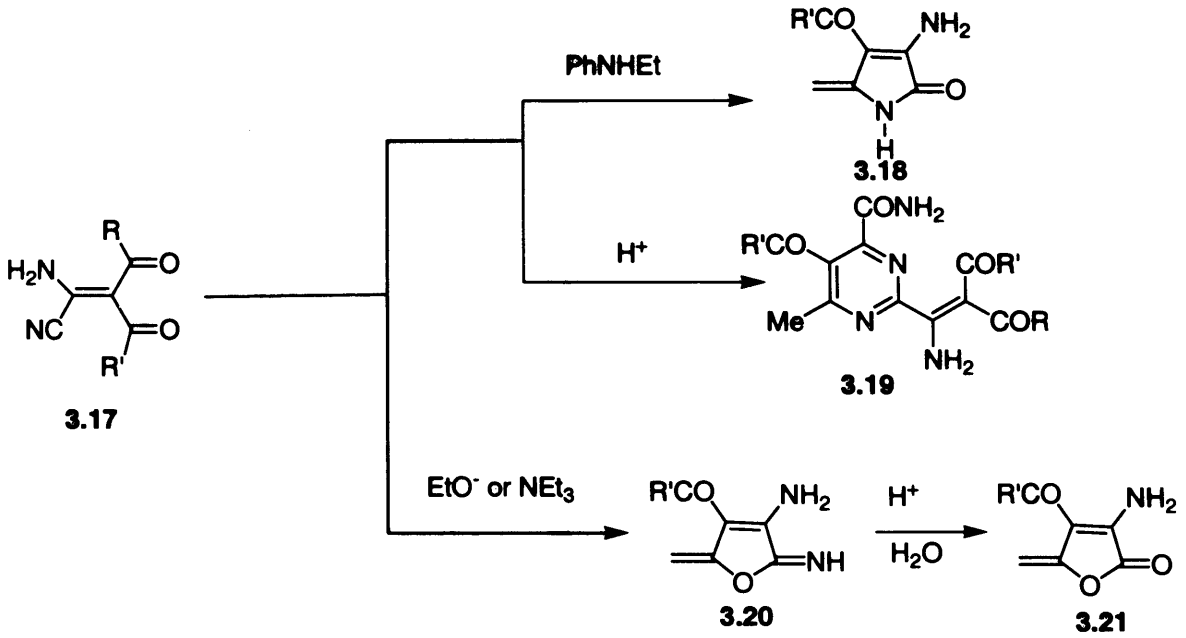
Lewis acid	Base	Solvent	Conditions	Yield (%)
$ZnCl_2$	NEt_3	DCM	Reflux 3 h	92
$ZnCl_2$	NEt_3	DCM	0 °C, 1 h→ RT, 6 h	85
$ZnCl_2$	Pyridine	DCM	RT, 6 h	20
$ZnCl_2$	n-BuLi	THF	0 °C, 30 min → RT, 24 h	42
$SnCl_4$	NEt_3	DCM	0 °C, 10 min → RT, 6 h	14
$TiCl_4$	NEt_3	DCM	0 °C, 10 min → RT, 6 h	12
$AlCl_3$	NEt_3	DCM	0 °C, 10 min → RT, 6 h	0

Table 3.1. Results obtained for the synthesis of enaminodiones using different Lewis acids and bases.

Corain *et al.*[6] performed the reaction of β-carbonyl enolate with cyanogen using $M(acac)_2$ (M= Cu, Zn). After synthesising the enaminodione, the product can easily be transformed into a pyrroline derivative. The same authors detail the transformation of an enaminodione into different heterocycles (**Scheme 3.3** and **Scheme 3.4**).[7] The treatment of the enaminodione product with acetic acid results in a pyrimidine derivative, whereas when it is treated with a weak base such as *N*-ethylaniline the result is a pyrroline derivative and when it is treated with a strong base such as EtO^- or NEt_3 the result is a furan derivative.

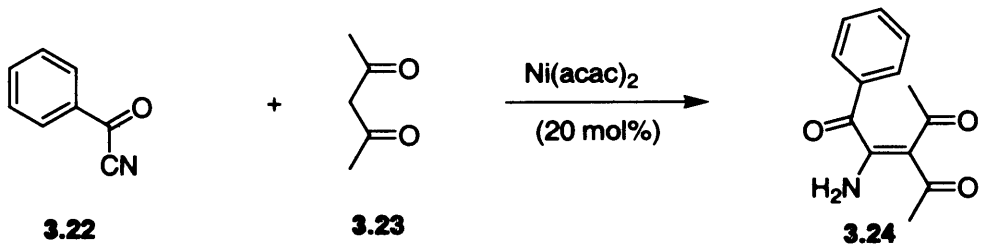


Scheme 3.3.



Scheme 3.4.

Corain *et al.*[8] claimed that the key step in these Lewis acid catalysed reactions is the coordination of the nitrile nitrogen to the metal. He demonstrated this by reacting 2,4-pentanedione with benzoylcyanide in the presence of 20 mol% of $Ni(acac)_2$ (**Scheme 3.5**). The success of this synthesis implies that the order of electrophilic character normally found in the CO and CN groups of benzoyl cyanide is reversed in the presence of the Lewis acid catalyst. It is most likely that the key step involves coordination of benzoyl cyanide to the metal through the nitrile nitrogen. This leads to the expected increase of the electrophilicity of the CN carbon atom, thereby favouring attack on it by the metal-coordinated β-diketonate nucleophile (**Scheme 3.5**). The results obtained were good (73- 87%).

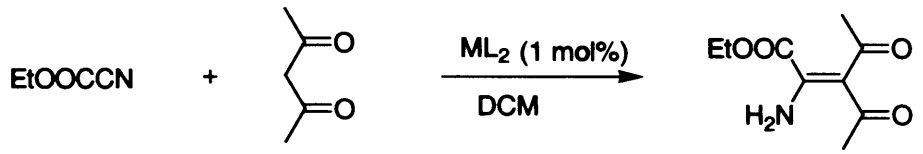


Scheme 3.5.

3.1.2 Synthesis of enaminodiones using fluorous catalysts.

As stated in Chapter 1, fluorous catalysts can be recycled and reused by a variety of methods. Throughout the earlier work on the synthesis of enaminodiones, no attempts had been made to

recover or reuse the catalyst. More recently, Stuart *et al.*[9] prepared a number of perfluoroalkylated β-diketonate metal complexes and evaluated their Lewis acid catalyst activity using the enaminodione reaction as a model reaction. The first experiments involved the reaction using 1 mol% catalyst with DCM as solvent under nitrogen for 24 hours using acetylacetone and ethylcyanoformate as substrates (**Tables 3.2**). The results clearly indicated that the complexes of hexafluoroacetylacetonate are poorer catalysts than either [Zn(acac)$_2$] or [Zn(acac2)$_2$], which both exhibited similar levels of activity. Unfortunately, the perfluoroheptyl derivative, [Zn(acac3)$_2$], was not very soluble in DCM, due to its high fluorine content, and consequently gave a poor yield.

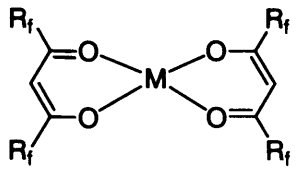


3.25 **3.26** **3.27**

Scheme 3.6.

acac	R_f	Yield for Ni catalyst (%)	Yield for Zn catalyst (%)
Hfacac	$-CF_3$	57	52
acac2	$-C_6F_{13}$	91	86
acac3	$-C_7F_{15}$	31	27

Table 3.2. Yields in the synthesis of enaminodiones using different fluorous acetylacetonates



3.28

Figure 3.4

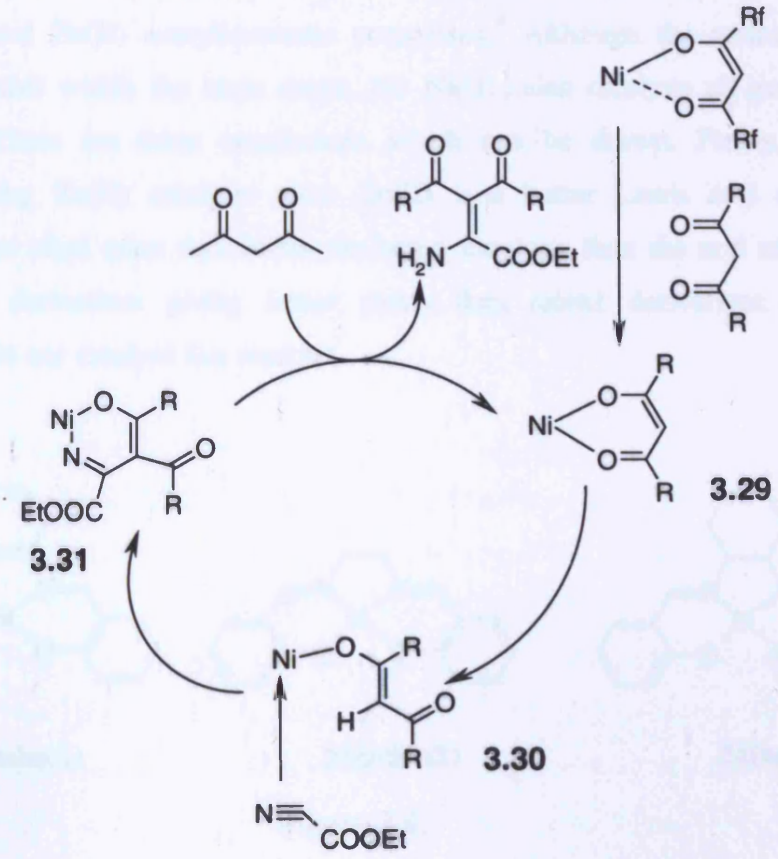
Better recoveries were obtained for the Ni(II) catalysts than those for the Zn(II) species (98% of the catalyst was recovered in the first run for Ni(II) but only 78% for Zn. The recovery of these catalysts represents a classic example of the use of Fluorous Solid Phase Extraction (FSPE) (see Chapter 1). At the end of the reaction, the solvent was removed, acetonitrile was added and the resulting solution passed through a column of fluorous silica allowing recovery of the organic product. Subsequently, diethyl ether was added allowing the catalyst to be recovered (**Figure 3.5**). As shown in **Table 3.3** there is a drop in the yield between the third and fifth run maybe due to a leaching into the organic phase of a mixed species Ni(acac)(R_f-acac).

Run	Yields (%)
1st	91
2nd	84
3rd	82
4th	67
5th	52

Table 3.3. Recycling results using Ni(Rfacac).

Figure 3.5

The mechanism of the reaction involves four steps: First, coordination of the catalyst to the diketone, forming a carbanion; second, coordination of ethyl cyanoformate; third, attack from the carbanion on the cyanoderivative and finally, dissociation of the enaminodione and coordination of 2,4-pentadione. The pKa of the ketoester or diketone is extremely important for the success of this reaction.However, the main problem was that although the catalyst could be recovered and reused, degradation of the catalyst in the fourth run caused a drop in yield (**Table 3.3**).



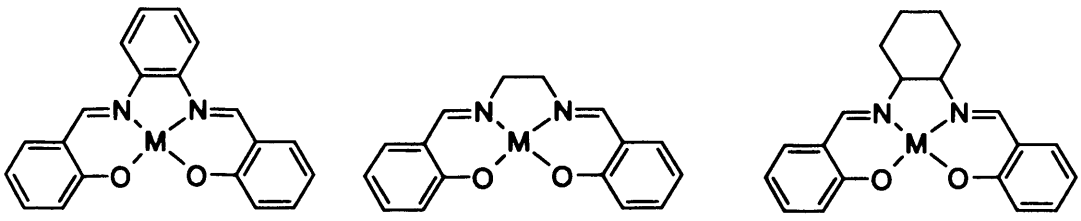
Scheme 3.7.

3.2 Results and Discussion

3.2.1 Catalysis using salen metal complexes

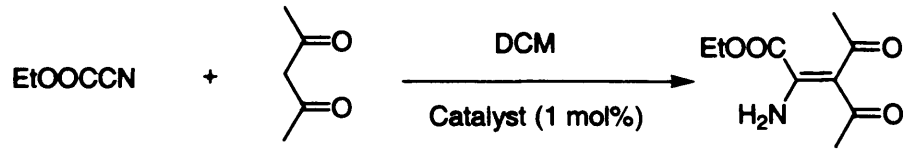
3.2.1.1 Results and Discussion

Since metal salen derivatives have never been used for this reaction, the reaction was initially screened using each of the Zn(II), Ni(II) and Cu(II) salen complexes (3-11). Before carrying out the catalysis, it was essential to ensure that each of the catalysts was completely anhydrous which was achieved by drying in the presence of a cold finger under vacuum. 2,4-Pentanedione was distilled and stored under nitrogen and ethylcyanoformate had to be stored under nitrogen. The reaction was carried out at room temperature for 24 h under nitrogen using dry dichloromethane as solvent with a 1 mol% loading of catalyst and the ratio of 2,4-pentanedione/ethylcyanoformate was 2/3. After removal of the solvent, ethylacetate was added, the mixture was filtered over Celite to eliminate the catalyst and the solvent was removed to yield a white powder which was weighed and analysed by ^{1}H NMR spectroscopy. Each reaction was carried out three times and the results are presented in **Table 3.4**. An additional reaction demonstrated that a catalyst is required as no product was obtained without any catalyst present. The results with the metal salen catalysts were compared with those for the Ni(II) and Zn(II) acetylacetonate complexes.[9] Although the series of Zn catalysts all produced yields within the same range, the Ni(II) salen catalysts all gave lower yields than $Ni(acac)_2$. There are three conclusions which can be drawn. Firstly, better yields were obtained using Zn(II) catalysts since Zn(II) is a better Lewis acid catalyst than Ni(II). Secondly, the alkyl salen derivatives are better catalysts than the aryl salen salts with salen2 and salen3 derivatives giving better yields than salen1 derivatives. Finally, the Cu(II) derivatives do not catalyse this reaction.



M(salen1) **M(salen2)** **M(salen3)**

Figure 3.6.



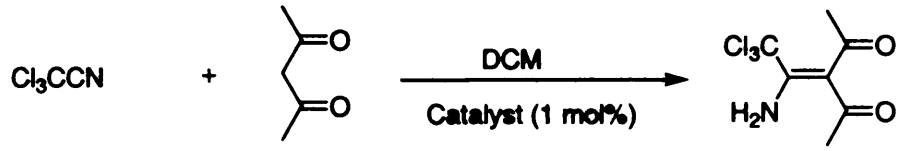
3.25 **3.26** **3.27**

Scheme 3.8.

Entry	Catalyst	Time (h)	Yield(%)
1	[Ni(acac)$_2$]	24	74
2	[Ni(salen1)]	24	<10
3	[Ni(salen2)]	24	25
4	[Ni(salen3)]	24	34
5	[Zn(acac)$_2$]	24	83
6	[Zn(salen1)]	24	70
7	[Zn(salen2)]	16	69
8	[Zn(salen2)]	24	93
9	[Zn(salen3)]	24	96
10	[Cu(salen1)]	24	0
11	[Cu(salen2)]	24	0
12	[Cu(salen3)]	24	0

Table 3.4. Results obtained for Msalen derivatives in the synthesis of enaminodiones.

When trichloroacetonitrile was used instead of ethylcyanoformate, similar yields were obtained, however, a reaction time of only three hours were necessary to achieve it, in comparison with the 24 hours for the reactions with ethyl cyanoformate (**Table 3.5**). Although both cyano derivatives have an electron withdrawing group (-COOEt or -CCl_3) close to the cyano group the trichloromethyl group is much more electron withdrawing than theester group. After the reaction was finished the residue obtained was recrystrallised from Ligroin to get a pale cream powder. This step is crucial because without this purification a brown tar was generated. Again, the results with the Zn(II) salen catalysts are very similar to the yields obtained with Zn(II) β- diketonate complexes.



3.32 **3.33** **3.34**

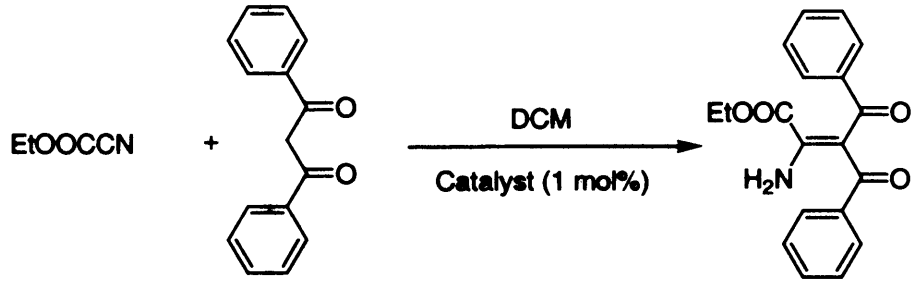
Scheme 3.9

Entry	Catalyst	Yield(%)
1	$[Ni(acac)_2]$	70[a]
2	$[Ni(C_6F_{13}COCHCOC_6F_{13})_2]$	66[a]
3	$[Zn(acac)_2]$	71[a]
4	$[Zn(C_6F_{13}COCHCOC_6F_{13})_2]$	75[a]
5	[Zn(salen1)]	79
6	[Zn(salen2)]	97
7	[Zn(salen3)]	93

[a] Values taken from reference 10

Table 3.5. Yields for different catalysts when Cl_3CCN was used as substrate.

When acetylacetone was substituted by dibenzoylmethane there was a dramatic decrease in the yields obtained (Table 3.6). In fact, only $[Zn(acac)_2]$ gave a high yield (86%) in this reaction. The coordination between dibenzoylmethane and the metal centre is much weaker due to both steric and electronic effects. The best yield amongst the salen catalysts tested was [Zn(salen2)] (34%).



3.35 **3.36** **3.37**

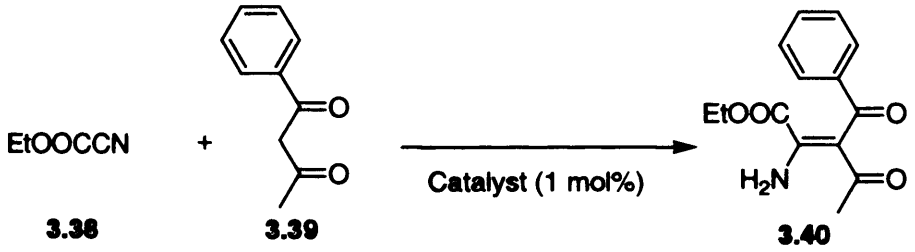
Scheme 3.10.

Entry	Catalyst	Yield(%)
1	$[Ni(acac)_2]$	34[a]
2	$[Ni(hfacac)_2]$	46[a]
3	$[Ni(C_6F_{13}COCHCOC_6F_{13})_2]$	20[a]
4	$[Zn(acac)_2]$	86[a]
5	$[Zn(hfacac)_2]$	64[a]
6	$[Zn(C_6F_{13}COCHCOC_6F_{13})_2]$	0[a]
7	[Zn(salen1)]	<10
8	[Zn(salen2)]	~34
9	[Zn(salen3)]	~20

[a] Values taken from reference 13

Table 3.6. Yields for different catalysts when dibenzoylmethane was used as substrate.

Benzoyl acetone was also used as a substrate (**Scheme 3.11**) and, not surprisingly, was more reactive than dibenzoylmethane. Here, the Zn salen complexes gave very similar catalytic activities to those for $[Zn(acac)_2]$ and $[Zn(hfacac)_2]$. Only the *E* isomer was obtained as shown by ^1H NMR spectroscopy.



3.38 **3.39** **3.40**

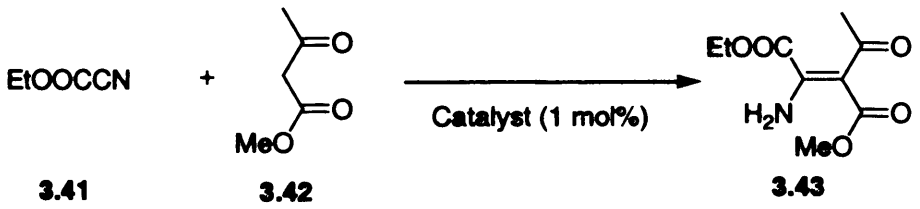
Scheme 3.11.

Entry	Catalyst	Yield(%)
1	$[Ni(acac)_2]$	51[a]
2	$[Ni(hfacac)_2]$	73[a]
3	$[Ni(C_6F_{13}COCHCOC_6F_{13})_2]$	70[a]
4	$[Zn(acac)_2]$	87[a]
5	$[Zn(hfacac)_2]$	67[a]
6	$[Zn(C_6F_{13}COCHCOC_6F_{13})_2]$	51[a]
7	[Zn(salen1)]	71
8	[Zn(salen2)]	83
9	[Zn(salen3)]	79

[a] Values taken from reference 13

Table 3.7. Yields for different catalysts when dibenzoylmethane was used as substrate.

The final substrate to be tested was a β-ketoester, methylacetoacetate. Lower yields were expected for this substrate because of the lower acidity of the proton in the β-position. When $[Zn(acac)_2]$ was used a 78 % yield was obtained; this result could not be emulated by any of the Zn salen derivatives due to their lower Lewis acidities. As in the case of the benzoyl acetone only the *E* isomer was obtained.



3.41 3.42 3.43

Scheme 3.11.

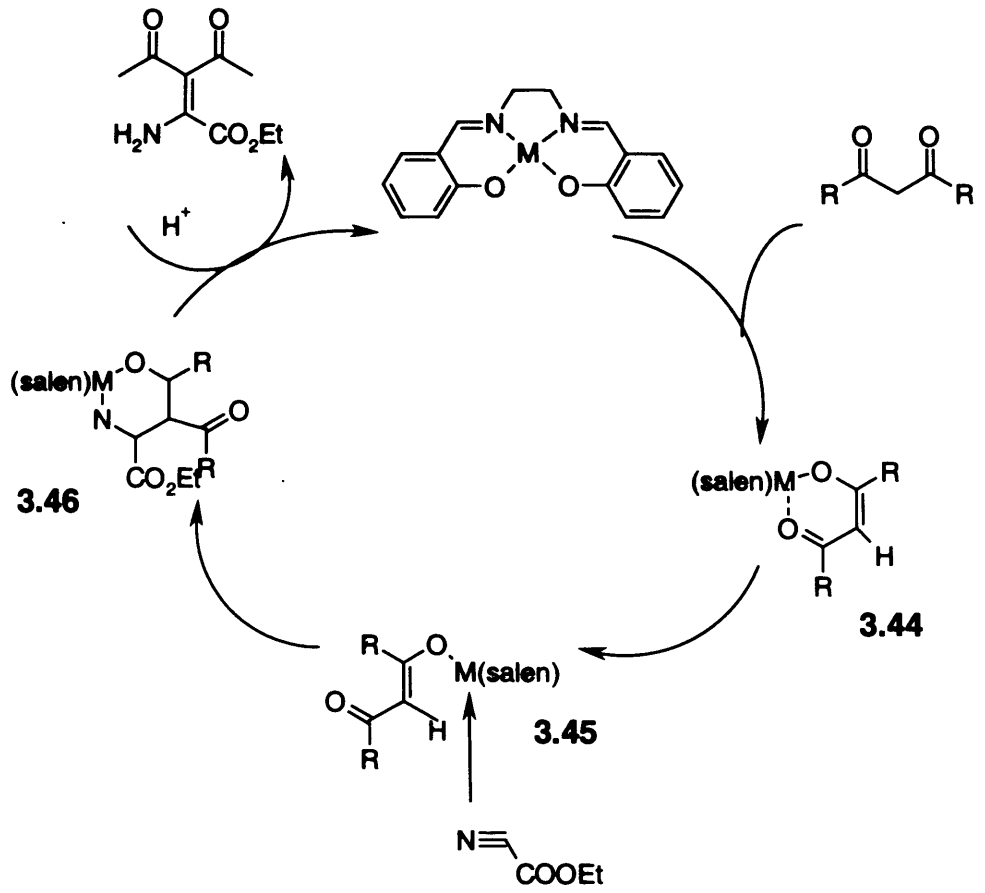
Entry	Catalyst	Yield(%)
1	$[Zn(acac)_2]$	78[a]
2	$[Zn(hfacac)_2]$	~10[a]
3	$[Zn(C_6F_{13}COCHCOC_6F_{13})_2]$	~15[a]
4	[Zn(salen1)]	21
5	[Zn(salen2)]	32
6	[Zn(salen3)]	23
7	[Zn(salen5)]	28

[a] Values taken from reference 13

Table 3.8. Yields for different catalysts when methylacetoacetate was used as substrate.

The mechanism involves three steps,

1) Coordination of the diketone to the M(salen) derivative is the key step in the reaction. If the coordination to the diketone is difficult (i.e. dibenzoylmethane because of the size of the Ph groups) the yields will be poor.
2) Coordination of the nitrile and attack of the carbanion of the diketone to the acidic carbon of the nitrile.
3) Disassociation of the enaminodione and coordination of another molecule of the diketone.



Scheme 3.12.

3.2.1.2 Conclusions

Conventional [M(salen)] complexes are useful catalysts for the synthesis of enaminodiones. [Zn(salen)] complexes showed higher activities than those of Ni(II) and Cu(II). The best results were obtained for [Zn(salen2)] and [Zn(salen3)], with [Zn(salen1)] being worse (**Table 3.9**). However, they showed lower activities than those for [M(acac)$_2$] derivatives due to the lower Lewis acidity of the metal centres. In this section a range of β-diketones and cyano derivatives were used as substrates showing a variety of results (**Table 3.10**). The sequence of reactivity for β-diketones is as follows: acetylacetone > benzoylacetone > benzoylmethane > methyl acetylacetonate as shown in (**Table 3.10**). For the cyano derivatives, trichloroacetonitrile showed higher activity than ethylcyanoformate as a consequence of the higher electron withdrawing effect of the trichloromethyl group.

Catalyst	Yield(%)
[Ni(acac)$_2$]	74
[Ni(salen2)]	25
[Zn(acac)$_2$]	83
[Zn(salen2)]	93
[Cu(salen2)]	0

Table 3.9

Results with [Zn(salen2)]		
β-diketone	**Cyano derivative**	**Yield(%)**
Acetylacetone	EtOOCCN	93
Acetylacetone	Cl_3CCN	97*
Benzoylacetone	EtOOCCN	83
Benzoylmethane	EtOOCCN	34
Methylacetoacetate	EtOOCCN	32

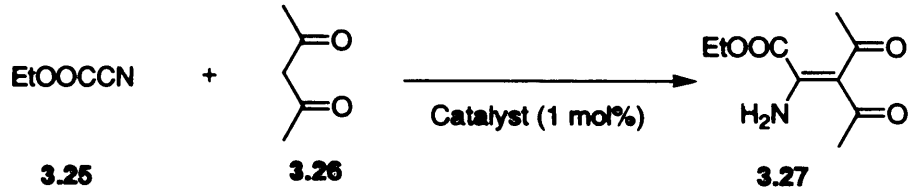
* After 3 h.

Table 3.10. Yields of different substrates tested with Zn(salen2).

3.2.1.3 Recycling of salen catalysts

The [Zn(salen2)] complex is an extremely interesting catalyst because it is insoluble in DCM. Its insolubility, as explained in Chapter 2, is due to the fact that it is probably a polymer in the solid state. However, when a dicarbonyl substrate is added to a slurry of the metal complex in DCM, the metal complex completely dissolves as shown by ^{1}H NMR. In all of catalytic reactions when the solvent was removed at the end of the reaction, acetonitrile was added and the mixture was cooled for 30 min at –20 °C. The solution was then filtered in order to recover the catalyst which was dried using an oil pump for 3 hours before being reused. **Table 3.11** shows that there was a dramatic drop in the yield after just one recycle; this is probably due to the small amount of

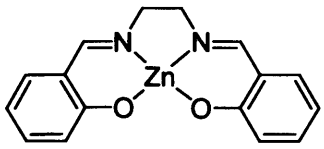
catalyst (33 mg) used in the first run which compounded the mechanical losses. In addition, ICP analysis demonstrated a large amount of Zn had leached into the organic phase making the recycling inefficient.



Scheme 3.13.

Run	Yield (%)	Zn lost (mg)	Zn lost (%)
1	93	1.624	26
2	70	2.779	44
3	12	---	---

Table 3.11. Recycling results for [Zn(salen2)] by filtration.



[Zn(salen2)]

Figure 3.7

In an attempt to reduce the high leaching of the [Zn(salen2] into the organic phase, the catalyst was supported on silica. Silica and [Zn(salen2)] were stirred in DCM at room temperature for 3 hours. After removing the solvent, the mixture was dried under oil pump vacuum for 6 hours at 70 °C. When the supported catalyst was used the recycling results were slightly better, but the loss of zinc to the organic phase (**Table 3.12**) remained high. These results suggested that the catalyst was not properly anchored to the silica possibility due to its negligible solubility in DCM.

Run	Yield (%)	Zn lost (mg)	Zn lost (%)
1	86	2.079	30
2	68	1.532	24

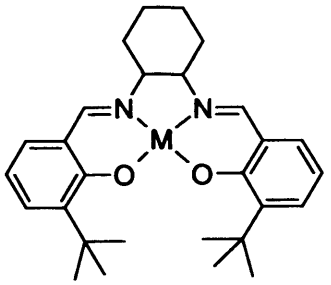
Table 3.12. Recycling results for Zn(salen2) supported on SiO_2.

The next catalyst to be recycled was [Zn(salen3)] which is slightly soluble in organic solvents. Not surprisingly, attempts to recycle the catalyst by filtration failed. [Zn(salen3)] was, therefore, supported on silica gel and, although there were massive losses of Zn to the organic phase, the catalytic activity remained moderate for a second and third run (**Table 3.13**).

Run	Yield (%)	Zn lost (mg)	Zn lost (%)
1	81	4.62	64
2	75	1.75	27
3	56	----	---

Table 3.13. Recycling results for Zn(salen3) supported on SiO_2.

A new salen ligand containing a ^{t}Bu group in the *ortho-* position was synthesised and Ni(II) and Zn(II) derivatives of this ligand were tested in the synthesis of enaminodiones. [Zn(salen7)] supported on silica gel gave good results. This catalyst could be recovered five times although a decrease in the catalyst activity was observed in the sixth run. ICP results showed less Zn lost than that obtained in the [Zn(salen2)] or [Zn(salen3)] experiments which suggests a better anchoring of the metal on the support and less decomposition.



M(salen7)

Figure 3.7.

Run	Yield (%)	Zn lost (mg)	Zn lost (%)
1	86	0.739	11
2	73	0.622	9
3	87	0.443	7
4	85	0.355	5
5	73	1.126	17
6	67	---	---

Table 3.14. Recycling results for Zn(salen3) supported on SiO_2.

[Ni(salen7)] supported on silica gel showed slightly lower yields (75 %) than [Zn(salen7)]. However, when this derivative was recycled lower levels of catalyst loss were obtained. The results obtained in the second and third runs showed drops in the yield due to the leaching to the organic phase.

Run	Yield (%)	Ni lost (%)
1	75	9
2	69	5
3	54	4
4	20	--

Table 3.15. Recycling results for Ni(salen7) supported on SiO_2.

3.2.1.4 Conclusions

The low solubility of [Zn(salen2)] in organic solvents made it suitable to be recycled by filtration. However, the leaching was so high that the activity was lost after just one recycle. No substantial changes were found when [Zn(salen2)] was used supported on silica gel.

[Zn(salen3)] was also used supported in silica gel giving the same amount of leaching into the organic phase. However, better results were obtained when [Zn(salen7)] was used as catalyst and the catalyst could be recovered up to five times.

3.2.2 Synthesis of enaminodiones using fluorous derivatives.

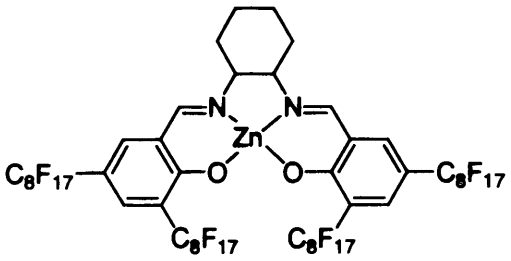
3.2.2.1 Introduction

As stated above poor recycling results were obtained with non-fluorinated salen catalysts. The leaching of catalyst into the organic phase which maybe the main problem, might be overcome by incorporating fluorous ponytails and recycling the catalysts using fluorous techniques (Chapter 1).

3.2.2.2 Results and Discussion.

The first catalyst to be tested was [Zn(salen5)] (**Figure 3.8**). The solubility of [Zn(salen5)] in any organic or fluorous solvent is negligible. After the reaction mixture was stirred in DCM for 24 hours at room temperature the solvent was removed, acetonitrile was added and the mixture was cooled to -17 °C for 30 min before filtering off the catalyst which was dried for 3 hours under oil pump vacuum and reused. As the table shows there was a direct correlation between the amount

of catalyst recovered and the yield of the reaction. The catalyst was recovered efficiently two times but the yield dropped substantially in the fourth run. The dramatic decrease in the yield was due to mechanical losses because of the small amount of catalyst used in the reaction.



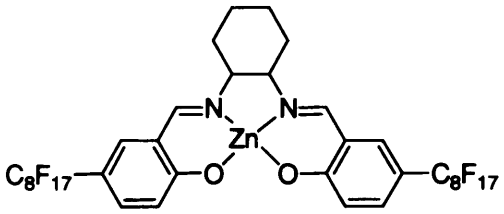
[Zn(salen5)]

Figure 3.8

Run	Yield (%)	Catalyst (%)
1	87	100
2	78	83
3	75	77
4	24	35

Table 3.16. Recycling results for Zn(salen5) recycled by filtration.

The lightly fluorinated catalyst [Zn(salen8)], contains only 2 fluorous ponytails in the *para*-positions and it is insoluble in all organic solvents. Filtration was first investigated for recycling [Zn(salen8)]. Despite the relatively low loss of Zn (11%), there was a dramatic drop in the yield in the second run.



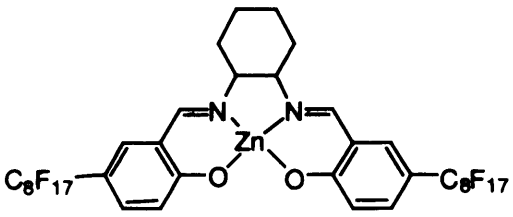
[Zn(salen8)]

Figure 3.9

Run	Yield (%)	Zn lost (mg)	Zn lost (%)
1	87	0.713	11
2	51	---	---

Table 3.17. Recycling results for Zn(salen8) recycled by filtration.

[Zn(salen8)] was then supported on silica gel and on fluorous reverse phase silica gel (FRPSG) and the reaction was performed using the same standard procedure. The yield for both reactions dropped dramatically in the second runs although the amount of Zn leached in the organic phase was the same as that in the non supported experiments.



[Zn(salen8)]

Figure 3.9

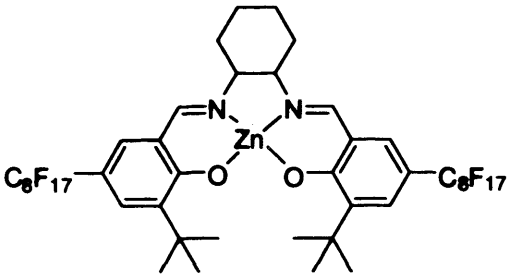
Run	Yield (%)	Zn lost (mg)	Zn lost (%)
1	90	0.739	12
2	36	---	---

Table 3.19. Recycling results for Zn(salen8) supported on SiO_2.

Run	Yield (%)	Zn lost (mg)	Zn lost (%)
1	81	0.746	12
2	36	----	---

Table 3.20. Recycling results for Zn(salen8) supported on FRPSG.

The final catalyst to be investigated was [Zn(salen9)] which is soluble in most organic solvents due to the two *tert*-butyl groups in *ortho-* positions. Consequently, this catalyst was supported on both conventional silica gel and FRPSG. Interestingly the colour of the catalyst changed from yellow to blue when it was supported on FRPSG and to pink when supported on silica gel due to metal silica gel interactions. Unfortunately, however, none of the supports seemed to be effective at retaining the catalyst as **Table 3.21** and **Table 3.22** illustrate. The amount of catalyst lost upon recycling was unacceptably high and very low yields were obtained in the third runs.



[Zn(salen9)]

Figure 3.10.

Run	Yield(%)	Zn lost (mg)	Zn lost (%)
1st	94	1.194	19
2nd	44	0.928	14
3rd	25	----	---

Table 3.21. Recycling results for Zn(salen9) supported on SiO_2.

Run	Yield (%)	Zn lost (mg)	Zn lost (%)
1st	93	2.248	34
2nd	55	1.257	19
3rd	25	----	----

Table 3.22. Recycling results for Zn(salen8) supported on FRPSG.

3.2.2.3 Synthesis of enaminodiones using fluorous derivatives. Conclusions.

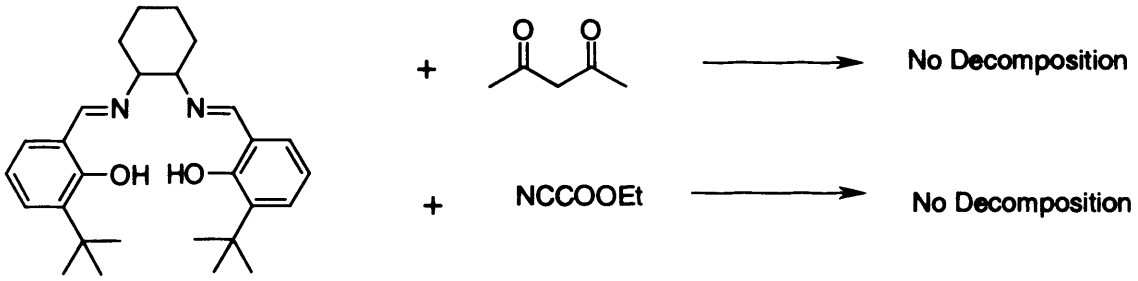
Zn salen derivatives showed high yields in the synthesis of enaminodiones (between 87- 94%). However, following attempts to recycle these catalysts, significant drops in yields were observed for [Zn(salen8)] and [Zn(salen9)] catalysts after just one reaction, whilst [Zn(salen5)] was able to perform the reaction three times more (**Table 3.23**). In the case of [Zn(salen8)] and [Zn(salen9)] no difference in the reactivity nor recyclability was observed when either silica gel or FRPSG was used as a support material.

	[Zn(salen5)]	[Zn(salen8)]			[Zn(salen9)]	
Run/Recovery by	Filtration	Filtration	Silica gel	FRPSG	Silica gel	FRPSG
1	87	87	90	81	94	93
2	78	51	36	36	44	55
3	75	--	--	--	25	25
4	77	--	--	--	--	--

Table 3.23.

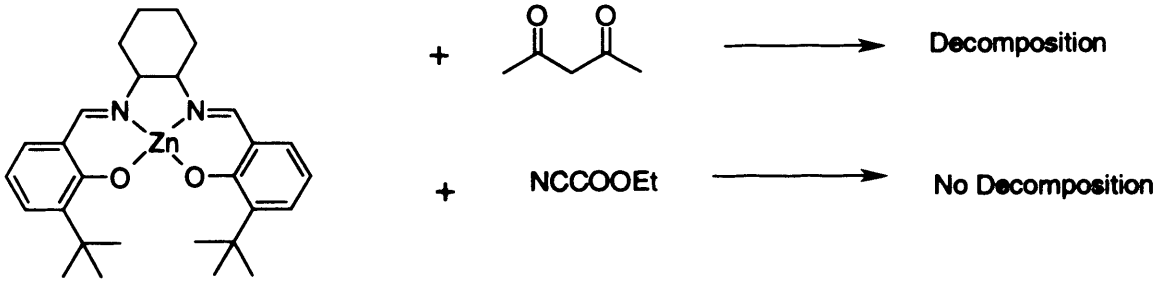
3.2.3 Studies regarding the decomposition of the catalyst.

The only reasonable results were obtained with [Zn(salen7)] which is by far the most active catalyst. In all of the other cases there was always a large amount of zinc leaching into the organic phase in each recycle. Consequently, a series of experiments were performed in order to determine the stability of the Zn(II) catalyst. Initially, the salen ligand on its own was tested in order to observe if it decomposed by the action of the acetylacetone or the ethylcyanoformate (**Scheme 3.14**). ^{1}H NMR spectroscopy showed no decomposition to the salicylaldehyde if the ligand was stirred with acetylacetone or ethyl cyanoformate. In both cases a 1:1 (ligand: reagent) ratio was chosen.



Scheme 3.14.

When the [Zn(salen7)] was stirred with ethyl cyanoformate under the same conditions no sign of decomposition was observed. However, when 1 equivalent of [Zn(salen7)] was stirred with 1 equivalent of acetylacetone under the same conditions, signs of decomposition of the Zn derivative to the salicylaldehyde were observed by ^{1}H NMR (a signal of salicylaldehyde about 10 ppm), which would explain the high percentage of Zn in the organic phase and the drops in the yields after a few runs.



Scheme 3.15.

3.3 Overall Conclusions.

The investigations described within this chapter have demonstrated the effectiveness and versatility of the non fluorinated and fluorinated salen derivatives to catalyse the synthesis of enaminodiones. Preliminary studies determined that the Zn(II) salen complexes were much more efficient catalysts than those of Ni(II) and that the Cu(II) salen complexes did not promote the synthesis of enaminodiones. Because of their reactivity, Zn salen derivatives were evaluated in catalytic reactions with a variety of substrates: four β-diketones (acetylacetone, dibenzoylmethane, benzoylacetone and methylacetoacetate) and two cyano derivatives (ethylcyanoformate and trichloroacetonitrile). The yields in the case of acetylacetone and benzoylacetone were good but decreased when the substrate used was dibenzoylmethane or a β-ketoester due to steric and electronic impediments. When trichloroacetonitrile was used in place of ethylcyanoformate reactions were faster.

Some of the catalysts were insoluble which made them suitable to be recycled by filtration, and some others were recycled by supporting the catalysts on silica gel. However, most of the catalysts showed signs of decomposition and showed low activities after a few runs, the only exception was [Zn(salen7)].

As has been stated in Chapter 2 some fluorous salen complexes have been synthesised and these have been tested as catalysts for this reaction. These catalysts were supported either on silica gel or Fluorous Reverse Phase Silica Gel (FRPSG). Unfortunately, neither support gave good results, which means that the important interaction is between the metal and the oxygen of the silica gel or the FRPSG, whilst the fluorine-fluorine interactions (Chapter 1) are less important. It has been demonstrated that the acidity of acetyl acetone resulted in the partial decomposition of these catalysts.

3.4 References

1 V. Pevere. PCT Intl. Appl., 1997, 9730037.

2 K. Ogura, G. Tsuchihashi. *J. Am. Chem. Soc.*, 1974, ***94***, 1960.

3 M. Basato, U. Vettori, A. C. Veronese, A. Grassi, G. Valle. *Inorg. Chem.*, 1998, ***37***, 6737.

4 J. H. Nelson, P. H. Powells, G. C. DeLullo, G. L. Landen. *J. Org. Chem.*, 1980, ***45***, 1246.

5 T. Timori, Y. Nii, T. Izawa, S. Kobayashi, M. Ohno, *Tetrahedron Lett.*, 1994, ***27***, 2525.

6 M. Basato, R. Campostrini, B. Corain, B. Longato, S. Sistran, A. C. Veronese, G. Valle. *J. Chem. Soc., Perkin Trans. II*, 1985, 2019.

7 M. Basato, B. Corain, A. C. Veronese, F. D'Angeli, G. Valle, G. Zanotti. *J. Org. Chem.*, 1984, ***49***, 4696.

8 M. Basato, B. Corain, M. Coffer, A. C. Veronese, G. Zanotti. *J. Chem. Soc., Chem. Commun.*, 1984, 1593.

9 B. Croxtall, E. G. Hope, A. M. Stuart, *Chem Commun.*, 2003, 2430.

10 B. Croxtall, Ph. D. Thesis, 2004, University of Leicester.

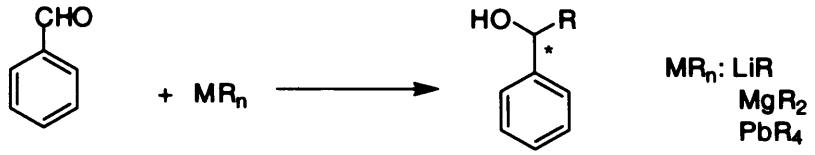
4 Asymmetric Addition of Diethylzinc

4.1 Alkylation of Carbonyl Compounds

4.1.1 Introduction

4.1.1.1 Asymmetric addition using organic catalysts

The reaction of organometallics with carbonyl compounds is a well-studied C-C bond-forming reaction.[1,2,3] Some of the first examples reported in the literature involved organolithium, dialkylmagnesium[4] or tetraalkyllead[5] reagents (**Scheme 4.1**). In most cases, however, the procedures required stoichiometric or even an excess of the organometallic species.[1]



Scheme 4.1.

Whilst monomeric dialkylzinc reagents have an sp-hybridized linear geometry and are inert to carbonyl compounds, their reactivity can be enhanced by structural modification with the appropriate ligands or auxiliaries. Replacement of one alkyl group by an electronegative substituent increases the acceptor character of the zinc and the donor property of the remaining alkyl group, thereby accelerating the reaction with carbonyl substrates. One example of such auxiliaries is chiral aminoalcohols. There are many examples of the use of chiral *β-tert*-aminoalcohols for the asymmetric alkylation of carbonyl compounds in the literature.[6,7,8] In one report[9] a range of *β-tert*-aminoalcohols were shown to give good yields and enantioselectivities using 5 mol% of the aminoalcohol and 2 equivalents of diethylzinc (**Table 4.1**). The reaction was carried out for 24 hours at -78 °C and the proposed intermediate is shown in Figure 4.2. The migration of the ethyl group only takes place from the bridging positions, so the tertiary aminoalcohols gave better enantioselectivities, as the methyl group (R'= Me) is more sterically hindered than a hydrogen (R'= H).

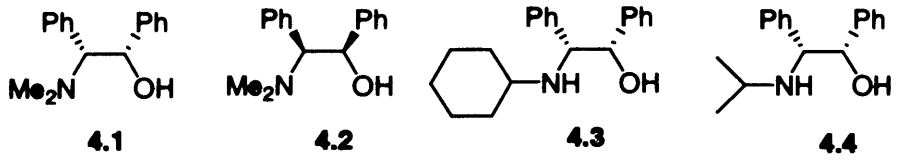
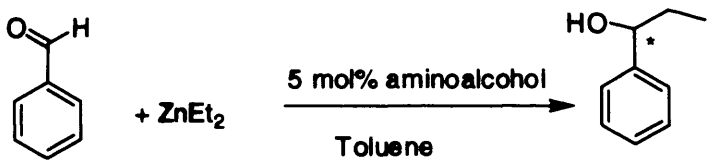


Figure 4.1



Scheme 4.2

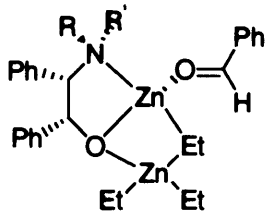


Figure 4.2.

Catalyst	Yield (%)	ee (%)
4.1	99	97 (*S*)
4.2	85	97 (*R*)
4.3	97	76 (*S*)
4.4	96	51 (*S*)

Table 4.1. Asymmetric addition of $ZnEt_2$ to benzaldehyde using aminoalcohols.

Another example of the successful use of chiral auxiliaries is the use of cinchona alkaloids in the addition of diethylzinc to benzaldehyde.[10] The reactions were carried out using 2 mol% of different cinchona alkaloids for 24 hours at room temperature. On the basis of the results (**Table 4.4**), coordinating the diethylzinc to the quinuclidine part of quinine seems reasonable. In this situation (**Figure 4.5**), the hydroxyl group of the catalyst is available for hydrogen bonding with the carbonyl function of the benzaldehyde. This can account for the large decrease in enantioselectivity when acetylquinine is used as the chiral auxiliary. Since the diethylzinc is orientated in the same way and activated, but the benzaldehyde is not. The authors proposed that good enantioselectivity was only obtained with quinine since the hydrogen bonding provides a rigid orientation of benzaldehyde, whereas in an acetylquinine catalysed reaction this orientation is lost. Since the enantioselectivity is much higher with a quinine-catalysed reaction compared to a quinidine-catalysed reaction the configuration at C8 and C9 is very important. This also affects the orientation of the vinyl group and, consequently, the vinyl group proved to be important for obtaining moderate enantioselectivities and yields. However, no evidence for this intermediate (**Figure 4.5**) is given in this contribution and it is more likely that an intermediate with "ZnEt" coordinated to both the nitrogen and the oxygen is formed similar to the last example (**Figure 4.2**).

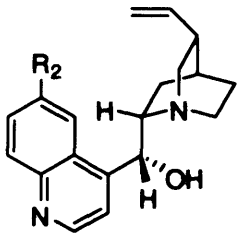


Figure 4.3.

Catalyst	R_2
Quinine	OMe
Cinchonidine	H

Table 4.2.

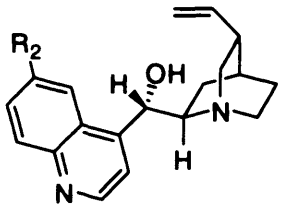


Figure 4.4.

Catalyst	R_2
Quinidine	OMe
Cinchonine	H

Table 4.3.

Auxiliary	Solvent	Yield (%)	ee (%)
Acetylquinine	Toluene	78	14
Quinine	Toluene	92	68
Quinidine	Toluene	90	48
Cinchonidine	Toluene	89	58
Cinchonine	Toluene	90	46

Table 4.4. Asymmetric addition of $ZnEt_2$ to benzaldehyde using aminoalcohols..

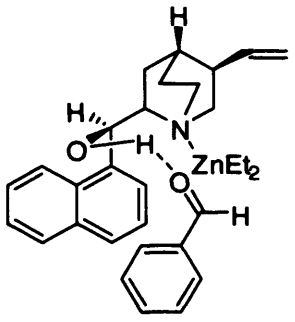


Figure 4.5.

4.1.1.2 Asymmetric addition of $ZnEt_2$ to aldehydes using metal catalysts

4.1.1.2.1 Asymmetric addition using non-fluorous metal catalysts

There have been a number of papers describing enantioselective reactions by a wide variety of metal complexes obtained by mixing alkylated derivatives, alkoxides, halides and hydrides of boron, tin, aluminium, titanium and zinc with a range of chiral ligands such as BINOL, salen and many others.

BINOL ligands are commonly used in asymmetric synthesis as exceptional ligands to introduce asymmetry in products (**Figure 4.6**).[11,12] Chan[13] and Nakai[14] have independently investigated the asymmetric alkylation of aldehydes catalysed by Ti/BINOL systems. When benzaldehyde was used as the substrate, yields higher than 98 % and 80-85 % enantiomeric excesses were achieved depending on the conditions used. It was found that an excess of both $Ti(^{i}PrO)_4$ and diethylzinc was required to produce good yields and enantioselectivities, although only 0.1 equivalents of BINOL were used. A range of substituted aldehydes could be alkylated using the same catalyst with good product yields and enantioselectivities. This catalyst has also been used in the asymmetric addition of allyltributyltin to a range of functionalised aldehydes.[15]

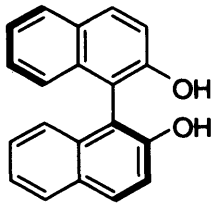


Figure 4.6

Metallosalen complexes have been widely used as catalysts since the nineties. One of the first examples was the use of *N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (H_2salen10) by Cozzi *et al.* [16] The complex was generated *in situ* by the addition of one equivalent of diethylzinc to the free H_2salen and Table 4.5 shows that moderate yields and enantioselectivities were obtained. The best conditions were to carry out the reaction at –40 °C and let it warm up to room temperature over 24 h in toluene with 10 mol% of the chiral catalyst (75% yield, 70% ee). However, Venkataraman *et al.*[17] improved these results (75% yield, 83% ee) by doing the addition at 0 °C and letting the reaction warm up to room temperature.

Solvent	Temperature (°C)	Yield (%)	Ee (%)
Toluene	0	50	35
DCM	0	75	30
Toluene	25	75	60
DCM	25	88	34
Hexane	-40→ 25	65	68
Toluene	-40 → 25	75	70

Table 4.5. Yields obtained using H_2salen10 as ligand.

Recently, a new generation of salen ligands were synthesised.[18] The novel ligands have different π-donor branches such as morpholine, pyridine and quinoline in the 3,3'-positions that act as a Lewis base attracting the diethylzinc to the reaction centre and slightly increasing both the yield and enantioselectivity (**Table 4.6**). In the proposed intermediate, shown in Figure 4.8, the diethylzinc is chelated by the Lewis basic arm of the salen ligand (10 mol%) and the benzaldehyde is attracted by the Lewis acidic metal centre of the catalyst.

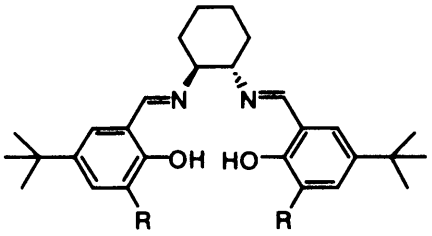


Figure 4.7.

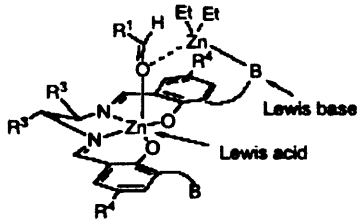


Figure 4.8.

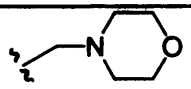
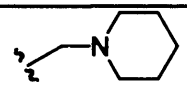
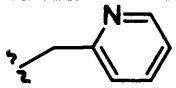
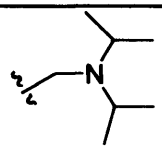
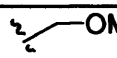
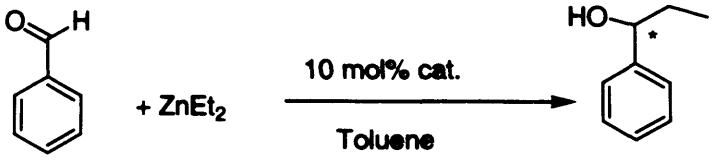
R	Temp. (°C)	Time (h)	Conv (%)	ee (%)
	-35	15	98	87
	-40	15	82	85
	-50	20	97	78
	25	6	90	48
	-30	30	85	18 (R)

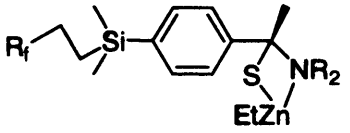
Table 4.6. Conversions obtained using salen with different substituents in 3 and 3'.

4.1.1.2.2 Asymmetric addition of diethylzinc to benzaldehyde using fluorous metal catalysts

There are a few examples of the asymmetric addition of diethylzinc to benzaldehyde by perfluoroalkylated transition metal catalysts. One of the first examples used fluorous arylzinc thiolates.[19] The use of non-fluorinated arylzinc thiolates had been reported before by van Koten *et al.*[20] obtaining good yields and enantioselectivities. The catalyst was rendered fluorous by attaching a silyl ponytail (**Figure 4.9**) with a two carbon spacer group in order to minimise the electron-withdrawing effect of the fluorous ponytail. The reaction was performed in a mixture of perfluoromethylcyclohexane and hexane as the biphasic solvent system at room temperature for 15 h. The fluorinated catalyst was recovered by a simple decantation of the fluorous phase from the organic phase, but the enantioselectivity of the catalyst decreased when the fluorous catalyst was reused (**Table 4.7**).



Scheme 4.3.



4.4: R=Me, R_f=C_6F_{13}
4.5: R= Me, R_f=$C_{10}F_{21}$
4.6: R=-$(CH_2)_4$-, R_f=C_6F_{13}

Figure 4.9.

Catalyst	Run 1	Run 2	Run 3	Run 4	Run 5
4.4	84	72	37	9	3
4.5	79	78	61	36	11
4.6	92	92	76	43	28

Table 4.7. Enantioselectivity obtained using different catalysts.

There are a few examples of Ti(R_f-BINOL) systems in the literature.[21,22,23] The first example was the synthesis and application of a tetra-perfluoroalkylated BINOL derivative by Chan *et al.* (**4.7**).[21] In this example the reaction was carried out using 20 mol% of the catalyst in a biphasic system consisting of perfluoromethyldecalin and hexane at 45 °C for 1 hour. The catalyst was recovered by decantation of the two phases and reused. Unfortunately, although the reaction worked in good yields, only poor enantioselectivities were achieved.

Another interesting approach by Curran *et al.*[22] is a highly fluorinated BINOL ligand that contains six fluorous ponytails due to its two silyl groups (**4.8**). In this case, the reaction was performed in BTF and hexane at 0 °C for 1 hour. With these conditions good yields and enantioselectivities were achieved and most of the ligand was recovered three times using FRP silica gel. However, when the reaction was performed in a biphasic system consisting of toluene and FC-72 (perfluorohexane), poor recovery was achieved.

The third example of a Ti and R_f-BINOL (**4.9**) system[23] used a ratio of $Ti(^iPrO)_4$/ R_f-BINOL of 7/1 suggesting that free $Ti(^iPrO)_4$ may act as a co-catalyst in the reaction. The yield of the reaction was 88 % and the ee was 74 %. The reaction was carried out at -20 °C for 5 hours in DCM. Unfortunately, it was not possible to recover the catalyst by fluorous solid phase extraction.

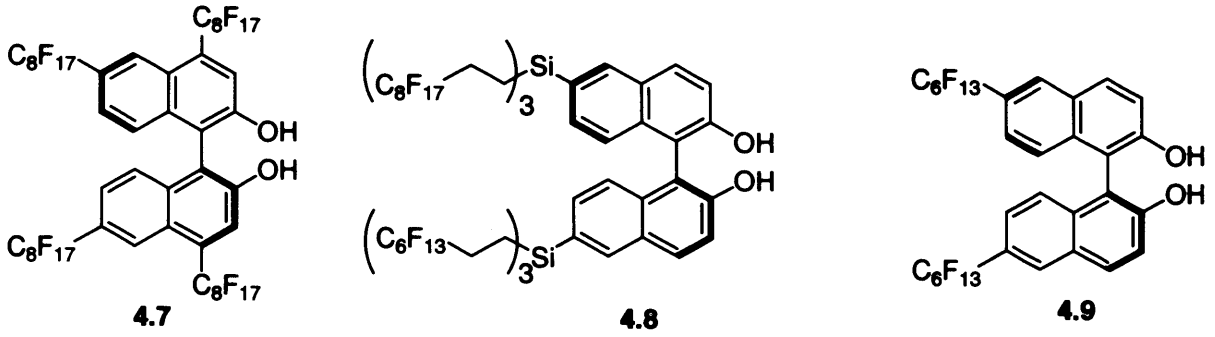


Figure 4.10.

4.1.2 Results and discussion

4.1.2.1 Asymmetric addition using non fluorous catalysts

The asymmetric alkylation of benzaldehyde using chiral catalysts is a reaction in which the temperature has great importance. The methodology described by Cozzi[16] and Venkataraman[17] has been followed in this work to synthesise the catalysts *in situ*, although preliminary results using pre-formed catalysts showed no differences in terms of conversion and enantioselectivity. The reactions were carried out twice and the results were reproducible. Conversions were determined using ^1H NMR spectroscopy and enantioselectivities were calculated using chiral GC (see Chapter 6). The first ligand tested was H_2salen7 which has one *tert*-butyl group in the 3,3'-positions and a hydrogen in the 5,5'-positions (**Figure 4.11**). The best results (86% yield, 48% ee) were obtained when the $ZnEt_2$ was added at -20 °C or 0 °C and then stirred at room temperature for 24 h (entries 4 and 5, **Table 4.9**). At lower temperatures there was a decrease in conversion and enantioselectivity and if the experiments were carried out at RT the yield was higher but the enantioselectivity was very low. The major enantiomer obtained was always the (*S*).

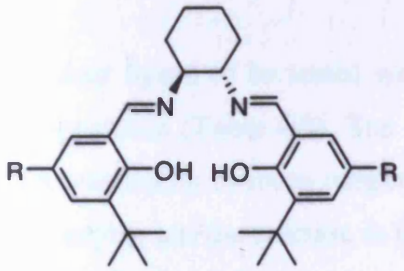
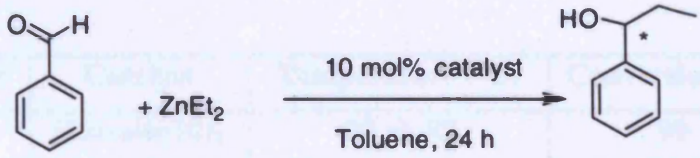


Figure 4.11.

Ligand	R
H_2salen7	H
H_2salen9	C_8F_{17}
H_2salen10	^tBu
H_2salen11	$SiMe_2(C_2H_4C_6F_{13})$

Table 4.8.



Scheme 4.3.

Entry	Catalyst	Temperature (°C)	Conversion (%)	Ee (%)
1	[Zn(salen7)]	-20	38	26
2	[Zn(salen7)]	0	44	24
3	[Zn(salen7)]	RT	99	10
4	[Zn(salen7)]	0→ RT	89	41
5	[Zn(salen7)]	-20→ RT	86	48

Table 4.9. Results obtained when [Znsalen7] was used as catalyst.

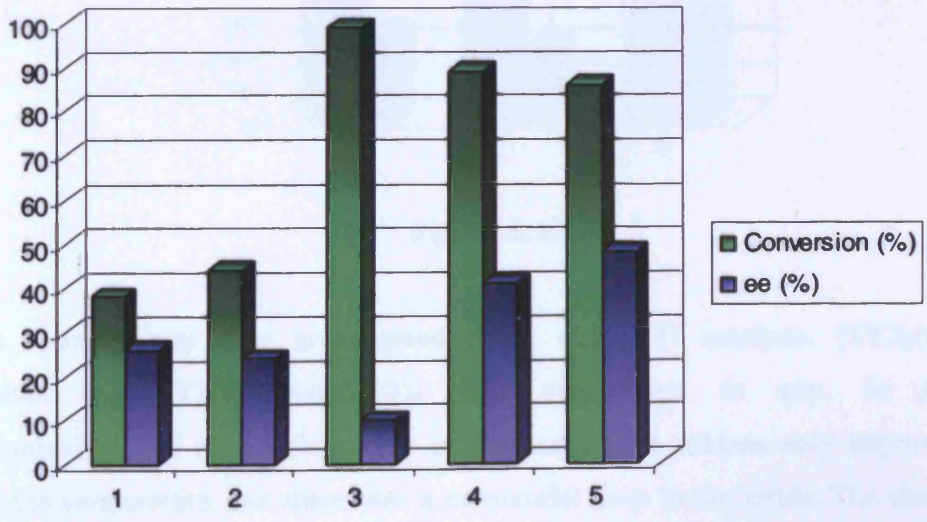


Figure 4.12.

The next ligand to be tested was H_2(salen10) which contains tert-butyl groups in the 3,3'- and 5,5'-positions (**Table 4.8**). The first experiments were carried out at 0 °C and -20 °C, and were then warmed up to room temperature, which resulted in lower enantioselectivities than expected. By carrying out the reaction at 0 °C for 24 h the enantioselectivity was improved dramatically to 83%. Comparing the results obtained for [Zn(salen10)] and [Zn(salen7)] at 0 °C, [Zn(salen10)] demonstrated better conversions and enantioselectivities due to the effect of the *tert*-butyl substituents in the 5,5'-positions.

Entry	Catalyst	Temperature (°C)	Conversion (%)	Ee (%)
1	[Zn(salen10)]	-20 → RT	99	25
2	[Zn(salen10)]	0 → RT	99	20
3	[Zn(salen10)]	0	79	83

Table 4.10. Results obtained when [Znsalen10] was used as catalyst.

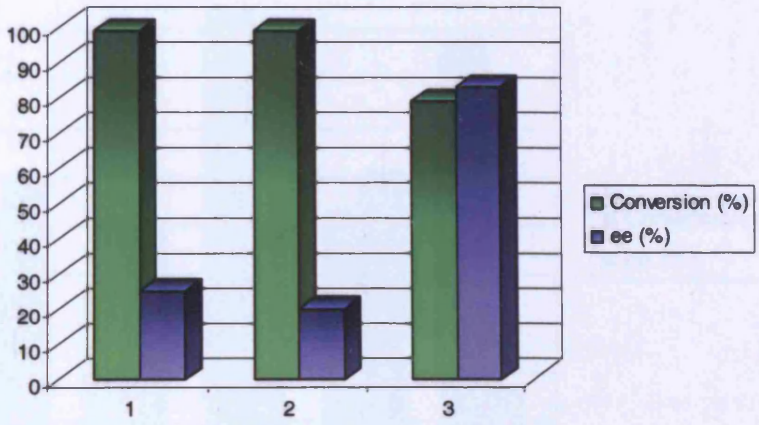


Figure 4.13.

The same reaction was also investigated using chiral Ti catalysts. [$TiCl_2$(salen10)] was presynthesised and [Ti(^{i}PrO)$_2$(salen10)] was synthesised *in situ*. In the case of [Ti(^{i}PrO)$_2$(salen10)], the enantioselectivity of the reaction in toluene only improved slightly by decreasing the temperature, but there was a substantial drop in the yields. The change of solvent

to dichloromethane decreased the yields with a small increase in the enantioselectivity and there was a change in the enantiomer obtained when the reaction was carried out in hexane.

In the case of [$TiCl_2$(salen10)], different catalyst loadings were investigated. As shown in **Table 4.12**, an increase in the amount of catalyst did not modify the yields but increased the enantioselectivity at 0 °C, whilst the opposite happened at room temperature; yields increased but enantioselectivities remained very low. Changing the solvent to toluene provided the best result (90 % conversion, 45 % ee). None of these systems seemed to be as effective as [Zn(salen10)].

Entry	Catalyst	Solvent	Temperature (°C)	Conversion (%)	Ee (%)
1	[Ti(^{i}PrO)$_2$(salen10)]	Toluene	-60	18	50
2	[Ti(^{i}PrO)$_2$(salen10)]	Toluene	-60 → 0	30	43
3	[Ti(^{i}PrO)$_2$(salen10)]	Toluene	-60 → RT	86	41
4	[Ti(^{i}PrO)$_2$(salen10)]	DCM	-60→ RT	45	53
5	[Ti(^{i}PrO)$_2$(salen10)]	Hexane	-60 → RT	80	9 (R)

Table 4.11. Results obtained when [Ti(^{i}PrO)$_2$(salen10)] was used as catalyst.

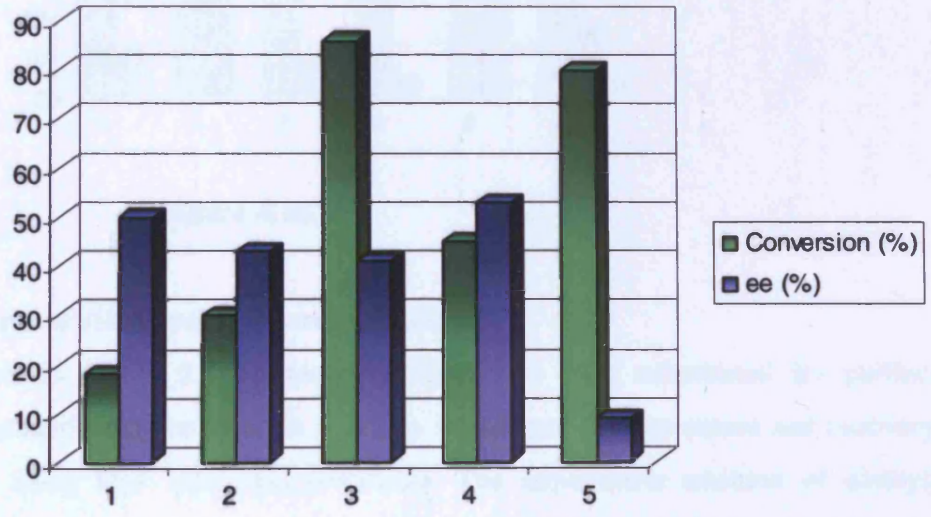


Figure 4.14.

Entry	[$TiCl_2$(salen10)] (mol %)	Solvent	Temp. (°C)	Conversion (%)	Ee (%)
1	0.1	DCM	0	55	10
2	1.0	DCM	0	49	35
3	0.1	DCM	RT	77	8
4	1.0	DCM	RT	91	3
5	1.0	Toluene	-60 → RT	90	45
6	1.0	Hexane	-60 → RT	63	16

Table 4.12. Results obtained when [$TiCl_2$(salen10)] was used as catalyst.

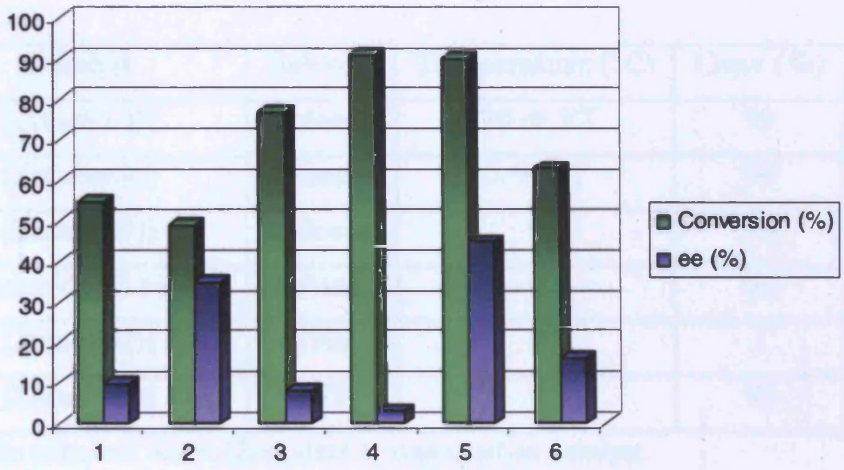


Figure 4.15.

4.1.2.2 Asymmetric addition using fluorous catalysts

The *tert*-butyl groups in the 5,5'-positions in H_2salen10 were substituted for perfluorooctyl substituents in H_2salen9 (**Figure 4.16**) in order to investigate the separation and recovery of the fluorous catalyst using FRP silica gel (FRPSG). The asymmetric addition of diethylzinc to benzaldehyde was carried out under a number of different conditions, varying both the temperature and the solvent. When the reaction was allowed to warm to room temperature after the addition of diethylzinc at 0 or -20 °C, high conversions but low enantioselectivities were observed. The reaction improved when it was performed at 0 °C obtaining 79 % yield and 50 % ee. Although this result was reproducible, a much lower enantioselectivity was obtained compared to the 83 % obtained with [Zn(salen10)] under the same reaction conditions. When

other more fluorophilic solvents like THF or benzotrifluoride were tested, the results showed a dramatic decrease in the enantioselectivity.

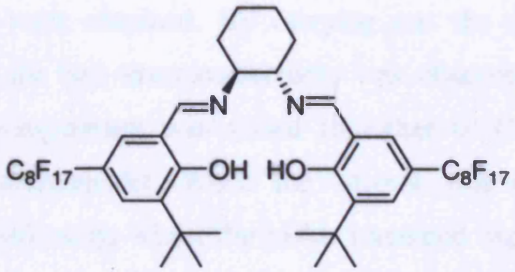


Figure 4.16.

Entry	Catalyst	Solvent	Temperature (°C)	Conv (%)	ee (%)
1	[Zn(salen9)]	Toluene	-20 → RT	99	25
2	[Zn(salen9)]	Toluene	0 → RT	99	20
3	[Zn(salen9)]	Toluene	0	79	50
4	[Zn(salen9)](15 mol%)	Toluene	0	99	3
5	[Zn(salen9)]	THF	0	1	10
6	[Zn(salen9)]	BTF	0	99	5

Table 4.13. Results obtained when [Zn(salen9)] was used as catalyst.

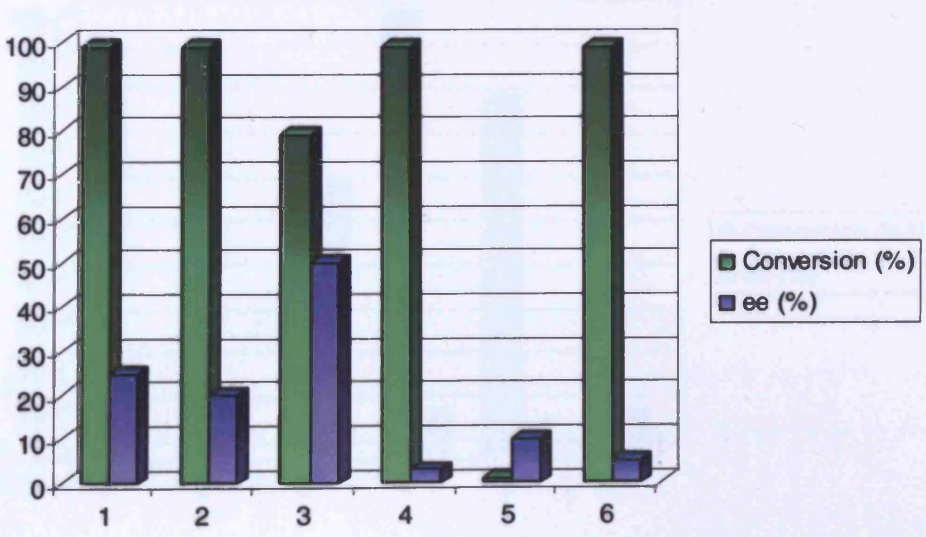


Figure 4.17.

Due to the low enantioselectivity obtained in these reactions, a change in the methodology was introduced. Instead of adding the solution of $ZnEt_2$ in hexane the reagent was added in toluene (diethylzinc is commercially available in hexane and toluene). With this change better results, in terms of enantioselectivities, were obtained. By carrying out the reaction at –60 °C a 62% conversion was obtained and the best enantioselectivity was observed (60 %). However, under these conditions, when the temperature was raised to either 0 °C or room temperature the enantioselectivity decreased dramatically. When the solvent was changed from toluene the enantioselectivity lowered significantly, whilst the yields remained high for hexane but decreased for ether. Since the enantioselectivity was so low even under the optimum reaction conditions, recycling studies of the chiral fluorous ligand were not performed.

Entry	Catalyst	Solvent	Temperature (°C)	Conv. (%)	ee (%)
1	[Zn(salen9)]	Toluene	0	90	8
2	[Zn(salen9)]	Toluene	-20 → RT	88	10
3	[Zn(salen9)]	Toluene	-60	62	60
4	[Zn(salen9)]	Hexane	0	99	8
5	[Zn(salen9)]	Hexane	-60	80	6
6	[Zn(salen9)]	Et_2O	0	59	8

Table 4.14. Results obtained when [Zn(salen9)] was used as catalyst.

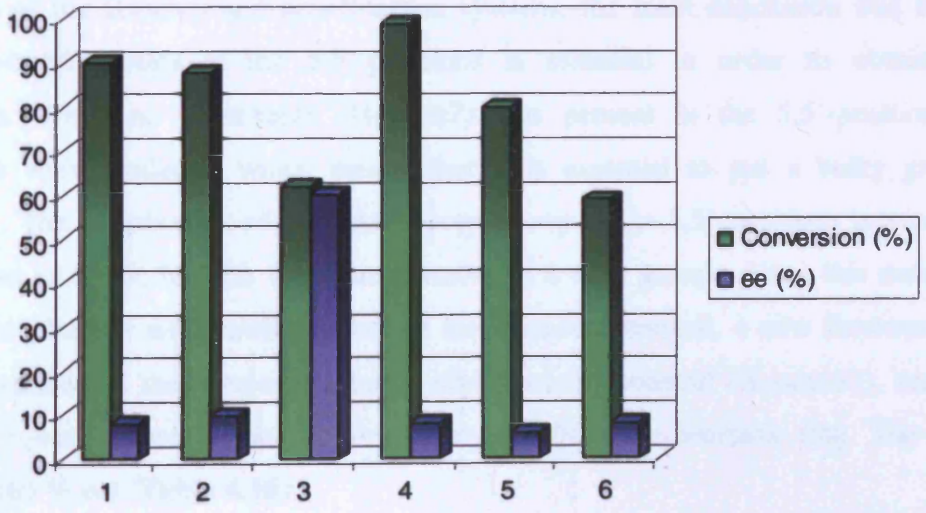


Figure 4.18.

The main conclusion after studying the reaction systems using [Zn(salen9)] as catalyst was that the electron withdrawing effect caused by the fluorous ponytails on the aromatic ring affects the enantioselectivity of the product. One solution to this problem would be to insulate the aromatic ring from the fluorous ponytails by using a silyl spacer group and synthesising a new salen-type ligand (H_2salen11, **Figure 4.19**). The same asymmetric addition was carried out for 24 hours under nitrogen using toluene as the solvent at 0 °C, as well as at -20 °C in order to try to improve the enantioselectivity. However, the results at -20 °C (30% conversion, 35% ee) were not as good as those obtained at 0 °C (60 % conversion, 65% ee) (**Table 4.15**).

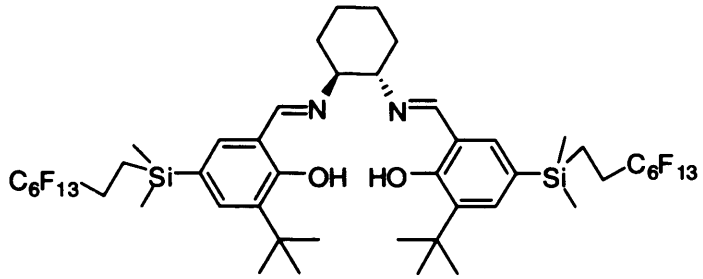


Figure 4.19

Catalyst	Temperature (°C)	Conv. (%)	Ee (%)
[Zn(salen11)]	0	60	65
[Zn(salen11)]	-20	30	35

Table 4.15. Results obtained when [Zn(salen11)] was used as catalyst.

After studying all of the fluorous and non-fluorous systems, the main conclusion was that the existence of *tert*-butyl groups in the 5,5'-positions is essential in order to obtain good enantioselectivities. When no substituent (H_2salen7) was present in the 5,5'-positions, the enantioselectivities were moderate which means that it is essential to put a bulky group in positions 5 and 5'. The introduction of a perfluorooctyl group at the 5,5'-positions increased the enantiomeric excess to 50 %, but this is not as effective as a t-Bu group. Since this decrease is associated with the electron withdrawing effect of the fluorous ponytail, a new fluorous salen-type ligand was synthesised that contains a bulky silyl fluorous ponytail (H_2salen11), removing the electron-withdrawing effects of the fluorous ponytails from the aromatic ring. The results improved slightly (65 % ee) (**Table 4.16**).

Entry	Catalyst	R	Temperature (°C)	Conv. (%)	Ee (%)
1	[Zn(salen7)]	H	0 → RT	89	41
2	[Zn(salen7)]	H	0	44	24
3	[Zn(salen9)]	C_8F_{17}	0	79	50
4	[Zn(salen11)]	$SiMe_2(C_2H_4R_{f6})$	0	60	65
5	[Zn(salen10)]	^{t}Bu	0	79	83

Table 4.16.

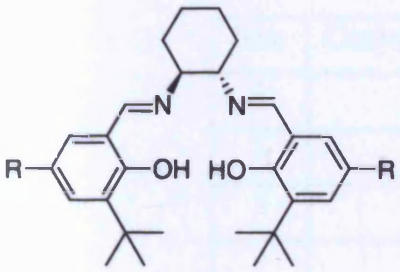


Figure 4.20.

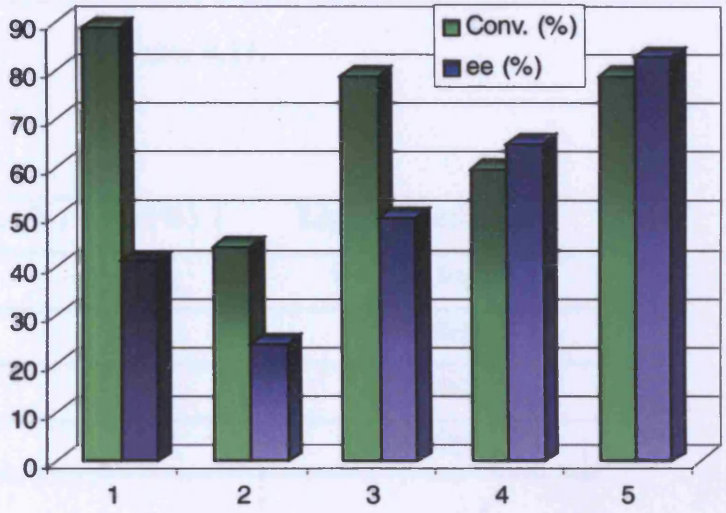


Figure 4.21.

After all of the catalysts were tested, the next step was to study the recyclability of the fluorous ligand, H_2salen11, which gave the best enantioselectivity. The reactions were performed under nitrogen for 24 hours at 0 °C using toluene as solvent. After water was added to quench the reaction (the use of acidic or basic solutions would attack the C-Si bond, **Table 4.17**) the mixture of fluorous ligand and organic product was charged on to a short column of Fluorous Reverse Phase Silica Gel (FRPSG). Methanol was first eluted through the column in order to obtain the pure organic product. By ^{1}H and ^{19}F NMR spectroscopy there was no evidence of the fluorous ligand in this fraction and it was used to calculate the conversion and enantiomeric excess by chiral GC. ICP-MS demonstrated that the amount of Zn in the organic product was extremely low (0.04 %). A solvent switch to diethyl ether was used in order to recover the perfluoroalkylated ligand which was obtained pure without any signs of decomposition by ^{1}H and ^{19}F NMR spectroscopy. The ligand was dried for 45 minutes under oil pump vacuum before

being used again. Since the recycling studies of the catalyst were performed on such a small scale (26 mg), the main problem was that a few milligrams of ligand (~ 5mg) were lost in each cycle due to mechanical losses resulting in a steady decrease in both the conversions and enantioselectivity in the subsequent runs.

Conditions of the work up	Catalyst
HCl (1.0 N)	Decomposed, cleavage of the silyl ponytail
NaOH (1.0 N)	Partly decomposed, cleavage of the silyl ponytail
H_2O	No evidence of decomposition, the spectra were clean

Table 4.17.

Run	Conversion (%)	Ee (%)	Ligand used(%)
1	60	65	100 (30 mg)
2	58	68	87 (26 mg)
3	53	58	70 (21 mg)
4	43	40	53 (16 mg)

Table 4.18. Recycling results using [Zn(salen11)].

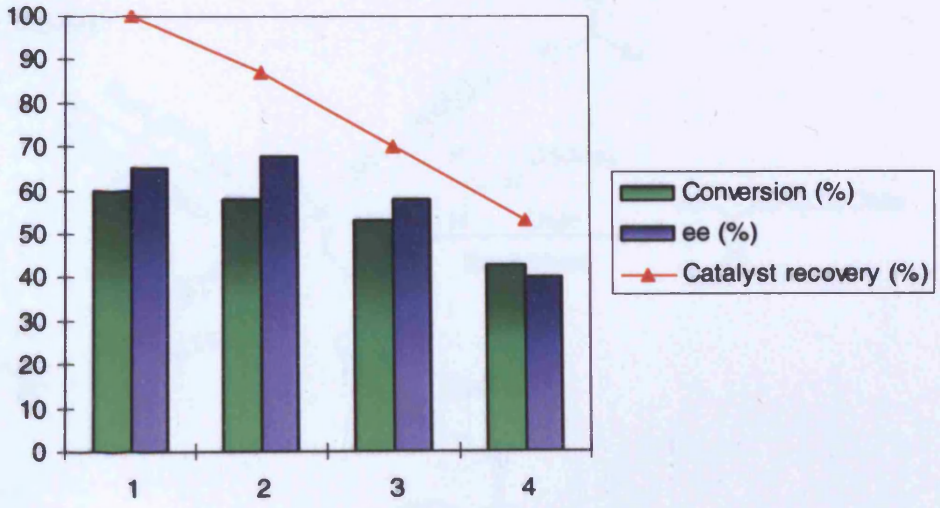


Figure 4.22.

4.2 Asymmetric Alkylation of Imines

4.2.1 Introduction

Nitrogen containing compounds are widely distributed in nature and are essential to life as they play a vital role in the metabolism of all living cells. As a consequence, a large number of drug candidates incorporate an amine functionality.[24] The synthesis of these nitrogen containing compounds from the readily available imine is one of the most important and convenient routes. However, as compared with the counterpart carbonyl double bond, the imine double bond chemistry is a less well explored area. Although imines and carbonyls are very similar, some differences exist between them:

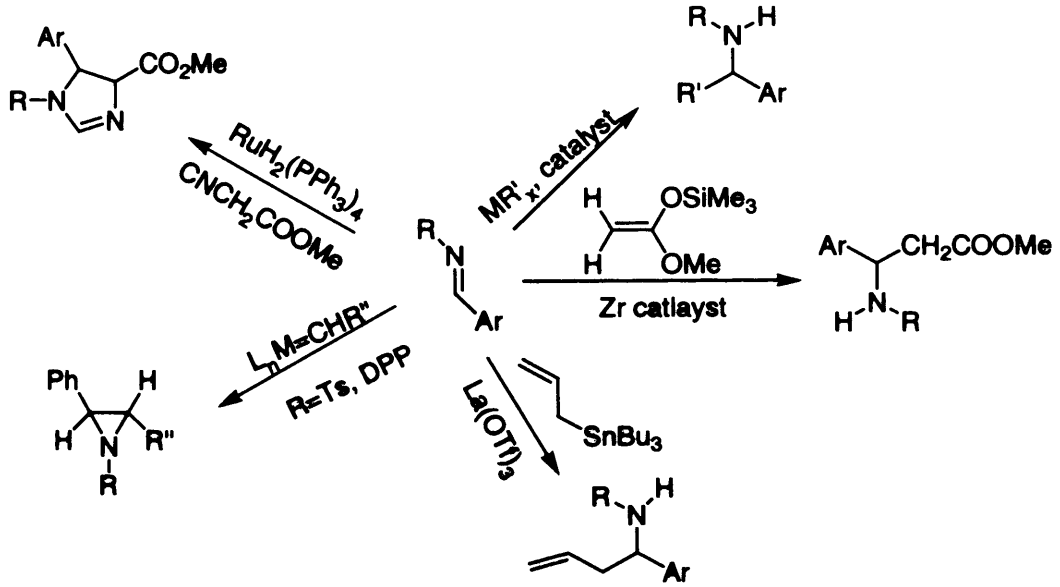
a) Imines are not always easy to prepare, especially ketimines.

b) Since there is an α-hydrogen in aliphatic imines, they can be isomerised to enamines.[25]

c) Although aldehydes or ketones have no geometric isomer, two geometric isomers are possible in imines. In general, the *trans* isomer is usually preferred due to stereochemical considerations.

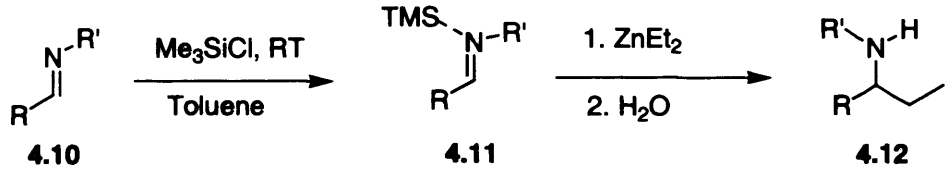
d) The reactivity of imines towards nucleophilic addition is quite different and it is well known that aldehydes are more reactive than imines to nucleophilic attack.

In the last decade, several examples have shown that the relative reactivity of the aldehydes and aldimines can be made more similar by using a number of metal complexes or Lewis acid catalysts.[26] Imines can be attacked by a high number of nucleophiles producing amines,[27] imidazoles[28] and aziridines,[37] amongst others (**Scheme 4.4**).



Scheme 4.4

Scheme 4.4 shows that there is a wide range of reactions for imines that give a series of products. The aim of the work in this section was to study the alkylation of imines using $ZnEt_2$ and $AlEt_3$ to produce amines. One of the simplest approaches for the alkylation of imines is the use of Lewis acid catalysts, for example Hou *et al.*,[29] introduced the use of chlorotrimethylsilane in stoichiometric amounts to promote the reaction. From Table 4.19 it can be seen that all of the reactions proceeded smoothly for N-aryl aldimines and furnished amines in good to excellent yields. The R group in the aldimines could be either aromatic or aliphatic. Higher yields were obtained, however, when aromatic aldimines with electron-withdrawing groups were employed, compared to those with electron-donating groups. The reaction with enolizable aliphatic aldimines also takes place successfully to afford the desired products. It is worthwhile to note that $BF_3.OEt_2$ and $ZnCl_2$ are also efficient Lewis acid catalysts for promoting the reaction but $Ti(O^iPr)_4$ gives products in lower yields.



4.10 **4.11** **4.12**

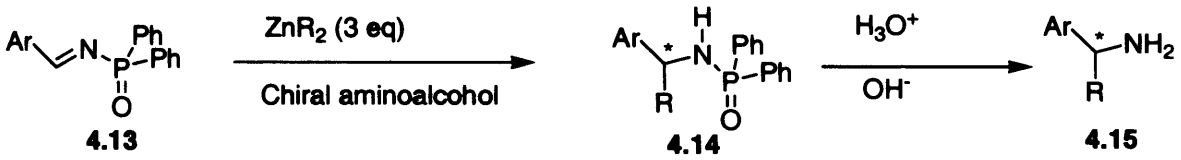
Scheme 4.5.

R	R'	Yield(%)
Ph	Ph	81
Ph	p-ClC_6H_4	78
p-ClC_6H_4	Ph	96
$C_{10}H_{17}$	Ph	78
$(CH_3)_2CHCH_2$	p-ClC_6H_4	60
$CH_3(CH_2)_8$	Ph	41
Ph	Bn	29

Table 4.19. Results using TMSCl to promote the alkylation.

One of the first asymmetric approaches to the alkylation of imines was by Soai *et al.*[30] The alkylation of *N*-diphenylphosphinoimines (**Scheme 4.5**) was catalysed by aminoalcohols in both stoichiometric and catalytic quantities. The imines were easily synthesised from benzaldehyde

and the corresponding diphenylphosphinic amide. When the *N*-diphenylphosphinoimines were treated with $ZnEt_2$ in the presence of a stoichiometric amount of (1*S*, 2*R*)-2-morpholino-1-phenylpropan-1-ol, the corresponding (*S*)-phosphoramide was obtained in good yields and enantioselectivities (**Table 4.20**), although when catalytic amounts of the catalyst were added lower yields were obtained. The phosphoramide was deprotected with acid to yield the chiral amine (**Scheme 4.5**) and there was no sign of racemisation during the acidic hydrolysis. Enantioselective methylation and butylation were also tried and, although lower yields were obtained, the enantioselectivities remained high.



Scheme 4.5.

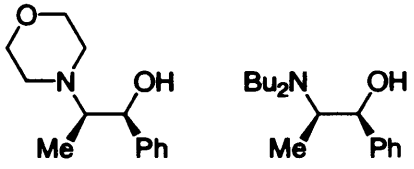
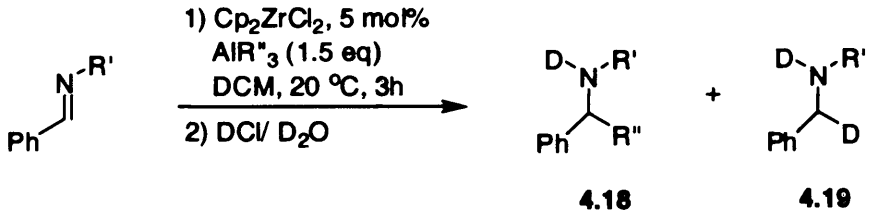


Figure 4.23.

Ar	R	Catalyst (eq)	Time (h)	Yield (%)	ee (%)
Ph	Et	4.16 (1.0)	22	89	90 (S)
Ph	Et	4.16 (0.5)	99	69	85(S)
Ph	Et	4.17 (1.0)	19	61	85(S)
4-MeC_6H_4	Et	4.16 (1.0)	90	75	90
4-MeC_6H_4	Et	4.16 (0.5)	112	69	87
Ph	Me	4.16 (1.0)	113	46	85
Ph	Bu	4.16 (1.0)	22	56	87
Ph	Et	4.17 (0.1)	8	12	75

Table 4.20. Results obtained using aminoalcohols to promote the reaction.

Another interesting approach, this time using a metal catalyst, was introduced by Szymoniak *et al.*[31] Using $AlEt_3$ as a nucleophile and Cp_2ZrCl_2 as catalyst (**Scheme 4.6**), the reaction was carried out using a range of aromatic substrates bearing *N*-aryl or *N*-alkyl groups (**Table 4.21**). Good yields were obtained for both *N*-aryl and *N*-alkyl groups and, interestingly, using a chiral imine, the amine was obtained as a single diastereomer (**Table 4.21**). Further work, included the use of tributylalane ($AlBu_3$) as the alkylating reagent but, contrary to the results of the hydroalumination of alkenes,[32] the competing reduction of the imine (to yield amine **4.18**) was observed (**Scheme 4.6**). However, when the zirconium catalyst was used a mixture of amines **4.18** and **4.19** was obtained (**Table 4.21**). When using an imine derived from an aliphatic aldehyde lower yields for the alkylation were obtained probably due to a slower zirconium-mediated alkylalumination reaction with respect to the direct side reduction reaction. When $AlMe_3$ was used as the nucleophile none of the desired product was formed.

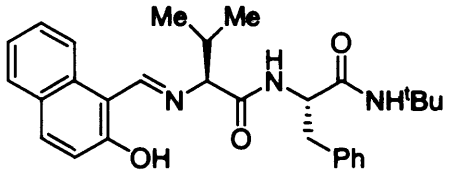


Scheme 4.6.

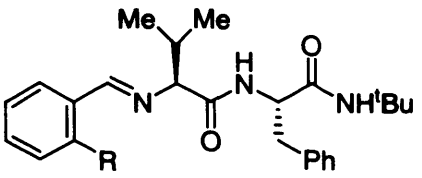
R'	R''	Time (h)	Yield(%) (4.18/4.19)
Ph	Et	3	91/0
Bn	Et	6	88/0
Pr	Et	8	85/0
(R)-2-hydroxy-1-phenylethyl	Et	3	92/0
Ph	Bu	12	67/28
Ph	Bu	24	75 /20
4-MeO-C_6H_4	Bu	24	71/22

Table 4.21. Results obtained using Zr catalyst to promote the reaction.

Finally, imines can be alkylated enantiomerically using chiral Zr- or Ti- catalysts.[33] Chiral peptide based ligands were used in combination with Zr and Ti alkoxides to deliver the best enantioselectivities (with other metals giving ee's of <5%). The comparison between $Zr(O^iPr)_4.^iPrOH$ (43% conversion and 62% ee) and $Ti(O^iPr)_4$ (>98% conversion and 88% ee) indicates a higher activity for Ti than Zr. The proportion of chiral ligand and metal derivative is important; while the chiral ligand can be added in low proportions (0.1 mol%), the metal derivative must be added in larger amounts (20 mol%) for the optimum reaction. The reaction also works well for other aryl substituents such as naphthalene. However, when electron deficient imines are used the reduced amine product is obtained, which means that the intermediate "ZrEt" or "ZnEt" species may undergo a rapid β-elimination to afford a metal hydride that effects C=N reduction.

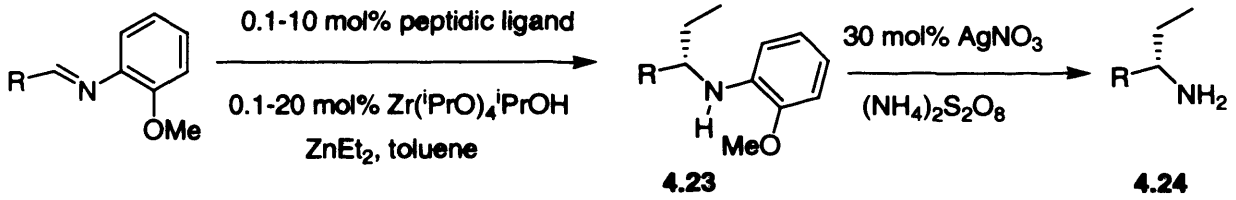


4.20



4.21 R=PPh_2
4.22 R=OH

Figure 4.24.



4.23 **4.24**

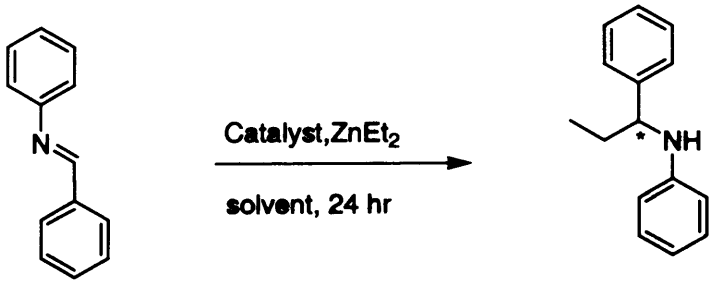
Scheme 4.24.

R	Ligand (mol%)	Ti (mol%)	Conv (%)	Ee (%)
Ph	10	10	>98	93
Ph	1	1	10	81
Ph	1	20	>98	95
Ph	0.1	20	>98	93
Furyl	1	20	>98	97
Naphthyl	1	20	95	92
Naphthyl	10	10	>98	91
4-CF_3-C_6H_4	10	11	95	88
2-Br-C_6H_4	10	11	95	90
4-MeO-C_6H_4	10	11	95	91

Table 4.22. Results obtained using Ti catalysts to promote the alkylation.

4.2.2 Results and discussion

The main purpose of the work in this section was to study the reactivity of imines with some $M(alkyl)_n$ nucleophiles to yield the corresponding amines. The first nucleophile tested was $ZnEt_2$ and the reactions were carried out in either DCM, toluene, ethyl acetate or THF at room temperature under an atmosphere of nitrogen. Unlike the alkylation of benzaldehyde, the lower reactivity of imines meant that the reaction could be performed at higher temperature. First, the activity of [Zn(salen10)] (25 mol%) was tested. Although many solvents were investigated none of the desired product was observed after 24 h, and this result was in stark contrast to the result obtained for this catalyst in the alkylation of benzaldehyde (79% conversion, 83% ee, see Section 4.1.2.1). The next catalyst to be tested was [Ti(O^iPr)$_2$(BINOL)]. In this case, the reaction was catalysed at room temperature but with low conversions (25%) and no asymmetry was induced by the catalyst. Even when the proportions of imine:ligand:Ti were changed, the results were almost the same in terms of conversion and enantioselectivity.



Scheme 4.25.

Catalyst	Temperature (°C)	Solvent	$ZnEt_2$ (eq.)	Conv. (%)	Ee (%)
No catalyst	RT	Tol	1.0	0	0
Me_3SiCl	RT	DCM	1.0	41	0
Me_3SiCl	65[c]	DCM	1.0	100	0
[Zn(salen10)]	RT	DCM	1.0	0	0
[Zn(salen10)]	RT	Toluene	1.0	0	0
[Zn(salen10)]	RT	EtOAc	1.0	0	0
[Zn(salen10)]	RT	THF	1.0	0	0
[Ti(O^{i}Pr)$_2$ (R-BINOL)][a]	RT	DCM	2.0	23	0
[Ti(O^{i}Pr)$_2$(R-BINOL)]	40	DCM	2.0	Decomposed	--
[Ti(O^{i}Pr)$_2$ (R-BINOL)][b]	RT	DCM	3.0	25	0

[a] Proportion imine:ligand:Ti 1:0.2:0.2.

[b] Proportion imine:ligand:Ti 1:0.2:1.2.

[c] Sealed system.

Table 4.23. Results obtained using various catalysts and reagentsand $ZnEt_2$ as alkylating agent.

Another more reactive nucleophile was also tested, $AlEt_3$. Since [Al(salen10)Cl] has been used in the addition of trimethylsilylcyanide (TMSCN) to aldehydes giving good yields and selectivities,[34] it was first tested in the addition of $AlEt_3$ to imine (**Scheme 4.25**). Unfortunately, only a low yield of the amine was observed. [Al(*R*-BINOL)Et] has also been used in the alkylation of aldehydes.[35] Although the yield of the amine was improved by using [Al(*R*-BINOL)Et], no asymmetry was induced. Finally, [Ti(O^{i}Pr)$_2$(*R*-BINOL)] was synthesised *in situ* by reaction of *R*-BINOL with Ti(O^{i}Pr)$_4$ and although much better yields were obtained no enantioselectivity was observed.

Catalyst	Temperature (°C)	Solvent	$AlEt_3$ (eq)	Conv (%)	ee (%)
No catalyst	RT	DCM	1.0	20	0
[Al(salen10)Cl]	RT	DCM	1.0	35	0
[Al(R-BINOL)Et]	RT	DCM	1.0	50	0
[Ti(R-BINOL)(^{i}PrO)$_2$]	RT	DCM	1.0	Decomposed	--
[Ti(R-BINOL)(^{i}PrO)$_2$]	0	DCM	1.5	42	0
[Ti(R-BINOL)(^{i}PrO)$_2$]	0	DCM	3.0	90	0

Table 4.24. Results obtained using various catalysts and reagentsand $AlEt_3$ as alkylating agent.

4.3 Conclusions

The main aim of this chapter was to study the asymmetric alkylation of benzaldehyde using principally, diethylzinc as nucleophile and different salen ligands as chiral auxiliaries. The effect of the substituents in the 5,5'-positions on the conversion and enantioselectivity were investigated. The main conclusions are:

- Best enantioselectivities were achieved using a ^{t}Bu substituent in the 5,5'-positions. When this substituent was changed to a H, there was a drastic reduction in the enantioselectivity.
- H_2salen9 containing a C_8F_{17} group in the 5,5'-position was synthesised in order to investigate the behaviour of the catalyst and its potential for recycling and reuse. However, lower enantioselectivities were obtained.
- In order to improve the results H_2salen11 containing a bulky $SiMe_2(C_2H_4C_6F_{13})$ substituent in the 5,5'-positions was synthesised and better enantioselectivities were obtained.
- Preliminary results demonstrated that H_2salen11 could be recycled and reused with no traces of decomposition. However, the small amount of [Zn(salen11)] used for the reactions made mechanical losses very important, so that the catalyst lost some efficiency over the three recycles.

Two organometallic reagents were tested, $AlEt_3$ and $ZnEt_2$, in the asymmetric alkylation of imines and the Al(III) derivative was more reactive than the Zn(II) derivative. Good yields were obtained when chiral Ti(IV) catalysts were used, but no enantioselectivity was obtained. In

conclusion, three different types of Lewis acid catalysts were tested using chiral salen ligands and BINOL. The overall results showed that even if the catalyst could improve the yields, they did not induce any enantioselectivity. Maybe if a 2-hydroxybenzylimine is used instead of a benzylimine the enantioselectivity could be improved.

4.4 References

1 T. Mukaiyama, K. Soai, T. Sato, H. Shimizu, K. Suzuki, *J. Am. Chem. Soc,* 1979, **101**, 1455.

2 J. P. Mazaleyrat, D. J. Cram, *J. Am. Chem. Soc.*, 1981, **103**, 4585.

3 J. Otera, Y. Kawasiki, H. Mizuno, Y. Shimizu, *Chem. Lett.*, 1983, 1527.

4 T. Mukaiyama, K. Soai, S. Kobayashi, *Chem. Lett.*, 1978, 219.

5 Y. Yamamoto, J. Yamada, *J. Am. Chem. Soc.*, 1987, **109**, 4395.

6 K. Sosai, M. Watanabe, *J. Chem. Soc., Chem. Comm.*, 1990, 43.

7 K. Soai, A. Ookawa, K. Ogawa, T. Kaba, *J. Chem. Soc., Chem. Comm.*, 1987, 467.

8 K. Tanaka, H. Ushio, H. Suzuki, *J. Chem. Soc., Chem. Comm.*, 1989, 1700.

9 L. Shengjian, J. Yaozhong, M. Aiqiao, *Tetrahedron Asymm.*, 1992, **3**, 1467.

10 A. A. Smaardijk, H. Wynberg, *J. Org. Chem.*, 1987, 52, 135.

11 D. Kimamoto, H. Imma, H Nakai, *Synlett,* 1995, 1229.

12 H. Imma, M. Mori, T. Nakai, *Synlett*, 1996, 439.

13 F.- Y. Zhang, C.- W. Yip, R. Cao, A. S. C. Chan, *Tetrahedron Asymm.*, 1997, **8**, 585.

14 M. Mori, T. Nakai, *Tetrahedron Lett.*, 1997, **38**, 6233.

15 G. E. Keck, L. S. Geraci, *Tetrahedron Lett.*, 1993, **34**, 7827.

16 P.G. Cozzi, A. Papa, A. Umani-Ronchi, *Tetrahedron Lett.*, 1996, **37**, 4613.

17 V. R. Venkataraman, U. K. Anyanwu, *Tetrahedron Lett.*, 2003, **44**, 6445.

18 M. W. Fennie, E. F. DiMauro, E. M. O'Brien, V. Annamalai, M. C. Kozlowski, *Tetrahedron,* 2005, **61**, 6249.

19 H. Klein, E. Rijnberg, J. T. B. H. Jastrzebski, G. van Koten, *Org. Lett.*, 1999, **1**, 853.

20 E. Rijnberg, N. J. Hovstad, A. W. Kleij, J. T. B. H. Jasttrebski, J. Boersma, M. D. Janssen, A. L. Spek, G. van Koten, *Organometallics,* 1997, **16**, 2847.

21 Y. Tian, K. S. Chan, *Tetrahedron Lett.*, 2000, **41**, 8813.

22 Y. Nakamura, S. Takeuchi, Y. Ohgo, D. P. Curran, *Tetrahedron Lett.*, 2000, **41**, 57.

23 J. Fawcett, E. G. Hope, A. M. Stuart, A. J. West, *Green Chem.*, 2005, **7**, 316.

24 G. Liu, O. A. Cogan, J. A. Ellman, *J. Am. Chem. Soc.*, 1999, **119**, 9913.

25 S. Patai, *The chemistry of the carbon nitrogen double bond*, 1975, Wiley, New York.

26 For some reviews: R. Bloch, *Chem. Rev.*, 1998, **98**, 1407, H. Nahamura, H. Iwama, Y. Yamamoto, *J. Am. Chem. Soc.*, 1996, **118**, 6641.

27 C. Denhez, J.-L. Vasse, J. Szymoniak, *Synthesis*, 2005, **12**, 2075.

28 L.-X. Dai, Y.-R. Lin, X.-L. Hou, Y.-G. Zhou, *Pure Appl. Chem.*, 1999, **71**, 1033.

29 X-L. Hou, X-L. Zheng, L-X. Dai, *Tetrahedron Lett.*, 1998, **39**, 6949.

30 K. Soai, T. Hatanaka, T. Miyazawa, *J. Chem. Soc., Chem. Comm.*, 1992, 1097.

31 J. Szymoniak, J.-L. Vasse, C. Denhez, *Synthesis*, 2005, **12**, 2075.

32 E. Negishi, S. Huo, *Titanium and Zirconium in Organic Synthesis*, 2002, Wiley, New York.

33 L. C. Akullian, J. R. Porter, J. F. Traverse, M. L. Snapper, A. H. Hoveyda, *Adv. Synth. Catal.*, 2005, **347**, 417; J. R. Porter, J. F. Traverse, A. H. Hoveyda, M. L. Snapper, *J. Am. Chem. Soc.*, 2001, **123**, 984.

34 S. S. Kim, D. H. Song, *Tetrahedron*, 2005, **61**, 12131.

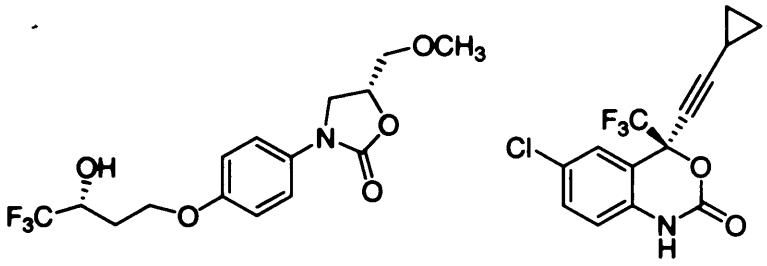
35 A. S. Chan, F.-Y. Zhang, *J. Am. Chem. Soc.*, 1997, **119**, 4080.

5 Asymmetric Reactions using Lewis Acid Catalysts

5.1 Asymmetric Trifluoromethylation

5.1.1 Introduction

Fluorinated organic compounds find wide applications in the pharmaceutical and agrochemical industries due to their unique properties and biological activity.[1] Amongst them, trifluoromethyl-substituted molecules constitute a particular class because of their properties, such as the high lipophilicity associated with this moiety. These compounds thus find applications in the pharmaceutical field. Recently, the emergence of drugs such as Befloxatone (antidepressant) and Efavirenz (anti-HIV) (**Figure 5.1**), in which the CF_3 moiety is located at the chiral centre, has underlined another important synthetic challenge: asymmetric trifluoromethylation.



Befloxatone 5.1 Efaverinz 5.2

Figure 5.1.

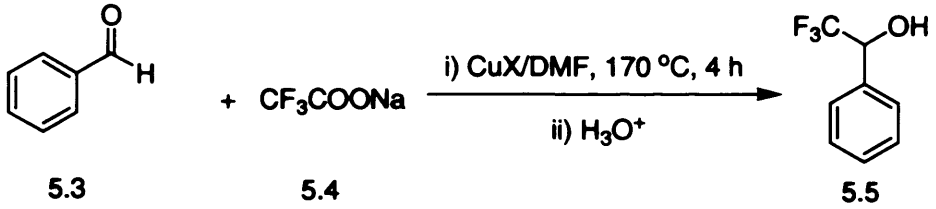
Trifluoromethylation can be achieved *via* 6 different methods such as:

1) Generation of trifluoromethyl radicals from precursors.[2]
2) Use of trifluoromethyl copper (or cadmium or zinc).[3]
3) Electrochemical methods.[4]
4) Indirect routes such as halogen exchange of CCl_3 with HF/ SbF_5.[5]
5) Using trifluoroacetate as a trifluoromethylating agent.[6]
6) Using Ruppert's reagent systems, CF_3SiMe_3/ KF (Me_4NF, ^tBuOK, etc.), as a trifluoromethylating agent.[7]

In the generation of radical precursors and the use of electrochemical methods special equipment is required. The low stability of the organometallic compounds makes their use difficult, however, $Cu(CF_3)_2$ is a useful tool in the trifluoromethylation of bromo alkenes.[8] One of the main problems with halogen exchange is the toxicity and difficulty of handling HF.

One of the most common trifluoromethylating agents is sodium trifluoroacetate. The use of sodium trifluoroacetate was first reported by Kiyohide *et al.*[9] for the trifluoromethylations of

aromatic halides. Further research by Chan *et al.*[6] showed that Cu(I) halides are effective catalysts for promoting the trifluoromethylation of aldehydes and ketones with sodium trifluoroacetate (**Scheme 5.1**). It is shown in **Table 5.1** high yields were obtained with a series of aromatic aldehydes including tolualdehydes (*ortho, meta and para*) and chlorobenzaldehydes (*ortho, meta and para*). Only the *meta-* substituted derivatives gave slightly lower yields (83-87%). Cyclohexanecarbaldehyde also gave a good yield (96%), but when ketones were used there was a drop in yields to 56% and 2% respectively for cyclohexanone and acetophenone. Initiators such as KF and ^{t}BuOK, widely used with silane trifluoromethylating agents, were also tested in an attempt to improve the yields acquired with the ketones. The results, however, were not significantly improved. Kiyohide indicated that evolution of CO_2 began around 140 °C. There was little difference between Cu(I) halides (X = Cl, Br, I gave 97%, 98%, 99% yield respectively) and the reaction also proceeded in the absence of catalyst (60%) for benzaldehyde.



5.3 5.4 5.5

Scheme 5.1

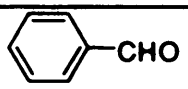
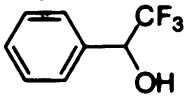
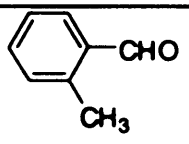
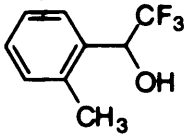
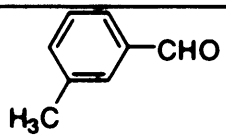
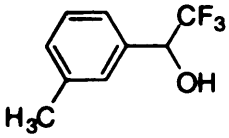
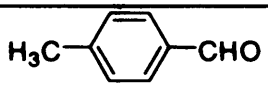
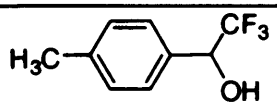
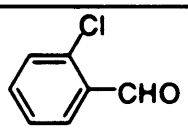
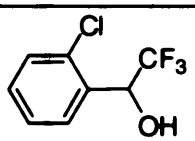
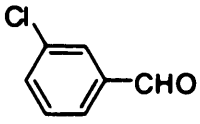
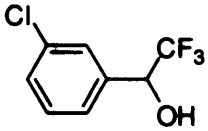
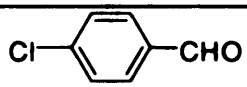
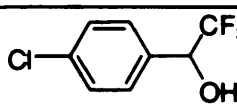
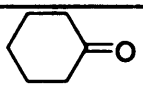
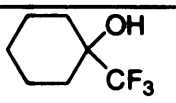
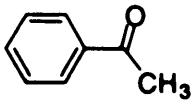
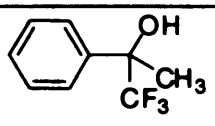
Carbonyl compound	Product	Yield (%)
		99
		92
		83
		96
		97
		87
		99
		56
		2

Table 5.1. Yields obtained using CuI as catalyst and CF_3COONa as reagent.

Despite its associated advantages, the use of sodium trifluoroacetate is restricted in the field of asymmetric catalysis due to the high temperatures necessary to perform the reaction. A common strategy that is used to obtain products containing a trifluoromethylated asymmetric carbon moiety, is the asymmetric reduction of, or nucleophilic addition onto, a trifluoroacetyl moiety.[10] In contrast, there are very few methods for the asymmetric nucleophilic addition of a

trifluoromethyl group. One of the species that can nucleophilically transfer CF_3 is trifluoromethyltrimethylsilane, (TMS)CF_3.

First reported by Prakash *et al.*,[11] (TMS)CF_3 belongs to a group of trimethylsilyl compounds substituted with electron-withdrawing substituents, such as CN, I, Cl, Br, N_3, NCO, CNO, etc., that have been used as synthetic reagents to attach these substituents to electron-deficient centres.[12] These reagents are generally based on the hard-soft reactivity principle, with the silicon atom attached to the electronegative substituent. Accordingly, the bond between the pseudohalide trifluoromethyl and trimethylsilyl centre should be sufficiently polarised with the trifluoromethyl group bearing the negative charge. The nucleophilic addition of the trifluoromethyl group is carried out at room temperature, as opposed to the high temperatures needed with sodium trifluoroacetate, using tetrabutylammonium fluoride (TBAF) as the initiator. Good conversions were obtained for almost all aliphatic and aromatic aldehydes and ketones (**Table 5.2**). The mechanism, shown in Scheme 5.2, indicates that the reaction was induced by fluoride ion with the irreversible formation of fluorotrimethylsilane in the first stage of the reaction. The trifluoromethylated oxoanion then catalyses the reaction in the propagation step (**Scheme 5.2**). The reaction can also be initiated with ^{t}BuOK.

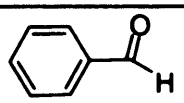
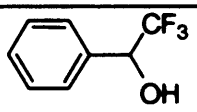
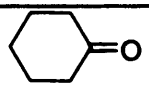
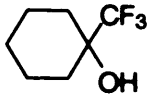
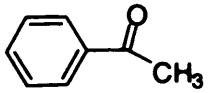
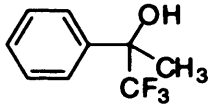
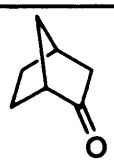
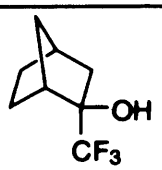
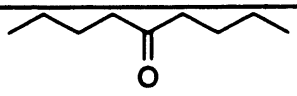
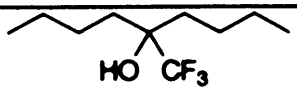
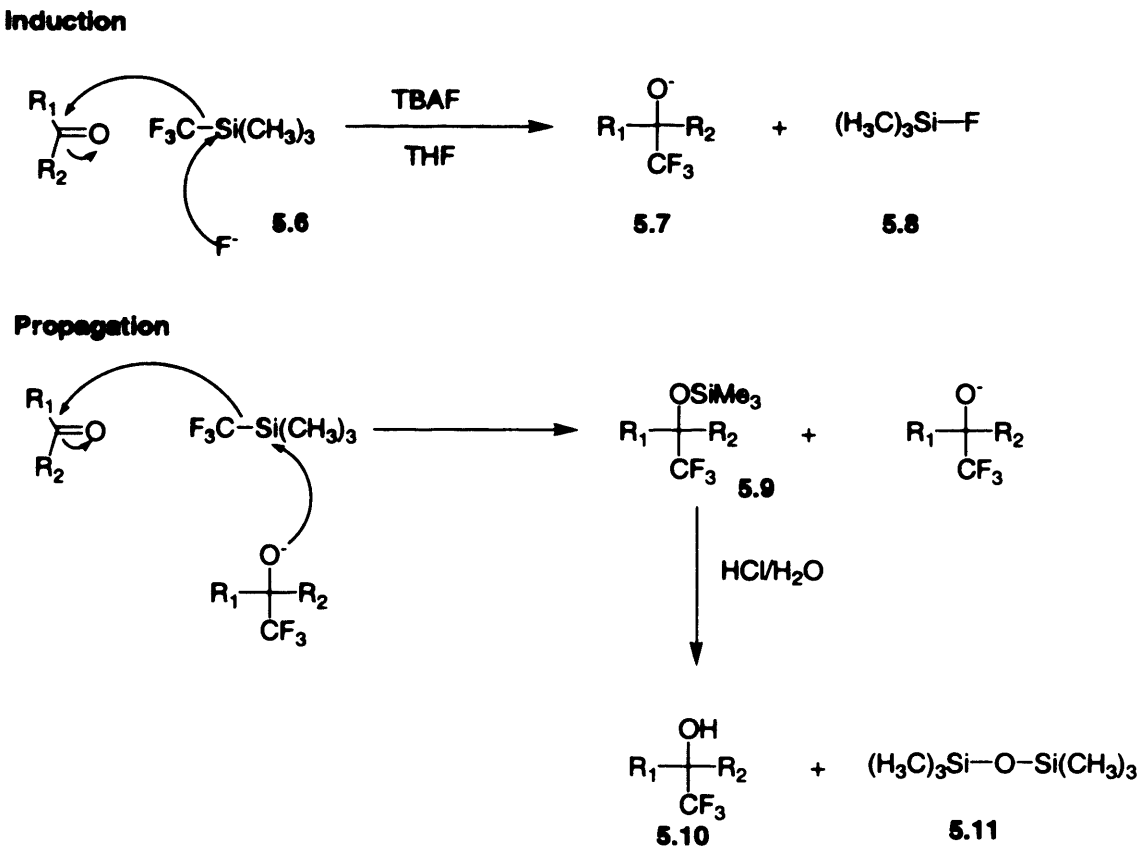
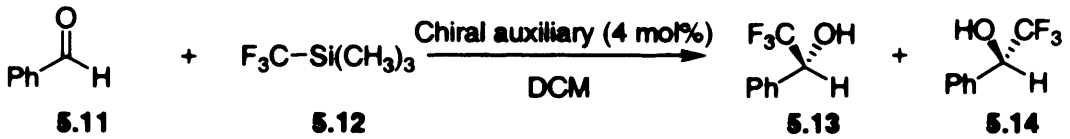
Substrate	Product	Yield (%)
		85
		77
		74
		92
		87

Table 5.2. Yields obtained using Ruppert's reagent.



Scheme 5.2.

Since Ruppert's reagent, $TMS(CF_3)$, does not require high temperatures, it is a suitable reagent for asymmetric trifluoromethylation. In the mechanism discussed above the ammonium cation interacts with the alkoxy adduct during the reaction. Prakash,[13] Yudin,[14] and Iseki *et al.*,[15] amongst others, reported good yields and enantioselectivities in the asymmetric trifluoromethylation using chiral phase transfer catalysts derived from cinchona alkaloids. More recently Caron *et al.*[16] developed a new type of cinchonium alkaloid (**Figure 5.2**) capable of performing the reaction more efficiently without the use of a separate initiator (**Scheme 5.3**). Using lower amounts of the cinchonium derivatives in DCM the reaction proceeds in good yields and enantioselectivities in the case of aldehydes. However, lower yields and enantioselectivities were achieved when ketones were used as substrates (**Table 5.3**).



Scheme 5.3.

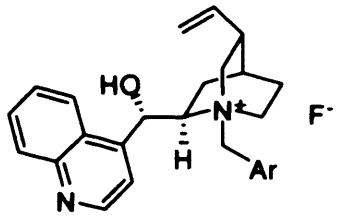
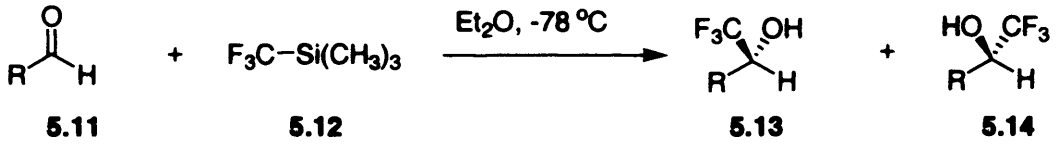


Figure 5.2.

Ar	Conversion (%)	ee (%)
3,5-$(MeO)_2C_6H_3$	98	83
4-$MeOC_6H_4$	88	58
3-$MeOC_6H_4$	86	74
3,5-$(CF_3)_2C_6H_3$	21	70
4-$CF_3C_6H_4$	77	69
9-anthracyl	95	85

Table 5.3. Results using cinchonium alkaloids as catalysts.

Iseki and co-workers have developed a chiral triaminosulfonium salt (**Figure 5.3**), which functions as a Lewis base catalyst in enantioselective trifluoromethylation.[17] The reaction is carried out using 10 mol % of the catalyst in diethyl ether at -78 °C and the enantioselectivities obtained were from 10 to 52 %.



5.11 **5.12** **5.13** **5.14**

Scheme 5.4.

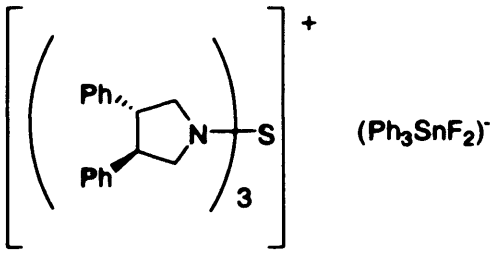
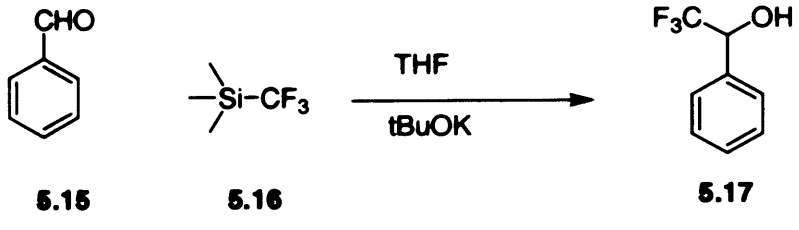


Figure 5.3.

5.1.2 Results and discussion

The aim of this work was to investigate whether chiral transition metal catalysts could be used to induce asymmetry in the trifluoromethylation of aldehydes. The use of chiral metal catalysts can normally improve both the yield and the enantioselectivity in Lewis acid catalysed reactions. The catalysts used in this reaction are salen derivatives, widely used as chiral catalysts in several asymmetric reactions such as the addition of diethylzinc to aldehydes (see Chapter 4). The conversion was calculated by ^{1}H NMR spectroscopy and the product enantioselectivities were determined by chiral GC.

The reaction was performed in THF under nitrogen for 24 hours at different temperatures. The results in **Table 5.4** demonstrate that the use of the initiator, KO^{t}Bu, was essential for forming the trifluoromethyl anion. Unfortunately, the reaction did not proceed in the absence of KO^{t}Bu. When KO^{t}Bu was added, no asymmetric induction was achieved regardless of the temperature used. The reaction between the trifluoromethyl anion and benzaldehyde appears to be too fast and does not enable the transition metal catalyst to take part in the catalytic process. [Ti(salen10)Cl_2] was synthesised by adding $TiCl_4$ to a solution of H_2salen10 (**Figure 5.4**) in THF. Neither [Zn(salen10)] nor [Ti(salen10)Cl_2] showed any enantioselective induction when they were tested as catalysts whatever the temperature. Finally, a 100 mol% of complex was used in order to try to coordinate all of the benzaldehyde, but unfortunately no enantioselectivity was achieved even under these reaction conditions.



5.15 **5.16** **5.17**

Scheme 5.5.

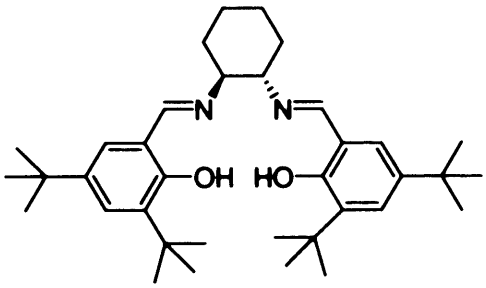
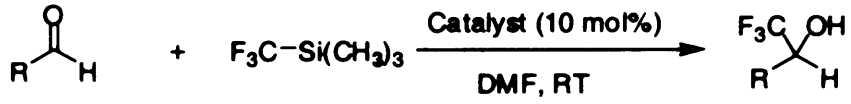


Figure 5.4.

Catalyst	mol (%)	^{t}BuOK (eq)	Temperature (°C)	Conversion (%)	ee (%)
No Catalyst	0	---	RT	0	0
No Catalyst	0	0.1 eq	RT	95	0
[Ti(salen10)Cl_2]	10	---	RT	0	0
[Ti(salen10)Cl_2]	10	0.1 eq	RT	93	0
[Zn(salen10)]	10	0.1 eq	0	73	0
[Ti(salen10)Cl_2]	10	0.1 eq	0	70	0
[Ti(salen10)Cl_2]	100	0.1 eq	-78	40	0

Table 5.4. Results obtained using salen catalysts.

Recently, Shibata *et al.*[18] studied the application of Lewis acid catalysts in trifluoromethylation of aldehydes with Ruppert's reagent. Initially, a series of different Lewis acid catalysts were screened for promoting the reaction using 2-naphthaldehyde with TMS(CF_3) in DMF (**Table 5.5**). The reaction was not promoted by $TiCl_4$, $AlCl_3$, $SnCl_4$, $BF_3.OEt_2$ but other Lewis acid catalysts, such as Ti(^{i}PrO)$_4$, TiF_4, $MgCl_2$, [Cu(AcO)$_2$] (**Table 5.5**), proved to be very effective catalysts for the trifluoromethylation reaction. Ti(^{i}PrO)$_4$, TiF_4 and Cu(AcO)$_2$ were then investigated in combination with mono and bi-dentate phosphines (PPh_3 and dppe (**Table 5.6**)) Excellent yields were obtained with [Cu(OAc)$_2$] in the presence of bidentate phosphines. In the case of Ti(O^{i}Pr)$_4$, when the solvent was changed to dichloromethane, THF or toluene a 0% yield was obtained. A highly desirable advance in this field would be to introduce enantioselectivity by using chiral Lewis acid catalysts.



Scheme 5.6.

Lewis acid	R	Time (h)	Yield (%)
$SnCl_4$	2-naphthyl	24	0
$AlCl_3$	2-naphthyl	24	0
BF_3/Et_2O	2-naphthyl	24	0
$TiCl_4$	2-naphthyl	24	0
$Cu(TfO)_2$	2-naphthyl	24	2
TiF_4	2-naphthyl	4	96
$MgCl_2$	2-naphthyl	16	91
$Ti(O^iPr)_4$	2-naphthyl	2	96
ZnF_2	2-naphthyl	24	33
$Ti(O^iPr)_4$	Ph	2	89
$Ti(O^iPr)_4$	Tolyl	0.5	86
$Ti(O^iPr)_4$	$4\text{-}NO_2C_6H_4$	4	84
$Ti(O^iPr)_4$	C_7H_{15}	6	67

Table 5.5. Yields using different Lewis acids.

Lewis acid	Ligand	Solvent	Yield (%)
$Ti(O^iPr)_4$	----	DCM	0
$Ti(O^iPr)_4$	----	THF	0
$Ti(O^iPr)_4$	----	Toluene	0
$Cu(AcO)_2$	dppe	Toluene	99
$Cu(AcO)_2$	dppp	Toluene	97
$Cu(AcO)_2$	PPh_3	Toluene	0

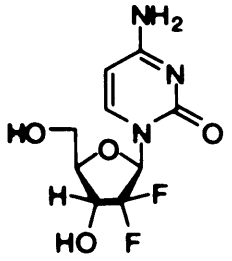
Table 5.6. Yields using different catalytic systems.

5.2 Asymmetric Reformatsky Reaction

5.2.1 Introduction

As has been stated in the section above organofluorine compounds have a great importance in pharmaceutical and agrochemical chemistry.[19] Fluorine, due to its high electronegativity and its size (second smallest after H, van der Waals radius: 1.35Å) has a considerable electronic effect on neighbouring groups in a molecule. The introduction of a difluoromethylene residue into bioactive peptides has led to the discovery of potent protease inhibitors mimicking the transition state for hydrolytic amide bond cleavage.[20] One of these derivatives is 2'-deoxy-2',2'-

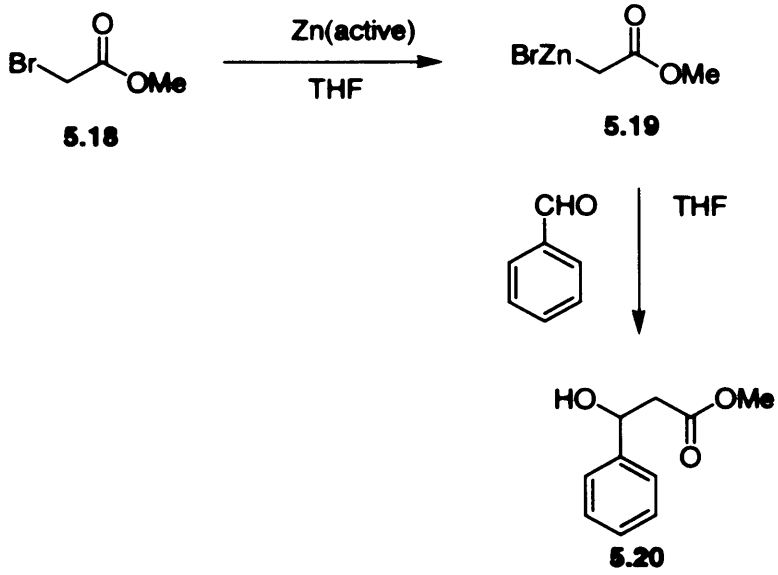
difluorocytidine[21] or gemcitabine (**Figure 5.5**). This is an antimetabolite with a broad spectrum of potent antitumour activity. One useful method for introducing difluoromethylene groups in unsaturated carbons is the Reformatsky reaction.



gemcitabine

Figure 5.5.

The classical form of the well-known Reformatsky reaction, introduced for the first time in 1887,[22] consists of the zinc-induced formation of β-hydroxyalkanoates from α-haloacetates in a reaction with aldehydes and ketones (**Scheme 5.7**). One of the advantages of the Reformatsky reaction is that the reaction proceeds under neutral conditions, in contrast to the aldol reaction that generally requires the addition of either a base to generate the enolate or an acid to activate the electrophile. A very important feature of the classical Reformatsky reaction is that no *O*-substituted products are obtained, and even reagents with strong affinities for oxygen, such as TMSCl, afford only C-silylated products in most cases.

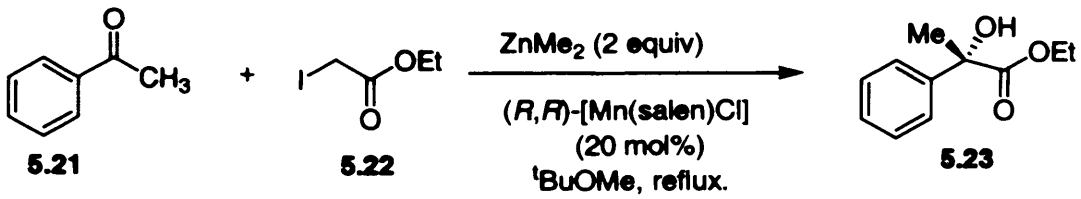


5.18 5.19 5.20

Scheme 5.7.

There are many examples of the asymmetric Reformatsky reaction, using both chiral auxiliaries[23] and ligands.[24,25,26] One of the most recent approaches by Cozzi.[27] Focused on the reaction of ketones and ethyl iodoacetate, and was based on the use of [Mn(salen10)Cl] as the chiral catalyst.

The enolates were prepared by the direct exchange of an iodo ester with $ZnMe_2$,[28] using acetophenone as the model substrate (**Scheme 5.8**). Of all the chiral salen catalysts used, [Mn(salen)Cl] gave the best enantioselectivity (**Table 5.7**). However, when 4-phenyl-pyridine-*N*-oxide was added the enantiomeric excesses were improved dramatically (**Table 5.8**), an additive used frequently in asymmetric epoxidation using [Mn(salen10)Cl].[29] The reaction works well with a wide range of substrates including aliphatic, aromatic, heterocyclic and α,β-unsaturated ketones, but the best results were obtained with aromatic ketones. Linear aliphatic ketones gave synthetically useless results and in general, steric hinderance seems to control selectivity in this reaction.



5.21 **5.22** **5.23**

Scheme 5.8.

Catalyst	Ee (%)
[Mn(salen)Cl]	63
[Zn(salen)]	20
[(salen)Ti=O]	0
[Ti(salen)Cl_2]	0
[Cu(salen)]	0
[Co(salen)(OAc)]	0
[Cr(salen)Cl]	0

Table 5.7. enantioselectivie's obtained with different M(salen).

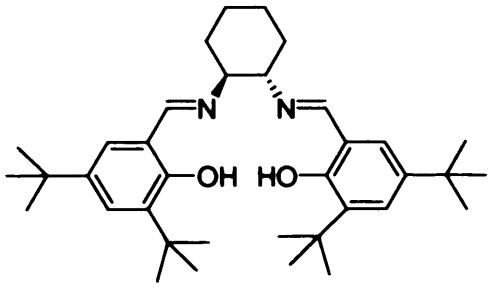
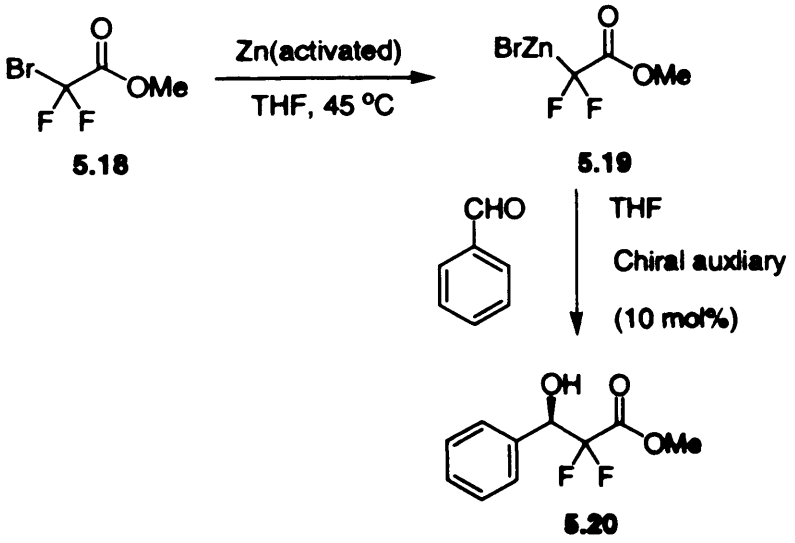


Figure 5.6.

Ketone	Time (h)	Yield (%)	Ee (%)
1-tetralone	48	45	86
2-chloroacetophenone	30	53	84
Cyclopropylacetone	72	78	86
4-phenylbutan-2-one	24	77	23
2-furylacetone	120	51	40
1-acetonaphthone	80	53	82

Table 5.8. Results obtained using different substrates.

The first approach to the synthesis of α,α-difluoro-β-hydroxyesters was proposed by Braun,[30] who used an enantioselective Reformatsky reaction. First, the organozinc derivative was generated by the addition of methyl bromodifluoroacetate to activated Zn powder (**Scheme 5.9**). This solution was then added to a solution of benzaldehyde containing a stoichiometric amount of chiral aminoalcohol or diol (**Table 5.9**). The best chemical yields and enantiomeric excesses were obtained with (1*R*,2*S*)-*N*-methylephedrine (**Figure 5.6**). The excess of the Reformatsky reagent over the chiral additive 5c turned out to be favorable because it also deprotonates the hydroxyl group of the aminoalcohol.



Scheme 5.9.

Aminoalcohol	Molar Ratio (Reformatsky reagent:aminoalcohol:PhCHO)	Yield (%)	ee (%)
5.21	2 : 1 : 1	62	62
5.22	3 : 1 : 1	62	55
5.23	1 : 0.1 : 1	45	54
5.23	1 : 0.3 : 1	47	79
5.23	3 : 2 : 1	93	79
5.23	3 : 1 : 1	61	84

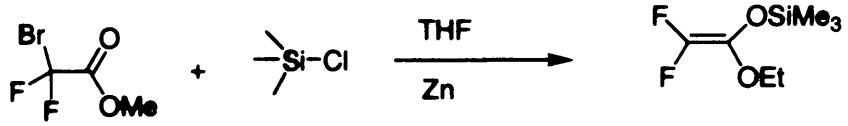
Table 5.9.

5.21 R=H
5.22 R=Me

5.23

Figure 5.7.

Iseki used a completely different approach to the asymmetric Reformatsky reaction by using the asymmetric aldol reaction after isolating the silyl enol ether (**Scheme 5.10**). The reason for using the trimethylsilylderivative is that the impure acetal containing zinc salts is not practical for use in an asymmetric aldol reaction catalysed by chiral Lewis acid catalysts since the zinc also competes as an achiral Lewis acid. After purification the fluorine ketene silyl acetal was isolated in an extremely low yield (12%).

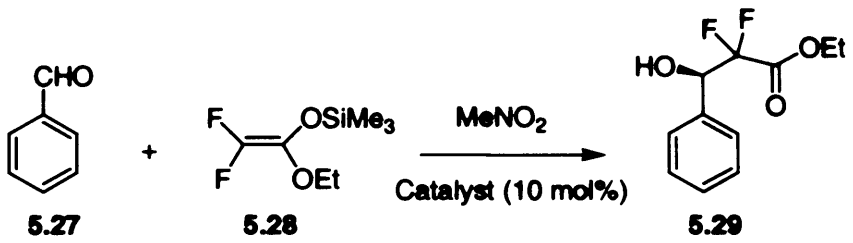


5.24 **5.25** **5.26**

Scheme 5.10.

Several catalysts, well known for their activity as chiral Lewis acid catalysts with ketene silyl acetals, were evaluated for their efficacy in the aldol reaction of benzaldehyde with the fluorine ketene silyl acetal. The catalysts chosen for this reaction were Masamune[31] and Kiyooka[32] catalysts, which are borohydrides (**Figure 5.7**). The reaction was more selective at low

temperatures although a curious effect of reverse enantioselectivity was observed when the reaction temperature was raised to –45 °C (**Table 5.10**). This reaction seems to resolve the problem of the free zinc effectively, however the low yields in the synthesis of the silyl acetal are a major obstacle for this method.



Scheme 5.11.

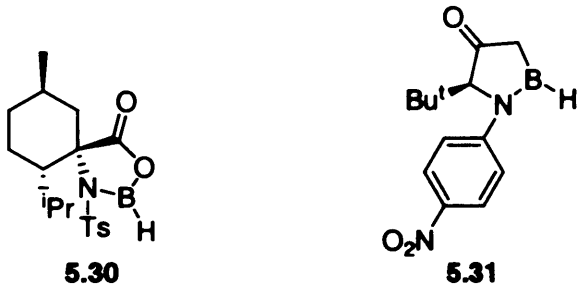


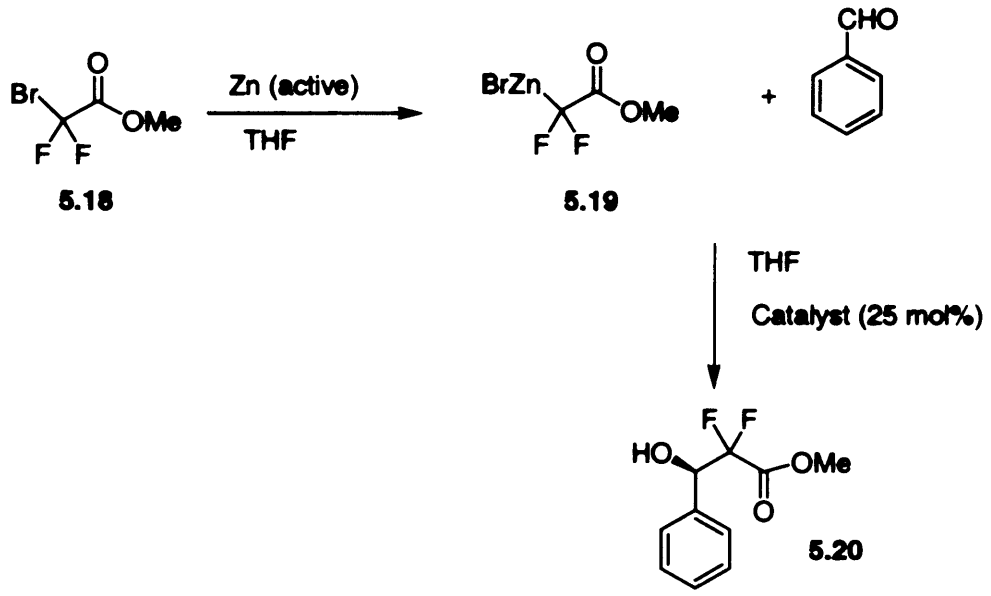
Figure 5.7.

Aldehyde	Catalyst	Temp (°C)	Yield (%)	Ee (%)
Benzaldehyde	5.30	-78	99	97 (R)
Benzaldehyde	5.30	-60	99	81 (R)
Benzaldehyde	5.30	-45	94	33 (S)
Benzaldehyde	5.30	-30	97	37 (S)
Benzaldehyde	5.31	-20	96	65 (S)
(E)-C_6H_5CH=CHCHO	5.30	-78	99	96
(E)-C_6H_5CH=CHCHO	5.31	-45	65	26

Table 5.10.

5.2.2 Results and discussion

The aim of this work was to study the effect of the chiral ligands on the conversion and overall enantioselectivity of the Reformatsky reaction with ethyl bromodifluoroacetate. Zinc was first activated using Me_3SiCl in THF under nitrogen, before adding ethyl bromodifluoroacetate and finally transferring the solution to another flask containing the benzaldehyde and the catalyst. When the reaction was performed without a catalyst at room temperature a 100% conversion was achieved. However, at 0 °C only a 40% conversion was obtained and there was no conversion in the absence of catalyst at -78 °C. To try to avoid unreacted Zn interfering with the reaction, the solution containing the organozinc compound was transferred through a slug of cotton wool under nitrogen. A small series of transition metal catalysts were used in our study, but unfortunately none of them showed any asymmetric induction. In the case of [Zn(salen10)], no difference to the reaction with no catalyst was observed by ^1H NMR spectroscopy. In the case of $[Ti(O^iPr)_2(BINOL)]$, good conversions were achieved at low temperature (-78 °C) but no asymmetric induction was observed. However, the conversion increased to 94% with the free H_2salen10 ligand (**Table 5.11**). Large amounts of by-products were always observed and the most common by-product resulted from homocoupling of the organozinc reagent to give diethyl 2,2,3,3-tetrafluorosuccinate, as shown by ^1H and ^{19}F NMR spectroscopy. However, when the proportion of organozinc reagent to aldehyde was reduced in order to minimise these by-products, there was a dramatic drop in conversion and no change in the enantioselectivity. The by-products were removed by column chromatography in order to calculate the conversion and enantioselectivity of the product. The enantioselectivities were analysed by using a chiral reagent.[33] Diisopropyl L-tartrate was added to chloroform and the resulting mixture analysed by ^{19}F NMR spectroscopy. Each fluorine signal split in to two signals, one for each of the enantiomers. The method was tested using methylephedrine as catalyst and comparing it with literature results.[30]



Scheme 5.12.

Catalyst	Solvent	Proportion (aldehyde:ester)	Temperature (°C)	Conversion[a] (%)	ee[b] (%)
None	THF	1:4	RT	100	0
"	THF	1:4	-78	0	0
"	THF	1:4	0	40	0
[Zn(salen10)]	THF	1:4	0	45	0
Salen10	THF	1:4	0	94	0
Methylephedrine[c]	THF	1:4	0	72	56
[Ti(O^{i}Pr)$_2$(S-BINOL)]	THF	1:4	-78	77	0
[Ti(O^{i}Pr)$_2$(R-BINOL)]	THF	1:4	-78	74	0
[Ti(O^{i}Pr)$_2$(R-BINOL)]	DCM	1:4	-78	74	0
[Ti(O^{i}Pr)$_2$(R-BINOL)]	THF	1:4	-78	79	0
[Ti(O^{i}Pr)$_2$(R-BINOL)]	THF	1:2	-78	16	0

[a] conversion was determined by ^{1}H NMR.
[b] ee calculated by ^{19}F NMR spectroscopy using chiral reagent.
[c] Similar to those obtained by Braun.[30]

Table 5.11. Results obtained using different metal catalysts.

5.3 Conclusions

The aim of this chapter was to extend the applications of chiral salen ligands and other chiral Lewis acid catalysts to asymmetric fluoroalkylation. The first reaction studied was asymmetric trifluoromethylation which is a valuable reaction in asymmetric catalysis due to the importance of the trifluoromethyl moiety in pharmaceutical chemistry. Unfortunately, the results showed no catalytic activity whatever the catalytic system tested and no asymmetric induction was obtained. The second reaction to be tested was the enantioselective Reformatsky reaction of benzaldehyde using ethyl bromodifluoroacetate. The reaction was catalysed by a range of Lewis acid catalyts under anhydrous conditions. Although good yields were obtained, no enantioselectivity could be induced.

5.4 References

1 Houben-Weyl, *Methods of organic chemistry*, 1990, **E10a**, 18, Thieme, Stuttgart.

2 C. Lai, E. M. Thomas, *J. Chem. Soc., Chem. Comm.*, 1993, 1359.

3 F. L. Qing, G. X. Zhang, Y. Y. Peng, *J. Fluorine Chem.*, 2001, **111**, 185.

4 R. Rarhdadi, M. Troupel, J. Perichon, *Chem. Commun.*, 1998, 1251.

5 S. Debarge, B. Violeau, N. Bendaud, M. P. Jouannetaud, J. C. Jacquesy, *Tetrahedron Lett.*, 2003, **44**, 1747.

6 Y. Chan, C. Cai. *Tetrahedron Lett.*, 2005, **46**, 3161.

7 R. P. Singh, J. M. Shreeve, *Tetrahedron*, 2000, **56**, 7613.

8 For a review: M. A. McClinton, D. A. McClinton, *Tetrahedron*, 1992, **48**, 6555.

9 M. Kiyohide, T. Etsuko, A. Midori, K. Kiyosi, *Chem Lett.*, 1981, 1719.

10 V. A. Soloshonok, *Enantiocontrolled synthesis of fluoroorganic compounds*, 1999, Wiley, New York.

11 G. K. Prakash, R. Krishnamurti, G. A. Olah., *J. Am. Chem. Soc.*, 1989, **111**, 393.

12 W. P. Weber, *Silicon Reagents for Organic Synthesis*, 1983, Springer-Verlag, Berlin.

13 G. K. S. Prakash, *29th Western Regional Meeting of the American Society*, 1993.

14 A. K. Yudin, Ph.D. Thesis, University of Southern California, 1996.

15 K. Iseki, T. Nagai, Y. Kobayashi, *Tetrahedron Lett.*, 1999, **40**, 8231.

16 S. Caron, N. N. Do, P. Arpin, A. Larivée, *Synthesis*, 2003, **11**, 1693.

17 K. Iseki, Y. Kiroki, *Tetrahedron Lett.*, 1999, **40**, 8231.

18 S. Mizuta, N. Shibata, S. Ogawa, H. Fujimoto, S. Nakamura, T. Toru, *Chem. Commun.*, 2006, 2575.

19 For reviews see: J. T. Welch, *Tetrahedron*, 1987, **43**, 3123. P. Bravo, G. Resnati, *Tetrahedron Asymm.*, 1990, **1**, 661.

20 M. H. Gelb, *J. Am. Chem. Soc.*, 1986, **108**, 3146.

21 L. W. Mertel, J. S. Kroin, J. W. Misner, J. M. Tustin, *J. Org. Chem.*, 1988, **53**, 2406.

22 S. Reformatsky. *Ber. Dtsch. Chem. Ges.*, 1887, **20**, 1210.

23 S. Marcotte, X. Pannecoucke, C. Feason, J-C. Quirion, *J. Org. Chem.*, 1999, **54**, 8461.

24 J. M. Andres, R. Pedrosa, A. Perez Encabo, *Tetrahedron*, 2000, **56**, 1217.

25 Y. Fujiwara, T. Katagiri, K. Uneyama, *Tetrahedron Lett.*, 2003, **44**, 6161.

26 D. Pini, A. Mastantuono, P. Salvadori, *Tetrahedron Asymm.*, 1994, **5**, 1875.

27 P. G. Cozzi, *Angew. Chem. Int. Ed.*, 2006, **45**, 2951.

28 A. Ojida, T. Yamano, N. Taya, A. Tasaka, *Org. Lett*, 2002, **4**, 3051.

29 E. McGarrigle, D. G. Gilheany, *Chem. Rev.*, 2005, **105**, 1563.

30 M. Braun, A. Vonderhagen, D. Waldmüller. *Liebigs Ann.*, 1995, 1447.

31 K. Iseki, Y. Kuroki, D. Asada, M. Takahashi, S. Kishimoto, Y. Kobayashi, *Tetrahedron*, 1997, **53**, 10271.

31 E. R. Parmee, O. Tempkin, S. J. Masamune, *J. Am. Chem. Soc.* 1991, **113**, 9365.

32 S. Kiyooka, Y. Kaneko, H. Matsuo, M. Nakano, *J. Org. Chem.*, 1991, **56**, 2276.

33 R. Roig, Ph.D. Thesis, University of Leicester, 2006.

5.4 Summary of Catalysis

From the results exposed in last chapters the main conclusion is that salen are versatile ligands able to carry out a wide variety of reactions in the field of Lewis acid catalysis. In the case of the synthesis of enaminodiones, these catalysts showed an outstanding catalytic activity, however, the decomposition of the catalyst due to the acidity of the substrate limits its application.

The next reaction tested was the asymmetric addition of $ZnEt_2$ to aldehydes and imines. In the case of the addition of $ZnEt_2$ to benzaldehyde, salen ligands showed good activites and enantioselectivies (lower in the case of the fluorous derivatives). The catalysts showed no decomposition and the catalysts could be recover up to 3 times. In the case of the asymmetric addition of diethylzinc to imines, no asymmetric induction was observed with any of the catalysts. Maybe the use of other substrates (modifying substituents in one of the aryl groups) would improve the enantioselectivities.

The next reaction to be tested was the asymmetric trifluoromethylation. This is an important reaction from the pharmaceutical point of view, as fluorinated organic compounds find wide applications in the pharmaceutical and agrochemical industries due to their unique properties and biological activity. However, no asymmetric induction was obtained when the catalysts were tested.

The last reaction tested was the asymmetric Reformatsky reaction. In this case, no asymmetric induction was induced with any of the catalyst. Further investigation on this issue is currently carried out in the University of Leicester.

6 Experimental Section

6.1 Introduction

6.1.1 Experimental procedures

The ^{1}H, $^{19}F\{^{1}H\}$ and $^{13}C\{^{1}H\}$ NMR spectra were recorded on either a Bruker AM 300 or a Bruker ARX 250 at the ambient temperature of the probe. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were referenced internally using the residual protio solvent resonance relative to $SiMe_4$ (δ= 0 ppm), whilst $^{19}F\{^{1}H\}$ NMR spectra were referenced to external $CFCl_3$ (δ= 0 ppm). All chemical shifts are quoted in δ (ppm) and coupling constants in Hertz (Hz) using the high frequency positive convention. The following spectrometer frequencies were used:

Bruker ARX 250 Spectrometer:	^{1}H NMR spectra, 250.13 MHz,
	$^{19}F\{^{1}H\}$ NMR spectra, 235.34 MHz,
	$^{13}C\{^{1}H\}$ NMR spectra, 75.47 MHz.
Bruker AM 300 Spectrometer:	^{1}H NMR spectra, 300.14 MHz,
	$^{19}F\{^{1}H\}$ NMR spectra, 282.41 MHz,
	$^{13}C\{^{1}H\}$ NMR spectra, 82.90 MHz.

The solvent most frequently used was deuterated chloroform ($CDCl_3$). However, if this was not possible due to solubility problems, an alternative deuterated solvent was employed. The NMR spectra of air-/moisture-sensitive compounds were obtained by preparing the samples under an inert atmosphere in a glove box using dried and freeze/pump/thaw degassed deuterated solvents. The solutions were loaded into a Teflon-sealed screw cap NMR tube.

Infrared spectra were recorded on a Perkin Elmer FT- IR spectrometer at 4 cm^{-1} resolution (16 scans) with a Universal ATR Sampling Accessory. Fast atom bombardment (FAB) mass spectra were recorded on a Kratos concept 1H, double focussing, forward geometry mass spectrometer. 3-Nitrobenzyl alcohol was used as the matrix for the FAB spectra. Electrospray (ES) mass spectra were obtained on a Micromass Quattro LC spectrometer. Elemental analyses were carried out by the University of North London Service. UV/ Visible spectra were measured on a Shimadzu model 1601 UV/visible Spectrophotometer. X-Ray crystallographic data were collected on a Bruker Apex SMART 2000 diffractometer. Crystal data and structure refinement can be found in the appendix.

ICP-AE spectroscopy was used in order to analyse the metal content of some samples on a JY Horiba Ultima 2 sequential ICP-AES with generator power and flow rates optimised for sensitivity.

Specific rotation analyses were carried out using a Perkin Elmer 341 Polarimeter at 589 nm using a sodium/halogen lamp. Samples were dissolved in the solvent indicated. Product enantiomeric excesses were determined by chiral HPLC or chiral GC. Chiral HPLC was performed using a Perkin Elmer Series 200 equipped with a Diacel Chiralpak AD or a Diacel Chiralcel OJ-H column, using isopropanol and hexane as eluents. Chiral GC was performed on a Perkin Elmer Clarus 500 Gas Chromatograph fitted with an SGE CYDEX-B column.

6.1.2 Anhydrous solvents

Unless otherwise stated, dry solvents were used that had been freeze/ pump/ thaw degassed three times before use.

Diethyl ether, Dichloromethane,	Obtained dried from a distillation machine model Puresolve™.
DMF	Purchased dry from Aldrich Chemical Co. and degassed.

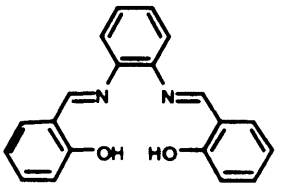
6.1.3 Starting materials

Compounds were usually supplied by Sigma-Aldrich although the fluorous materials were supplied by Fluorochem.

6.2 Synthesis of conventional salen ligands

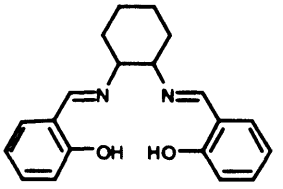
6.2.1 Synthesis of conventional ligands

6.2.1.1 Synthesis of *N,N'*-bis(salicylidene)-1,2-phenylenediamine (H_2salen1) (1)



Salicylaldehyde (18.32 g, 0.15 mol) was added to a solution of 1,2-phenylenediamine (16.21 g, 0.15 mol) in ethanol (30 mL), and the reaction was refluxed for three hours. After removing the solvent, hexane (50 mL) was added. The yellow solid was filtered and washed with hexane to give a yellow powder (29.87 g, 85%). mp 131 °C (lit, [1]128 °C). m/z (ES^+) 317 (M^+, 40%). δ_H (CD_2Cl_2): 6.66 (1H, t, $^3J_{HH}$ 8.0 Hz, ArH), 6.92 (1H, d, $^3J_{HH}$ 8.1 Hz, ArH), 7.30 (2H, m, ArH), 7.68 (2H, m, ArH), 8.81 (1H, s, N=CH), 12.95 (1H, s, OH). δ_C ($CDCl_3$): 117.55 (CH), 119.01 (CH), 119.25 (C), 119.72 (CH), 127.74 (CH), 132.38 (CH), 133.39 (CH), 142.55 (C), 161.37 (C), 163.72 (CH). ν_{max} (solid): 1610 cm^{-1} (C=N), 1275 cm^{-1} (C-OH).

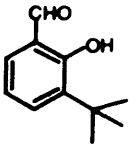
6.2.1.2 Synthesis of *N,N'*-bis(salicylidene)-1,2-cyclohexanediamine (H_2salen3) (2)



Salicylaldehyde (16.05 mL, 0.15 mol) was added to a solution of 1,2-diaminocyclohexane (18.21 mL, 0.15 mol) and sodium acetate (13.60 g, 0.30 mol) in hot ethanol (30 mL). After refluxing for 2 h, the resulting solution was filtered to give a yellow crystalline powder, which was recrystallized from DCM and hexane (20.35 g, 58%). mp 134 °C (lit,[2] 132 °C). m/z (ES^+) 323 (MH^+, 100%). δ_H (CD_2Cl_2): 1.72 (1H, m, $CH_{cyclohexyl}$), 1.89 (1H, m, $CH_{cyclohexyl}$), 1.95 (2H, m, $CH_{cyclohexyl}$), 3.31 (1H, s, $CH_{cyclohexyl}$), 6.79 (1H, m, ArH), 6.88 (1H, m, ArH), 7.14 (1H, m, ArH), 7.23 (1H, m, ArH), 8.25 (1H, s, N=CH), 13.33 (1H, s, OH). δ_C ($CDCl_3$): 24.17 (CH_2), 33.08 (CH_2), 72.53 (CH), 118.69 (CH), 118.98 (CH), 119.07 (C), 132.56 (CH), 133.76 (CH), 161.67 (C), 165.16 (CH). ν_{max} (solid): 1632 cm^{-1} (C=N), 1279 cm^{-1} (C-OH).

6.2.2 Synthesis of new generation salen ligands

6.2.2.1 Synthesis of 3-*tert*-butylsalicylaldehyde[3] (3)

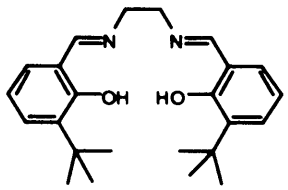


Paraformaldehyde (4.05 g, 135 mmol) was added to a mixture of 2-*tert*-butylphenol (3.00 g, 20 mmol), anhydrous $MgCl_2$ (2.85 g, 30 mmol) and triethylamine (10.52 mL, 75 mmol) in acetonitrile (100 mL). The mixture was refluxed for 3 h. After adding HCl (5%, 75 mL), the product was extracted with diethylether (3 x 30 mL). The organic layers were then combined, dried with $MgSO_4$ and the solvent was removed to yield a yellow oil (2.68 g, 75%). m/z (ES^+) 177 (M^+, 40%). δ_H ($CDCl_3$): 1.40 (9H, s, ^tBu), 6.87 (1H, t, $^3J_{HH}$ 8.0 Hz,

ArH), 7.32 (1H, dd, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 2.0 Hz, ArH), 7.45 (1H, dd, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 2.0 Hz, ArH), 9.81 (1H, s, CHO), 11.78 (1H, s, OH). δ_C: 29.87 (CH_3), 34.85 (C), 119.22 (C), 120.65 (C), 132.00 (CH), 134.12 (CH), 138.24 (CH), 161.22 (C), 197.17 (CH).

6.2.2.1 Synthesis of *N,N'*-bis(3,3'-*tert*-butylsalicylidene)-1,2-ethylenediamine (H_2salen6)[4] (4)

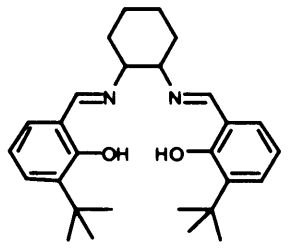
Ethylenediamine (1.3 mL, 20 mmol) was added to a solution of 3-*tert*-butylsalicylaldehyde (7.1 g, 40 mmol) in ethanol (25 mL). The solution was then refluxed for 5 h. After cooling the reaction mixture to –17 °C for 12 h, the solvent was removed to yield a yellow oil (4.91 g, 64%).



m/z (ES^+) 381 (M^+, 100%). δ_H ($CDCl_3$): 1.39 (9H, s, ^{t}Bu), 3.85 (2H, s, CH_2), 6.65 (1H, t, $^3J_{HH}$ 7.6 Hz, ArH), 6.97 (1H, d, $^3J_{HH}$ 7.6 Hz, ArH), 7.21 (1H, d, $^3J_{HH}$ 7.9 Hz, ArH), 8.31 (1H, s, HC=N) 13.8 (1H, s, OH). δ_C: 29.55 (CH_3), 34.82 (C), 59.57 (CH_2), 117.87 (CH), 118.57 (C), 129.52 (CH), 129.81 (CH), 137.37 (CH), 160.38 (C), 167.21 (C). ν_{max} (solid): 1631 cm^{-1} (C=N), 1435 cm^{-1} (CO).

6.2.2.2 Synthesis of *N,N'*-bis(3,3'-*tert*-butylsalicylidene)-1,2-cyclohexyldiamine (H_2salen7)[5] (5)

(1*R*,2*R*)-(-)-1,2-cyclohexanediamine (1.82 mL, 15 mmol) was added to a solution of 3-*tert*-butylsalicylaldehyde (5.50 g, 30 mmol) in hot ethanol (30 mL). The reaction was then refluxed for 5 h. After cooling the reaction mixture at –17 °C for 12 h, the solvent was removed to obtain a yellow oil (3.33 g, 53%). $[\alpha]_D^{25}$: -291.59 (*c* 1.0 in EtOH). m/z (ES^+) 435 (MH^+, 100%). δ_H ($CDCl_3$): 1.39 (9H, s, ^{t}Bu), 1.81 (4H, m, $CH_{cyclohexyl}$), 3.25 (1H, m, $CH_{cyclohexyl}$), 6.63 (1H, t, $^3J_{HH}$ 7.3 Hz, ArH), 6.97 (1H, d, $^3J_{HH}$ 7.5 Hz, ArH), 7.15 (1H, d, $^3J_{HH}$ 7.4 Hz, ArH), 8.31 (1H, s, HC=N), 13.6 (1H, s, OH). δ_C: 24.30 (CH_2), 29.55 (CH_3), 33.14 (C), 34.75 (CH_2), 69.31 (CH), 117.71 (CH), 118.59 (C), 129.22 (CH), 129.78 (CH), 137.06 (C), 160.33 (C), 165.48 (CH). ν_{max} (solid): 1627 cm^{-1} (C=N), 1436 cm^{-1} (CO).

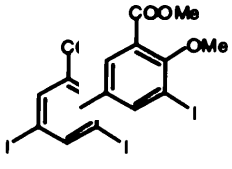


6.2.3 Synthesis of fluorous salen ligands

6.2.3.1 Synthesis of first generation fluorous salen ligands

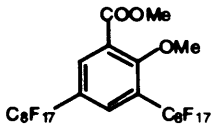
6.2.3.1.1 Synthesis of 2-methoxy-3,5-diiodomethylbenzoate[6] (6)

Dimethylsulphate (5.0 mL, 50 mmol) was added to a solution of 3,5-diiodosalicylic acid (10.0 g, 0.025 mol) and K_2CO_3 (17.5 g, 0.125 mol) in acetone



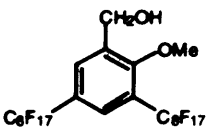
(300 mL). The mixture was then refluxed for 24 hours. After adding water (100 mL), the mixture was refluxed for a further 90 min. The solvent was then removed on the rotary evaporator and the residue was extracted with CH_2Cl_2 (3 x 150 mL) and washed with brine (100 mL). Finally, the solution was dried over anhydrous $MgSO_4$ and the solvent was removed to obtain a white powder (8.16 g, 65%). mp 204 °C (lit[6] 205 °C). m/z (ES^+) 418 (M^+, 100%). δ_H ($CDCl_3$): 3.86 (3H, s, CH_3), 3.91 (3H, s, CH_3), 8.05 (1H, d, $^4J_{HH}$ 2.2, ArH), 8.23 (1H, d, $^4J_{HH}$ 2.2 Hz, ArH). δ_C: 52.72 (CH_3), 62.43 (CH_3), 87.81 (C), 95.47 (C), 127.04 (C), 140.39 (CH), 150.64 (CH), 159.31 (C), 164.05 (C).

6.2.3.1.2 Synthesis of 2-methoxy-3,5-bis(heptadecafluorooctyl)methylbenzoate[6] (7)



A few crystals of iodine were added to a mixture of copper powder (28 g) in acetone (40 mL). The solution was stirred for 1 h at room temperature. After filtering the mixture, it was washed with HCl/acetone (2/3, v:v) and then acetone. Finally, the copper was dried for 2 hours under oil pump vacuum. This copper (6.5 g, 0.1 mol), 2,2'-bipyridine (1.1 g, 0.7 mmol), 2-methoxy-3,5-diiodomethylbenzoate (5.70 g, 10 mmol) and dry DMF (50 mL) were heated to 90 °C, and $C_8F_{17}I$ (16.8 g, 30 mmol) was added dropwise for 3 h. The solution was then stirred for 60 h at 90 °C. After cooling to room temperature, water (100 mL) and Et_2O (250 mL) were added and the solution was stirred for 2 hours at room temperature. After filtering off the copper salts the organic phase was separated and the aqueous phase was extracted with Et_2O (150 mL). The organic layers were combined, washed with brine and dried with $MgSO_4$. The solvent was finally removed to obtain an oil, which was purified by column chromatography (petroleum ether/Et_2O, 7/3) on silica gel to yield a white solid (3.75 g, 62%). mp 48 °C (lit,[6] 47- 48 °C). m/z (ES^+) 1003 (M^+, 25%), 971 ([M-OMe^+], 100%). δ_H ($CDCl_3$): 3.95 (3H, s, OCH_3), 4.05 (3H, s, CO_2CH_3), 7.88 (1H, d, $^4J_{HH}$ 2.3 Hz, ArH), 8.22 (1H, d, $^4J_{HH}$ 2.3 Hz, ArH). δ_F: -81.21 (6F, t, $^4J_{FF}$ 10.5 Hz, 2x CF_3), -107.23 (2F, t, $^4J_{FF}$ 12.8 Hz), -111.37 (2F, t, $^4J_{FF}$ 12.8 Hz, CF_2), -121.54 to –122.22 (16F, m, 4 x CF_2), -123.18 (4F, m, CF_2), -126.53 (4F, m, CF_2). δ_C: 53.03 (CH_3), 64.24 (CH_3), 124.08 (C), 124.56 (C), 126.39 (C), 131.32 (CH), 134.74 (CH), 162.64 (C), 164.45 (C).

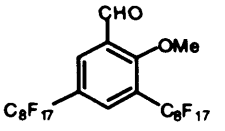
6.2.3.1.3 Synthesis of 2-methoxy-3,5-bis(heptadecafluorooctyl)benzylalcohol[6] (8)



A solution of 2-methoxy-3,5-bis(heptadecafluorooctyl)methylbenzoate (3.50 g, 4 mmol) in dry Et_2O (20 mL) was added over 30 min to a suspension of $LiAlH_4$ (1.91 g, 5 mmol) stirring at –50 °C in Et_2O (40 mL) under nitrogen. The mixture was stirred for 4 h at –50 °C, and then EtOAc (15 mL) was added. The reaction

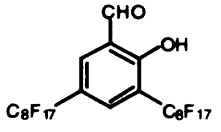
mixture was allowed to warm to room temperature and then, H_2SO_4 (10%, 40 mL) was added cautiously, followed by Et_2O (40 mL). The upper organic phase was removed, washed with brine and dried with $MgSO_4$. The solvent was removed, to yield a white solid (3.05 g, 76%). mp 63 °C (lit,[4] 62 °C). m/z (ES^-) 989 (M^-, 10%), 959 ([M-CH_3O^-], 100%). δ_H ($CDCl_3$ + $CF_2ClCFCl_2$): 2.01 (1H, t, $^3J_{HH}$ 5.7 Hz, CH_2OH), 3.90 (3H, s, OCH_3), 4.87 (2H, d, $^3J_{HH}$ 5.7 Hz, CH_2OH), 7.67 (1H, d, $^4J_{HH}$ 1.7 Hz, ArH), 7.99 (1H, d, $^4J_{HH}$ 1.7 Hz, ArH).

6.2.3.1.4 Synthesis of 2-methoxy-3,5-bis(heptadecafluorooctyl)benzaldehyde[6] (9)



A solution of 2-methoxy-3,5-bis(heptadecafluorooctyl)benzylalcohol (2.45 g, 2.59 mmol) in benzotrifluoride (20 mL) was transferred to a two neck flask containing KBr (0.30 g, 0.15 mmol), $Cu(AcO)_2$ (0.025 g, 0.1 mmol) and water (1 mL). The two phase mixture was then cooled to 5 °C, and a solution of TEMPO (0.015 g, 0.11 mmol) in benzotrifluoride (10 ml) was added. Aqueous NaOCl (2.21 mL, 3.75 mmol) saturated in $NaHCO_3$ in water (10 mL) was then added drop wise with vigorous stirring. The solution was heated at 80 °C for 60 h. After separating the two layers, the aqueous layer was extracted with Et_2O (75 mL). The combined organic layers were washed with brine, dried with $MgSO_4$ and the solvent was removed to yield a residue which was purified by column chromatography (Et_2O/petroleum ether, 3/7) to yield a white solid (1.96 g, 79%). mp 52 °C (lit,[6] 52 °C). m/z (ES^-) 957 (M-CHO^-, 100%). δ_H ($CDCl_3$+ CF_2ClCCl_2F): 4.07 (3H, s, OCH_3), 7.96 (1H, d, $^4J_{HH}$ 2.2 Hz, ArH), 8.31 (1H, d, $^4J_{HH}$ 2.2 Hz, ArH), 10.38 (1H, s, CHO).

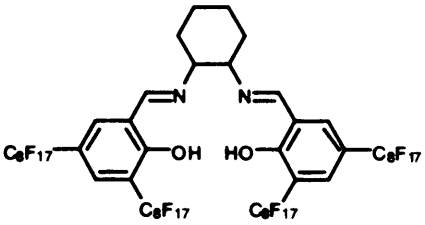
6.2.3.1.5 Synthesis of 3,5-bis(heptadecafluorooctyl)salicylaldehyde[6] (10)



A solution of BBr_3 (4.2 mL, 1.0 M solution in CH_2Cl_2, 4.2 mmol) was added under nitrogen to a solution of 2-methoxy-3,5-bis(heptadecafluorooctyl) benzaldehyde (1.96 g, 2.05 mmol) in benzotrifluoride (15 mL) and CH_2Cl_2 (35 mL) at –40 °C. The solution was then allowed to warm to room temperature and the solution was stirred for 10 h. After that, a solution of $NaHCO_3$ was cautiously added drop wise until the pH of the aqueous phase was neutral. The organic phase was then separated, washed with brine and dried with $MgSO_4$. The solvent was finally removed under vacuum to yield a residue which was purified by column chromatography (Et_2O/petroleum ether, 3/7) to yield a pale cream solid (1.57 g, 73%). mp 80 °C (lit[6] 80 °C). m/z (ES^-) 973 (M^-, 100%). δ_H ($CDCl_3$): 7.93 (1H, d, $^4J_{HH}$ 1.9 Hz, ArH), 8.02 (1H, d, $^4J_{HH}$ 2.3 Hz, ArH), 10.02 (1H, s, CHO), 12.23 (1H, s, OH). δ_F: -80.70 (6F, t, $^4J_{FF}$ 10.2 Hz, 2 x CF_3), -109.19 (2F, t, $^4J_{FF}$ 14.2 Hz, CF_2), -110.67 (2F, t, $^4J_{FF}$ 14.2 Hz, CF_2), -

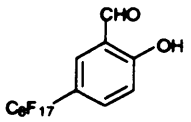
121.80 to –122.70 (16F, m, 8 x CF_2), -122.71 (4F, m, CF_2), -126.13 (4F, m, CF_2). δ_C: 118.76 (C), 124.04 (C), 128.36 (C), 130.58 (CH), 138.18 (CH), 164.32 (C), 196.45 (CH).

6.2.3.1.6 Synthesis of *N,N'*-bis(3,5-bis(heptadecafluorooctyl))salicylene-1',2'-cyclohexane diamine (H_2salen5).[6] (11)



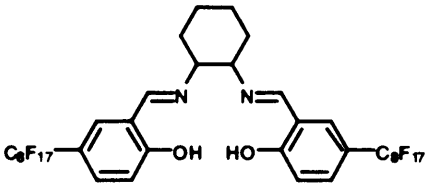
1,2-Diaminocyclohexane (0.21 ml, 1.83 mmol) was added to a solution of 3,5-bis(heptadecafluorooctyl)salicylaldehyde **(10)** (3.50 g, 3.66 mmol) in hot ethanol (60 mL). The solution was then refluxed for four hours. After removing the solvent, cold hexane was added and the mixture was filtered to give a yellow solid (1.75 g, 48%). mp 107 °C (lit,[6] 109 °C). m/z (ES^-) 997 ($M\text{-}2H^{2-}$, 10%). δ_H ($CDCl_3$ + CF_2ClCCl_2F): 1.88 (4H, m, $CH_{cyclohexyl}$), 3.43 (1H, m, $CH_{cyclohexyl}$), 7.44 (1H, m, ArH), 7.65 (1H, m, ArH), 8.29 (1H, s, HC=N), 13.45 (1H, s, OH). ν_{max} (solid): 1644 cm^{-1} (C=N), 1488 cm^{-1} (CO), 1199-1115 (C-F).

6.2.3.1.7 Synthesis of 5-(heptadecafluorooctyl)salicylaldehyde[6] (12)



A three-neck round bottom flask was charged with Cu powder (3.18 g, 50 mmol), 5-bromosalicylaldehyde (1.83 g, 10 mmol), 2,2'-bipyridine (1.83 g, 0.7 mmol) and dry DMF (70 mL) under nitrogen. The reaction mixture was heated at 90 °C before adding $C_8F_{17}I$ (11.38 g, 20 mmol) in four portions, each taking 45 min. The reaction was then stirred for 72 h at 90 °C. After cooling down to RT, water (100 mL) and Et_2O (150 mL) were added and the solution was stirred for 2 h. The two phases were separated and the aqueous phase was extracted with Et_2O (100 mL). The organic phases were then combined, washed with brine, dried with $MgSO_4$ and finally the solvent was removed to yield an oil which was purified by column chromatography on silica gel (Et_2O/ petroleum ether, 65/35) to obtain a yellow oil (2.55 g, 47%). m/z (ES^-) 539 ($M\text{-}H^-$, 100%). δ_H ($CDCl_3$): 7.08 (1H, d, $^3J_{HH}$ 8.6 Hz, ArH), 7.63 (1H, dd, $^3J_{HH}$ 8.6 Hz, $^4J_{HH}$ 2.3 Hz, ArH), 7.75 (1H, d, $^4J_{HH}$ 2.3 Hz, ArH), 9.95 (1H, s, CHO), 11.31 (1H, s, OH). δ_F: -80.72 (3F, t, $^4J_{FF}$ 10.3 Hz, CF_3), -110.11 (2F, t, $^4J_{FF}$ 14.3 Hz, CF_2), -121.23 to -122.53 (8F, m, 4 x CF_2), -122.72 (2F, m, CF_2) -126.07 (2F, m, CF_2). δ_C: 124.29 (CH), 126.61 (C) 128.70 (CH), 133.10 (CH), 153.36 (C), 155.48 (C), 187.30 (CH).

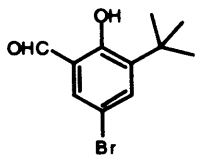
6.2.3.1.8 Synthesis of *N,N'*-Bis(5-(heptadecafluorooctyl))salicylidene-1,2-cyclohexane diamine (H_2salen8)[6] (13)



1,2-Diaminocyclohexane (0.15 mL, 1.22 mmol) was added to a solution of 5-(heptadecafluorooctyl)salicylaldehyde (1.31 g, 2.43 mmol) in ethanol (40 mL). The solution was then refluxed for 16 h. After cooling to room temperature, the solvent was removed and the residue was recrystallized from acetonitrile to obtain a yellow powder (1.20 g, 73%). mp 115 °C (lit,[6] 115-117 °C). m/z (ES^+) 1157 (M^+, 30%). δ_H ($CDCl_3$): 1.43-2.13 (4H, m, $CH_{cyclohexyl}$), 3.25-3.42 (1H, m, $CH_{cyclohexyl}$), 6.98 (1H, d, $^3J_{HH}$ 8.6 Hz, ArH), 7.35 (1H, d, $^4J_{HH}$ 2.2 Hz, ArH), 7.42 (1H, dd, $^3J_{HH}$ 8.7 Hz, $^4J_{HH}$ 2.3 Hz, ArH), 8.30 (1H, s, HC=N), 11.57 (1H, s, -OH). δ_F ($CDCl_3$): -80.71 (3F, t, $^4J_{FF}$ 10.2 Hz, CF_3), -109.75 (2F, t, $^4J_{FF}$ 15.1 Hz, CF_2), -121.81 to –122.74 (8F, m, 4 x CF_2), -123.67 (2F, m, CF_2), -127.02 (2F, m, CF_2). δ_C: 23.1 (CH_2), 32.33 (CH_2), 71.25 (CH), 118.71 (CH), 119.18 (CH), 129.65 (CH), 134.85 (C), 158.09 (C), 163.23 (C), 164.67 (CH).

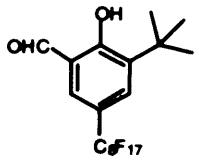
6.2.4 Synthesis of new generation fluorous salen ligands

6.2.4.1 Synthesis of 5-bromo-3-*tert*-butylsalicylaldehyde (14)



A solution of bromine (0.53 mL, 10.3 mmol) in acetic acid (2 mL) was added drop wise at room temperature to a solution of 3-*tert*-butylsalicylaldehyde (1.78 g, 9.98 mmol) in acetic acid (5 mL). After 1 h the reaction was diluted with DCM (30 mL) and washed with water (10 mL), saturated $Na_2S_2O_5$ (10 mL), aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried with Na_2SO_4 and the solvent was removed to yield a colourless oil (1.28 g, 50%). m/z (ES^-) 255 (M^-, 100%). δ_H ($CDCl_3$): 1.39 (9H, s, ^{t}Bu), 7.35 (1H, d, $^4J_{HH}$ 2.5 Hz, ArH), 7.51 (1H, d, $^4J_{HH}$ 2.5 Hz, ArH), 9.70 (1H, s, CHO), 11.71 (1H, s, OH). δ_C: 29.26 (CH_3), 35.72 (C), 111.40 (C), 121.66 (C), 133.63 (CH), 136.98 (CH), 141.05 (C), 160.17 (C), 196.84 (CH).

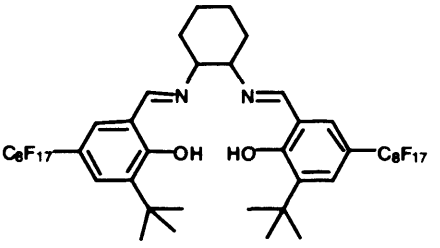
6.2.4.2 Synthesis of 3-*tert*-butyl-5-(heptadecafluorooctyl)salicylaldehyde[7] (15)



Copper powder (3.52 g, 53 mmol), 5-bromo-3-*tert*-butylsalicylaldehyde (1.16 g, 4.50 mmol), 2,2'-bipyridine (1.1 g, 7 mol%) and dry DMF (55 mL) were charged to a three neck round bottom flask. The reaction was heated at 90 °C and $C_8F_{17}I$ (4.81 g, 9 mmol), was added in four portions, each taking 45 min. After stirring the reaction for 60 h at 90 °C, water (100 mL) and Et_2O (150 mL) were added and the solution was stirred for a further 2 h. The phases were separated and the aqueous phase was extracted with

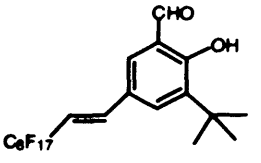
Et_2O (100 mL). The organic phases were then combined, washed with brine, dried with $MgSO_4$ and finally the solvent was removed to yield an oil which was purified by column chromatography (Et_2O/ petroleum ether, 3/7) to obtain a pale yellow powder (1.46 g, 55%). mp 54 (lit.[7] 54 °C). m/z (ES^-) 595, ($[M-H]^-$, 100%). δ_H ($CDCl_3$): 1.39 (9H, s, ^tBu), 7.61 (2H, m, ArH), 9.87 (1H, s, CHO), 11.71 (1H, s, OH). δ_F ($CDCl_3$): -81.10 (3F, t, $^4J_{FF}$ 10.2 Hz, CF_3), -111.17 (2F, t, $^4J_{FF}$ 13.5 Hz, CF_2), -121.77 to –122.30 (4F, m, 2 x CF_2), -123.01 (2F, br s, CF_2), -126.42 (6F, br s, 3 x CF_2). δ_C: 28.87 (CH_3), 35.21 (C), 118.77 (C), 120.13 (C), 131.04 (CH), 131.47 (CH), 139.81 (C), 163.74 (C), 196.52 (CH).

6.2.4.3 Synthesis of *N,N'*-bis(3,3'-tert-butylsalicylaldehyde)-bis(5,5'-heptadecafluorooctyl)-1,2-cyclohexyldiamine (H_2salen9) (16)



(1*R*,2*R*)-(-)-1,2-cyclohexyldiamine (1.15 mL, 9.41 mmol) was added to a solution of 3-*tert*-butyl-5-(heptadecafluorooctyl) salicylaldehyde (11.21 g, 18.82 mmol) in hot ethanol (30 mL). The solution was then refluxed for 16 h. After removing the solvent, the crude product was purified by flash chromatography on silica gel (Et_2O/light petroleum ether, 2/98) to obtain the pure compound as a yellow oil (6.42 g, 51%). $[\alpha]_D^{25}$ -237.61 (*c* 1.0 in EtOH). m/z (ES^-) 1269, ($M\text{-}H^-$, 40%). δ_H ($CDCl_3$): 1.38 (9H, s, ^tBu), 1.60-2.05 (4H, m, $CH_{cyclohexyl}$), 3.40 (1H, m, $CH_{cyclohexyl}$), 7.17 (1H, m, ArH), 7.35 (1H, m, ArH), 8.20 (1H, s, HC=N). δ_F: -81.03 (3F, t, $^4J_{FF}$ 9.3 Hz, CF_3), -110.98 (2F, t, $^4J_{FF}$ 13.4 Hz, CF_2), -120.10 to –122.03 (8F, m, 4 x CF_2), -122.76 (2F, m, CF_2), -126.28 (2F, m, CF_2). δ_C: 23.21 (CH_2), 28.74 (CH_3), 31.71 (C), 33.92 (CH_2), 76.41 (CH), 118.02 (C), 126.35 (CH), 127.63 (CH), 131.52 (C), 137.71 (C), 163.34 (C), 164.11 (CH).

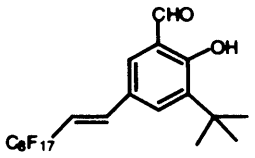
6.2.4.4 Attempted synthesis of 3-*tert*-butyl-5-(heptadecafluorodec-1-ene) salicylaldehyde (17)



A solution of 5-bromo-3-*tert*-butylsalicylaldehyde (1.16 g, 4.5 mmol), 1*H*,1*H*,2*H*-heptadecafluorodecene (3.20 g, 9 mmol), Herrmann's catalyst (100 mg, 10^{-4} mmol) and NaOAc (1.03 g, 13 mmol) in dry and degassed DMF (40 mL) was stirred under nitrogen for 72 h at 120 °C. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was partitioned between EtOAc (40 mL) and water (40 mL). The organic layer was then separated, washed with water and brine, dried with $MgSO_4$ and the solvent was removed under reduced

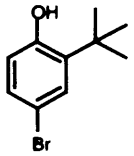
pressure to yield a dark tar. ^{1}H and ^{19}F NMR analysis suggested that the product had decomposed to a wide range of products and the desired product was not observed.

6.2.4.5 Attempted synthesis of 3-tert-butyl-5-(heptadecafluorodec-1-ene)salicylaldehyde (18)



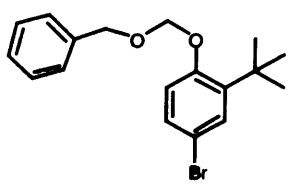
A solution of 5-bromo-3-*tert*-butylsalicylaldehyde (0.78 g, 3 mmol), a spatula of $Pd(AcO)_2$, and NaOAc (1.25 g, 15 mmol) in DMF (60 mL) was heated under nitrogen at 90 °C. Four portions of *1H,1H,2H*-heptadecafluorodecene (2.57 g, 6 mmol) were added, one every 45 min, and the reaction mixture was then stirred for 72 h at 90 °C. After cooling to room temperature, the solvent was removed and the residue was partitioned between EtOAc (40 mL) and water 40 (mL). The organic layer was then separated washed with water and brine, dried with $MgSO_4$ and the solvent was removed under reduced pressure to yield a dark tar. ^{1}H and ^{19}F NMR analysis showed that only starting material was recovered.

6.2.4.6 Synthesis of 4-bromo-2-*tert*-butylphenol[8] (19)



A solution of bromine (2.18 g, 15 mmol) in acetic acid (15 mL) was added to a solution of 2-*tert*-butylphenol (2.00 g, 13 mmol) in acetic acid (2 mL), in three portions every fifteen minutes. After stirring the solution for 1 h at room temperature, the reaction mixture was quenched with a solution of saturated $Na_2S_2O_5$ (15 mL) and DCM (20 mL) The organic phase was washed with $NaHCO_3$ and brine, dried over $MgSO_4$ and the solvent was removed to yield the pure product as a pale yellow solid (2.30 g, 78%). mp 98 °C.[8] m/z (ES^-) 227, ($M\text{-}H^-$, 100%). δ_H ($CDCl_3$): 1.39 (9H, s, ^tBu), 6.45 (1H, d, $^3J_{HH}$ 8.4 Hz, ArH), 7.05 (1H, dd, $^3J_{HH}$ 8.4 Hz, $^4J_{HH}$ 2.4 Hz, ArH), 7.41 (1H, d, $^4J_{HH}$ 2.4 Hz, ArH). δ_C: 29.26 (CH_3), 35.72 (C), 112.87 (CH), 129.58 (CH), 130.16 (CH), 138.61 (C), 153.40 (C), 177.72 (C).

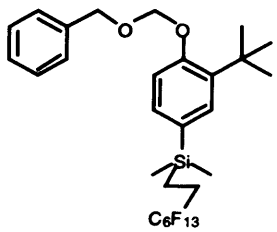
6.2.4.7 Synthesis of 4-bromo-2-*tert*-butyl-benzyloxymethoxybenzene[9] (20)



A solution of 4-bromo-2-*tert*-butylphenol (2.02 g, 8.80 mmol) was added to a mixture of NaH (0.64 g, 16.10 mmol) in THF (20 mL) over 5 h at 0 °C under nitrogen. Benzyloxymethylchloride (2.5 mL, 13.2 mmol) was then added drop wise and the mixture was left stirring overnight at room temperature. After quenching the reaction mixture with water, the aqueous phase was extracted with EtOAc (2 x 20 mL), the organic phases combined, dried over $MgSO_4$ and the solvent was removed to yield a crude product which was purified by flash chromatography (petroleum

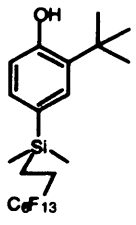
ether/Et_2O, 95/5) to give the pure product as a colourless oil (1.55 g, 50%). m/z (ES^-) 347 (M^-, 10%). δ_H ($CDCl_3$): 1.40 (9H, s, ^tBu), 4.64 (2H, s, CH_2Ph), 5.28 (2H, s, OCH_2O), 7.05 (1H, d, $^3J_{HH}$ 8.8 Hz, ArH), 7.25 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.0 Hz, ArH), 7.23-7.40 (5H, m, ArH) 7.41 (1H, d, $^4J_{HH}$ 2.7 Hz, ArH). δ_C: 29.65 (CH_3), 35.13 (C), 70.18 (CH_2), 92.11 (CH_2), 114.13 (C), 116.21 (CH), 128.04 (CH), 128.56 (CH), 128.72 (CH), 129.74 (CH), 129.81 (CH), 137.14 (C), 140.86 (C), 155.43 (C).

6.2.4.8 Synthesis of 4-(1*H*,1*H*,2*H*,2*H*-tridecafluorooctyldimethylsilyl-2-*tert*-butyl-benzyloxy methoxybenzene[9] (21)



^{t}BuLi (2.94 mL, 1.7 M solution in pentane, 5.0 mmol) in hexane (3 mL) was added drop wise at –78 °C to a stirred solution of 4-bromo-2-*tert*-butyl-benzyloxymethoxybenzene (1.59 g, 4.5 mmol) in THF (40 mL) under nitrogen. The mixture was stirred at –78 °C for 3 h and then $C_6F_{13}C_2H_4Me_2SiCl$ (2.50 g, 4.6 mmol) in THF (10 mL) was added over 30 min. After 2 h the cooling bath was removed and the solution was stirred for 16 h at room temperature. The mixture was then quenched with a saturated solution of NH_4Cl (20 mL) and the aqueous layer was extracted once with hexane (20 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed to yield a crude product which was purified by column chromatography (petroleum ether/Et_2O, 90/10) to yield a clear oil (1.75 g, 58%). m/z (ES^-) 674, ($M\text{-}H^-$, 30%). δ_H ($CDCl_3$): 0.20 (6H, s, $SiMe_2$), 0.75 (2H, m, $SiCH_2CH_2C_6F_{13}$), 1.40 (9H, s, ^tBu), 1.90 (2H, m, $SiCH_2CH_2C_6F_{13}$), 4.61 (2H, m, OCH_2O), 5.02 (2H, m, CH_2Ph), 6.78 (1H, d, $^3J_{HH}$ 8.2 Hz, ArH), 7.20 (1H, dd, $^3J_{HH}$ 7.9 Hz, $^4J_{HH}$ 1.9 Hz, ArH) 7.30-7.50 (6H, m, ArH). δ_F: -80.81 (3F, t, $^4J_{FF}$ 10.4 Hz, CF_3), -115.92 (2F, t, $^4J_{FF}$ 14.1 Hz, CF_2), -121.74 to –123.38 (6F, m, 3 x CF_2), -126.09 (2F, m, CF_2). δ_C: -3.14 (CH_3), 5.5 (CH_2), 28.32 (CH_2), 30.03 (CH_3), 31.06 (C), 70.12 (CH_2), 91.78 (CH_2), 114.65 (C), 115.22 (CH), 124.53 (CH), 125.12 (CH), 127.97 (C), 128.07 (CH), 128.13 (C), 128.56 (CH), 131.78 (CH), 174.60 (C).

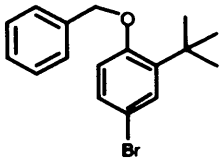
6.2.4.9 Attempted synthesis of 4-(1*H*,1*H*,2*H*,2*H*- tridecafluorooctyldimethylsilyl)-2-*tert*-butyl-phenol (22)



A mixture of 4-(1*H*,1*H*,2*H*,2*H*-tridecafluorooctyldimethylsilyl)-2-*tert*-butyl-benzyloxy methoxybenzene (0.46 g, 0.5 mmol) and Pd/C (10% Pd/C, 0.040 mg, 40 mmol) in EtOH (20 mL) was added to a hydrogenation reactor and stirred at 72 h at room temperature. After filtering the solution over celite, it was diluted with Et_2O (30 mL), washed with a saturated solution of Na_2CO_3 (30 mL) and brine (20 mL), dried with $MgSO_4$

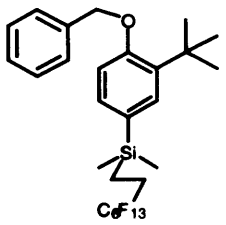
and the solvent was removed. When the pressure in the reactor was 15 bar only the starting material was obtained, however, when the pressure was increased to 50 bar the product decomposed to 2-*tert*-butylphenol.

6.2.4.10 Synthesis of 4-bromo-1-benzyloxy-2-*tert*-butyl-benzene (23)



A solution of 4-bromo-2-*tert*-butylphenol (2.02 g, 8.08 mmol) in THF (10 mL) was added drop wise to a mixture of NaH (0.576 g, 13 mmol) in THF (20 mL) at 0 °C under nitrogen. After 5 h a solution of benzylbromide (0.97 mL, 8.08 mmol) in THF (5 mL) was added. The mixture was then refluxed for 16 h. After quenching the reaction with H_2O, the phases were separated and the aqueous phase was extracted with DCM (2 x 20 mL). The organic phases were dried and the solvent was removed to yield an oil which was purified by recrystallisation from petroleum ether to yield a creamy powder (1.77 g, 68%). X-ray quality crystals were obtained by evaporation of $CHCl_3$. Found: C 63.94, H 6.08. Calc. for $C_{17}H_{19}BrO$: (319.24): requires C 63.96, H 6.00. mp 104 °C. m/z (FAB$^+$) 318 (M^+, 80%). δ_H ($CDCl_3$): 1.40 (9H, s, ^{t}Bu), 5.01 (2H, s, CH_2Ph), 6.71 (1H, d, $^3J_{HH}$ 8.4 Hz, ArH), 7.21 (1H, dd, $^3J_{HH}$ 8.5 Hz, $^4J_{HH}$ 2.4 Hz, ArH), 7.23-7.40 (6H, m, ArH). δ_C: 29.62 (CH_3), 35.13 (C), 70.34 (CH_2), 113.12 (C), 114.18 (CH), 127.36 (CH), 127.95 (CH), 128.64 (CH), 129.54 (CH), 129.93 (CH), 136.92 (C), 141.01 (C), 156.1 (C).

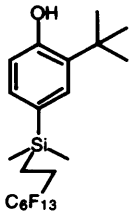
6.2.4.11 Synthesis of 4-(1*H*,1*H*,2*H*,2*H*- tridecafluorooctyldimethylsilyl)-2-*tert*-butyl-benzyloxybenzene (24)



^{t}BuLi (2.94 mL, 1.7 M solution in pentane, 5.0 mmol) in hexane (3 mL) was added dropwise at –78 °C to a stirred solution of 4-bromo-2-*tert*-butyl-benzyloxybenzene (0.75 g, 2.34 mmol) in THF (30 mL) under nitrogen. The mixture was stirred at –78 °C for 3 h and then $C_6F_{13}CH_2CH_2Me_2SiCl$ (2.50 g, 4.61 mmol) in THF (10 mL) was added over 30 min. After 2 h the cooling bath was removed and the solution was stirred for 16 h at room temperature. The mixture was then quenched with a saturated solution of NH_4Cl (20 mL) and the aqueous layer was extracted once with Et_2O (20 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed to yield a crude product which was purified by column chromatography (petroleum ether/Et_2O, 90:10) to yield a white solid (1.75 g, 58%). X-ray quality crystals were obtained by evaporation of $CHCl_3$. Found: C 46.85, H 4.05. Calc. for $C_{27}H_{29}F_{13}OSi$: (319.24): requires C 46.78, H 3.93. mp 74 °C. m/z (ES$^-$) 674, (M-H$^-$, 30%). δ_H ($CDCl_3$): 0.20 (6H, s, $SiMe_2$), 0.79-0.93 (2H, m, SiCH_2CH$_2$C$_6$F$_{13}$), 1.37 (9H, s, ^{t}Bu), 1.92-2.04 (2H, m, SiCH$_2$CH_2C$_6$F$_{13}$), 5.05 (2H, s,

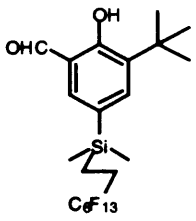
CH_2Ph), 6.84 (1H, d, $^3J_{HH}$ 8.3 Hz, ArH), 7.02-7.30 (7H, m, Ar). δ_F: -80.82 (3F, t, $^4J_{FF}$ 9.7 Hz, CF_3), -115.78 (2F, t, $^4J_{FF}$ 13.9 Hz, CF_2), -121.61 to –122.82 (4F, m, 2 x CF_2), -123.21 (2F, m, CF_2), -126.12 (2F, m, CF_2). δ_C: -3.17 (CH_3), 5.35 (CH_2), 27.12 (CH_2), 29.71 (CH_3), 35.03 (C), 70.01 (CH_2), 112.27 (CH), 127.33 (CH), 127.70 (C), 127.82 (CH), 128.61 (CH), 131.74 (CH), 132.82 (CH), 137.27 (C), 137.86 (C), 159.10 (C).

6.2.4.12 Synthesis of 4-(1*H*,1*H*,2*H*,2*H*- tridecafluorooctyldimethylsilyl)-2-*tert*-butyl-phenol (25)



A mixture of 4-(1*H*,1*H*,2*H*,2*H*- **tridecafluorooctyldimethylsilyl**)-2-*tert*-butyl-benzyloxybenzene (0.46 g, 0.5 mmol) and Pd/C (10% Pd/C 0.04 g, 0.04 mmol) in EtOAc (20 mL) was placed in a hydrogenation reactor and filled with hydrogen (15 bar). The mixture was stirred for 72 h at room temperature. After filtering the reaction mixture through celite, it was diluted with Et_2O (20 mL), washed with Na_2CO_3, dried over $MgSO_4$ and the solvent was removed to yield a clear oil (0.25 g, 93%). Found: C 43.36, H 4.12. Calc. for $C_{20}H_{23}F_{13}OSi$: (554.13) requires C 43.32, H 4.18. m/z (ES^-) 553, ($M\text{-}H^-$, 50%). δ_H ($CDCl_3$): 0.21 (6H, s, $SiMe_2$), 0.79-0.93 (2H, m, $SiCH_2CH_2C_6F_{13}$), 1.40 (9H, s, ^tBu), 1.90-2.04 (2H, m, $SiCH_2CH_2C_6F_{13}$), 5.05 (1H, s, OH), 6.55 (1H, d, $^3J_{HH}$ 7.9 Hz, ArH), 7.13 (1H, dd, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 1.8 Hz, ArH), 7.32 (1H, d, $^4J_{HH}$ 2.0 Hz). δ_F: -80.89 (3F, t, $^4J_{FF}$ 9.8 Hz, CF_3), -116.18 (2F, t, $^4J_{FF}$ 14.6 Hz, CF_2), -122.02 to –123.14 (4F, m, 2 x CF_2), -123.15 (2F, m, CF_2), -126.33 (2F, m, CF_2). δ_C: -4.20 (CH_3), 4.36 (CH_2), 25.01 (CH_2), 28.53 (CH_3), 33.63 (C), 115.56 (CH), 126.95 (C), 131.24 (CH), 134.73 (CH), 135.21 (C), 154.54 (C).

6.2.4.13 Synthesis of 5-(1*H*,1*H*,2*H*,2*H*- tridecafluorooctyldimethylsilyl)-3-*tert*-butyl-salicyl aldehyde (26)



Paraformaldehyde (0.46 g, 15.26 mmol) was added to a mixture of 4-(1*H*,1*H*,2*H*,2*H*-tridecafluorooctyldimethylsilyl)-2-*tert*-butylphenol (1.17 g, 2.18 mmol), $MgCl_2$ (0.30 g, 3.12 mmol) and NEt_3 (1.31 mL, 8.72 mmol) in CH_3CN (40 mL) under nitrogen. After refluxing the reaction mixture for 24 h, it was quenched with H_2O (50 mL) and the aqueous phase was extracted with Et_2O (3x 30 mL). The organic layers were dried with $MgSO_4$ and the solvent was removed to yield an oil which was purified by column chromatography (Et_2O/ petroleum ether, 2/98) to yield a clear oil (0.51 g, 41%). Found: C 43.45, H 4.04. Cal. for $C_{21}H_{23}F_{13}O_2Si$: (582.47) requires C 43.30, H 3.98. m/z (ES^-) 581 ($M\text{-}H^-$, 100%). δ_H ($CDCl_3$): 0.32 (6H, s, $SiMe_2$), 0.79-0.85 (2H, m, $SiCH_2CH_2C_6F_{13}$), 1.30 (9H, s, ^tBu), 1.85-2.04 (2H, m, $SiCH_2CH_2C_6F_{13}$), 7.40 (1H, d, $^4J_{HH}$ 1.5 Hz, ArH), 7.54 (1H,

d, $^4J_{HH}$ 1.5 Hz, ArH), 9.71 (1H, s, CHO), 11.68 (1H, s, OH). δ_F: -80.87 (3F, t, $^4J_{FF}$ 9.4 Hz, CF_3), -115.83 (2F, t, $^4J_{FF}$ 14.4 Hz, CF_2), -122.02 to –123.15 (4F, m, 2 x CF_2), -123.22 (2F, m, CF_2), -126.09 (2F, m, CF_2). δ_C: -3.31 (CH_3), 5.32 (CH_2), 26.03 (CH_2), 29.23 (CH_3), 35.06 (C), 112.22 (CH), 120.71 (C), 126.85 (C), 131.27 (CH), 135.23 (C), 162.36 (C), 197.41 (CH).

6.2.4.14 Synthesis of *N,N'*-bis(3,3'-tert-butylsalicylaldehyde)-bis(5,5'-1*H*,1*H*,2*H*,2*H*-tridecafluorooctyldimethylsilyl)-1,2-cyclohexyldiamine (H_2salen11) (27)

(1*R*,2*R*)-(-)-1,2-cyclohexyldiamine (0.04 g, 0.36 mmol) was added to a solution of 5-(1*H*,1*H*,2*H*,2*H*-tridecafluorooctyldimethylsilyl)-3-*tert*-butyl-salicylaldehyde (0.40 g, 0.71 mmol) in ethanol (30 mL) and refluxed for 16 h. After removing the solvent to yield a yellow solid, it was purified by column chromatography (Et_2O/ petroleum ether, 2/98) to give a yellow oil (0.195 g, 48%). $[\alpha]_D^{25}$: -4.46 (*c* 1.0 in EtOH). m/z (ES)$^-$ 1243, (M-H$^-$, 100%). δ_H ($CDCl_3$): 0.24 (3H, s, $SiMe_2$), 0.28 (3H, s, $SiMe_2$), 0.82-1.00 (2H, m, $SiCH_2CH_2C_6F_{13}$), 1.41 (9H, s, ^{t}Bu), 1.85-2.04 (6H, m, $CH_{cyclohexyl}$, $SiCH_2CH_2C_6F_{13}$), 3.41 (1H, s, $CH_{cyclohexyl}$), 7.14 (1H, d, $^4J_{HH}$ 1.7 Hz, ArH), 7.35 (1H, d, $^4J_{HH}$ 1.5 Hz, ArH), 8.36 (1H, s, HC=N). δ_F: -80.52 (3F, t, $^4J_{FF}$ 9.8 Hz, CF_3), -115.94 (2F, t, $^4J_{FF}$ 14.3 Hz, CF_2), -120.01 to –124.45 (6F, m, 3 x CF_2), -126.18 (2F, m, CF_2). δ_C: -4.62 (CH_3), 4.23 (CH_2), 23.21 (CH_2), 24.98 (CH_2), 28.51 (CH_3), 32.24 (CH_2), 33.82 (C), 76.19 (CH), 117.62 (C), 123.61 (C), 132.92 (CH), 134.75 (CH), 135.82 (C), 160.71 (C), 164.56 (CH).

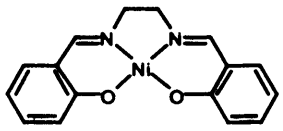
6.3 Coordination chemistry of conventional salen ligands

6.3.1 Synthesis of conventional salen coordination compounds

6.3.1.1 Synthesis of [Ni(salen1)] (28)

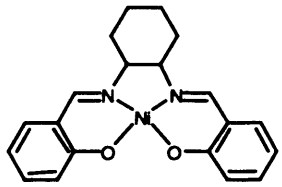
A solution of [$NiCl_2.6H_2O$] (2.62 g, 0.01 mol) in ethanol (20 mL) was added to a solution of H_2salen1 (**1**) (3.16 g, 0.01 mol) in ethanol (30 mL). A red precipitate was formed and the reaction was refluxed for five hours. After cooling to room temperature, the reaction mixture was filtered to give a red solid which was washed with hexane and dried with a cold finger (1.87 g, 35%). mp 350 °C (lit,[10] 352 °C). m/z (ES$^+$) 373 (M$^+$, 100%). δ_H (CD_2Cl_2): 6.64 (1H, t, $^3J_{HH}$ 8.7, ArH), 6.93 (1H, d, $^3J_{HH}$ 6.7 Hz, ArH), 7.18 (1H, dd, $^3J_{HH}$ 6.1 Hz, $^4J_{HH}$ 2.3 Hz, ArH), 7.33 (2H, m, ArH), 7.65 (1H, d, $^3J_{HH}$ 7.9 Hz, ArH), 8.26 (1H, s, N=CH). ν_{max} (solid): 1602 cm^{-1} (C=N), 1371 cm^{-1} (CO).

6.3.1.2 Synthesis of [Ni(salen2)] (29)



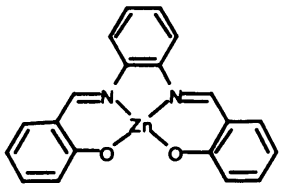
A solution of [Ni(acetate)$_2$.2H$_2$O] (2.49 g, 0.01 mol) in ethanol (30 mL) was added to a solution of *N,N'*-bis(salicylidene)-1,2-ethylenediamine (H$_2$salen2) (2.68 g, 0.01 mol) in ethanol (30 mL). An orange precipitate was formed and the reaction was stirred at room temperature for three hours. The solution was then filtered and washed with diethyl ether to obtain an orange salt (1.88 g, 35%). mp 339 °C (lit,[3] 345 °C). m/z (ES$^+$) 325 (M$^+$, 100%). δ_H (CD_2Cl_2): 3.52 (2H, s, CH_2), 6.47 (1H, d, $^3J_{HH}$ 6.3 Hz, ArH), 6.90 (1H, t, $^3J_{HH}$ 6.3 Hz, ArH), 6.95 (1H, d, $^3J_{HH}$ 7.8 Hz, ArH), 7.15 (1H, t, $^3J_{HH}$ 7.8 Hz, ArH), 7.39 (1H, s, N=CH). ν_{max} (solid): 1623 cm^{-1} (C=N), 1347 cm^{-1} (CO).

6.3.1.3 Synthesis of [Ni(salen3)] (30)



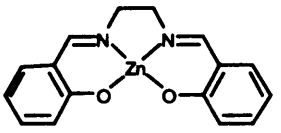
A solution of [Ni(acetate)$_2$.2H$_2$O] (2.49 g, 0.01 mol) in water (20 mL) was added to a solution of H$_2$salen3 (**2**) (3.23 g, 0.01 mol) in MeOH (30 mL) and the mixture was refluxed for 4 hours. The solution was then filtered, washed with diethyl ether and recrystallised from DMF and THF. After drying under oil pump vacuum an orange powder was obtained (19.32 g, 52%). mp 355 °C (lit,[1] 356 °C). m/z (ES$^+$) 379 (M$^+$, 100%). δ_H ($CDCl_3$): 1.30 (2H, m, $CH_{cyclohexyl}$), 1.95 (1H, m, $CH_{cyclohexyl}$), 2.45 (1H, m, $CH_{cyclohexyl}$), 3.11 (1H, m, $CH_{cyclohexyl}$), 6.45 (1H, m, ArH), 6.95 (2H, m, ArH), 7.15 (1H, m, ArH), 7.30 (1H, s, HC=N). ν_{max} (solid): 1612 cm^{-1} (C=N), 1330 cm^{-1} (CO).

6.3.1.4 Synthesis of [Zn(salen1)] (31)



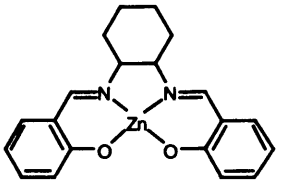
A solution of $ZnEt_2$ (10 mL, 0.01 mol, 1.0 M in hexane) was added to a solution of H$_2$salen1 (**1**) (3.16 g, 0.01 mol) in dry hexane (40 mL). The solution was stirred for twelve hours at room temperature under nitrogen. The precipitate was then filtered and washed with hexane to yield a yellow powder (2.97 g, 78%). mp 339 °C (lit,[3] 342 °C). m/z (ES$^+$) 379 (M$^+$, 10%), 757 (2M$^+$, 20 %). δ_H (CD_2Cl_2): 6.50 (1H, m, ArH), 6.70 (1H, m, ArH), 6.95 (2H, m, ArH), 7.12 (2H, m, ArH), 8.22 (1H, s, HC=N). ν_{max} (solid): 1611 cm^{-1} (C=N), 1390 cm^{-1} (CO).

6.3.1.5 Synthesis of [Zn(salen2)] (32)



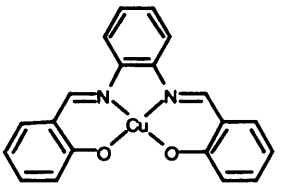
A solution of $ZnEt_2$ (10 mL, 1.0 M in hexane, 0.01 mol) was added to a solution of H_2salen2 (2.68 g, 0.01 mol) in dry THF (30 mL). The solution was stirred for twelve hours at room temperature under nitrogen. The precipitate was then filtered and washed with hexane to give a yellow powder. (3.55 g, 65%). mp 358 °C (lit,[3] >350 °C). δ_H (CD_2Cl_2-Hacac): 3.48 (2H, s, CH_2), 6.60 (2H, m, ArH), 7.05 (2H, m, ArH), 8.18 (1H, s, N=CH). ν_{max} (solid): 1653 cm^{-1} (C=N), 1340 cm^{-1} (CO).

6.3.1.6 Synthesis of [Zn(salen3)] (33)



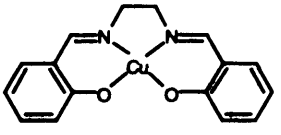
A solution $ZnEt_2$ (10 mL, 1.0 M in hexane, 0.01 mmol) was added to a solution of H_2salen3 (3.23 g, 0.01 mol) in dry hexane (30 mL) and the mixture was then refluxed for 3 hours. After filtering the solution, the product was recrystallised from pyridine and diethyl ether, to give a yellow powder (23.48 g, 60%). mp 340 °C. m/z (ES^+) 385 (M^+, 100%). δ_H ($CDCl_3$): 1.40 (2H, m, $CH_{cyclohexyl}$), 1.95 (1H, m, $CH_{cyclohexyl}$), 2.45 (1H, m, $CH_{cyclohexyl}$), 3.22 (1H, m, $CH_{cyclohexyl}$), 6.75-7.48 (4H, m, ArH), 8.00 (1H, s, HC=N). ν_{max} (solid): 1634 cm^{-1} (C=N), 1330 cm^{-1} (CO).

6.3.1.7 Synthesis of [Cu(salen1)] (34)



A solution of $[Cu(NO_3)_2.3H_2O]$ (2.41 g, 0.01 mol) in ethanol (30 mL) was added to a solution of H_2salen1 (3.16 g, 0.01 mol) in ethanol (30 mL). A 1.0 M solution of NaOH (42 mL) was added and the reaction mixture was then refluxed. After one hour the solution was cooled in a fridge overnight. Finally, the precipitate was filtered to yield a dark violet powder (2.76 g, 73%). Found: C 63.35, H 4.37 N 7.35. Calc. for $C_{20}H_{16}CuN_2O_2$: (378.45) requires C 63.23, H 4.25 N 7.37. mp 320 °C (lit,[3] 318 °C). m/z (ES^+) 378 (M^+, 100%). ν_{max} (solid): 1605 cm^{-1} (C=N), 1348 cm^{-1} (CO). λ_{max} (DCM) = 660 nm.

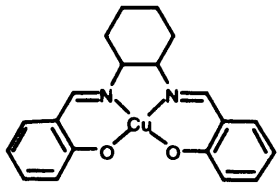
6.3.1.8 Synthesis of [Cu(salen2)] (35)



A solution of $[Cu(NO_3)_2.3H_2O]$ (2.41 g, 0.01 mol) in ethanol (30 mL) was added to a solution of H_2salen2 (2.68 g, 0.01 mol) in ethanol (30 mL). A 1.0 M solution of NaOH (42 mL) was added and the reaction mixture was then refluxed. After one hour, the purple solution was cooled to RT to yield a dark-purple powder (2.68 g, 83%). Found: C 63.35, H 4.37, N 7.35. Calc. for $C_{16}H_{14}CuN_2O_2.H_2O$: (347.86)

requires C 55.24, H 4.64, N 7.37. mp 312 °C decomposed (lit,[3] 318 °C decomposed). m/z (ES^+) 330 (M^+, 100%). ν_{max} (solid): 1647 cm^{-1} (C=N), 1334 cm^{-1} (CO). λ_{max} (DCM) = 564 nm.

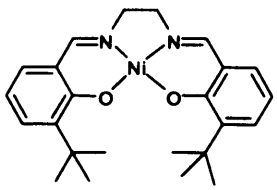
6.3.1.9 Synthesis of [Cu(salen3)] (36)



A solution of [Cu(acetate)$_2$.3H$_2$O] (1.99 g, 0.01 mol) in water (20 mL) was added to a solution of H$_2$salen3 (3.23 g, 0.01 mol) in MeOH (30 mL). The solution was then refluxed for 4 h. After filtering the solution and washing with hexane, a purple dust was obtained that was dried under vacuum for 24 h, to give a purple powder (1.77 g, 49%). Found: C 60.12 H 5.74 N 6.68. Calc. for $C_{20}H_{20}CuN_2O_2.H_2O$: (401.95) requires C 59.76 H 5.52 N 6.97. mp 320 °C (lit,[3] 315 °C). m/z (ES^+) 384 (M^+, 100%). ν_{max} (solid): 1627 cm^{-1} (C=N), 1322 cm^{-1} (CO). λ_{max} (DCM) = 562 nm.

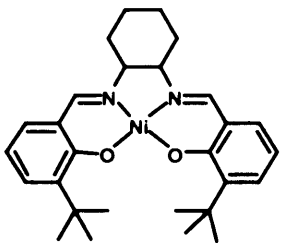
6.3.2 Synthesis of new generation salen coordination compounds

6.3.2.1 Synthesis of [Ni(salen6)] (37)



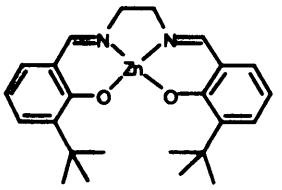
[Ni(acetate)$_2$.2H$_2$O] (0.19 g, 0.80 mmol) was added to a solution of *N,N'*-bis(3,3'-*tert*-butylsalicylidene)-1,2-ethylenediamine (H$_2$salen6) (0.31 g, 0.80 mmol) in methanol (30 mL). The mixture was then refluxed for 3 h. After cooling the reaction mixture to –17 °C for 12 h, the reaction mixture was filtered to yield an orange powder (0.20 g, 56%). mp: 278 °C (decomposed). m/z (ES^+) 437, (M^+, 100%). δ_H ($CDCl_3$): 1.39 (9H, s, ^{t}Bu), 3.41 (2H, s, CH_2), 6.40 (1H, t, $^3J_{HH}$ 7.6 Hz, ArH), 6.82 (1H, d, $^3J_{HH}$ 7.6 Hz, ArH), 7.14 (1H, d, $^3J_{HH}$ 7.3 Hz, ArH), 7.31 (1H, s, HC=N). ν_{max} (solid): 1622 cm^{-1} (C=N), 1541 cm^{-1} (CO).

6.3.2.2 Synthesis of [Ni(salen7)] (38)



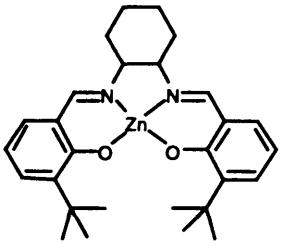
[Ni(acetate)$_2$.2H$_2$O] (0.19 g, 0.80 mmol) was added to a solution of *N,N'*-bis(3,3'-*tert*-butylsalicylene)-1,2-cyclohexyldiamine (H$_2$salen7) (0.39 g, 0.80 mmol) in methanol (30 mL). The mixture was then refluxed for 3 h. After cooling the reaction mixture to -17 °C for 12 h, it was filtered to yield an orange powder (0.19 g, 48%). mp: 248 °C. m/z (ES^+) 491 (M-H^+, 100%). δ_H ($CDCl_3$): 1.39 (9H, s, ^{t}Bu), 1.81 (4H, m, $CH_{cyclohexyl}$), 3.25 (1H, m, $CH_{cyclohexyl}$), 6.40 (1H, t, $^3J_{HH}$ 7.3 Hz, ArH), 6.88 (1H, d, $^3J_{HH}$ 7.7 Hz, ArH), 7.14 (1H, d, $^3J_{HH}$ 7.3 Hz, ArH), 7.35 (1H, s, HC=N). ν_{max} (solid): 1617 cm^{-1} (C=N), 1540 cm^{-1} (CO).

6.3.2.3 Synthesis of [Zn(salen6)][3] (39)



A solution of $ZnEt_2$ (17 mL, 1.0 M in hexane, 17 mmol) was added to a solution of H_2salen6 (4.52 g, 17 mmol) in hot THF (30 mL). The solution was refluxed for 16 hours under nitrogen. After removing the solvent, hexane was added and the solution was filtered to obtain a yellow powder that was dried with a cold finger (3.51 g, 48%). mp: 285 °C (decomposed). m/z (ES^+) 441, ($M-H^+$, 10%). δ_H ($CDCl_3$): 1.36 (9H, s, ^tBu), 3.72 (1H, d, $^3J_{HH}$ 12.8 Hz, CH_2), 4.00 (1H, d, $^3J_{HH}$ 12.8 Hz, CH_2), 6.47 (2H, m, ArH), 7.28 (1H, d, $^3J_{HH}$ 7.7 Hz, ArH), 7.65 (1H, s, HC=N). ν_{max} (solid): 1607 cm^{-1} (C=N), 1539 cm^{-1} (CO).

6.3.2.4 Synthesis of [Zn(salen7)][3] (40)



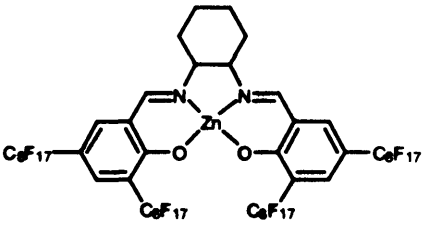
A solution of $ZnEt_2$ (3.45 mL, 1.0 M in hexane, 3.45 mmol) was added to a solution of H_2salen7 (1.51 g, 3.45 mmol) in hot THF (30 mL). The solution was refluxed for 16 hours under nitrogen. After removing the solvent, hexane was added and the solution was filtered to obtain a yellow powder that was dried with a cold finger (1.19 g, 78%). mp: 300 °C (decomposed). $[\alpha]_D^{25}$ -50.72 (*c* 1.0 in EtOH). m/z (FAB^+) 497 ($M-H^+$, 100%). δ_H ($CDCl_3$): 1.36 (9H, s, ^tBu), 1.60-2.05 (4H, m, $CH_{cyclohexyl}$), 3.25 (1H, m, $CH_{cyclohexyl}$), 6.60 (1H, t, $^3J_{HH}$ 7.9 Hz, ArH), 6.91 (1H, dd, $^3J_{HH}$ 7.6 Hz, $^4J_{HH}$ 1.7 Hz, ArH), 7.28 (1H, d, $^3J_{HH}$ 7.6 Hz, $^4J_{HH}$ 1.5 Hz, ArH), 8.20 (1H, s, HC=N). ν_{max} (solid): 1594 cm^{-1} (C=N), 1539 cm^{-1} (CO).

6.3.2.5 Immobilisation of [Zn(salen7)] on SiO_2

In a 100 mL flask, dry SiO_2 (2 g) and [Zn(salen7)] (0.304 g, 0.781 mmol) were stirred together in DCM (40 mL) under nitrogen for 2 h. After removing the solvent, the mixture was dried under oil pump vacuum at 70 °C for 5 h.

6.3.3 Coordination chemistry of fluorous salen ligands

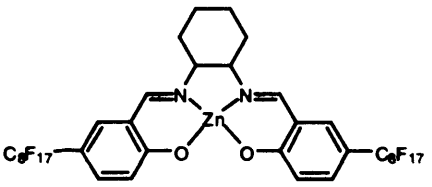
6.3.3.1 Synthesis of [Zn(salen5)] (41)



A solution of $ZnEt_2$ (0.88 mL, 1.0 M hexane, 0.88 mmol) was added to a solution of H_2salen5 (1.75 g, 0.88 mmol) in hot ethanol (30 ml). The solution was refluxed for four hours under nitrogen before removing the solvent. After cooling to room temperature, the solvent was removed and hexane was added and the solution was filtered to obtain a yellow powder that was dried with a cold finger (0.98 g, 56%). mp 256 °C

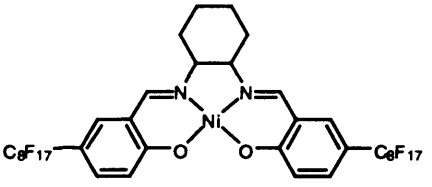
(decomposed). Found: C 31.35, H 1.35, N 1.70. Calc. for $C_{52}H_{18}F_{68}N_2O_2Zn$ requires: C 31.03, H 1.16, N 1.34. ν_{max} (solid): 1644 cm^{-1} (C=N), 1468 cm^{-1} (CO), 1199- 1115 cm^{-1} (C-F).

6.3.3.2 Synthesis of [Zn(salen8)] (42)



A solution of $ZnEt_2$ (1.14 mL, 1.0 M in hexane, 1.14 mmol) was added to a solution of H_2salen8 (1.32 g, 1.14 mmol) in dry ethanol (30 mL). The mixture was then refluxed for 2 h. The resulting mixture was filtered to obtain a pale yellow solid which is insoluble in most organic solvents (1.14 g, 82%). mp 272 °C (decomposed). ν_{max} (solid): 1637 cm^{-1} (C=N), 1484 cm^{-1} (CO), 1198- 1113 cm^{-1} (C-F).

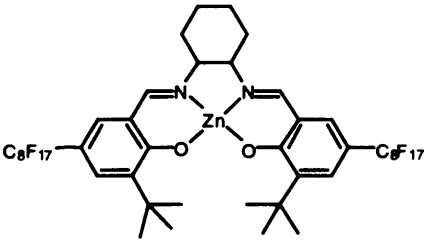
6.3.3.3 Synthesis of Ni(salen8) (43)



$[Ni(AcO)_2.4H_2O]$ (0.060g, 0.25 mmol) was added to a solution of H_2salen8 (0.289 g, 0.25 mmol) in EtOH (30 mL) and refluxed for 16 hours. After that, the solution was filtered and washed with EtOH (20 mL) to yield an orange powder (0.195 g, 65%). mp 256 °C (decomposed). ν_{max} (solid): 1563 cm^{-1} (C=N), 1401 cm^{-1} (CO), 1199- 1115 cm^{-1} (C-F).

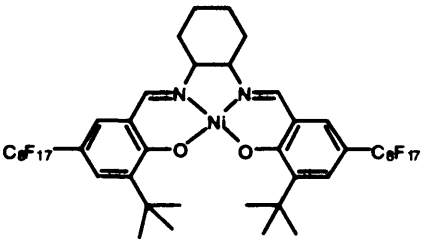
6.3.4 Synthesis of new generation fluorous salen coordination compounds

6.3.4.1 Synthesis of [Zn(salen9)] (44)



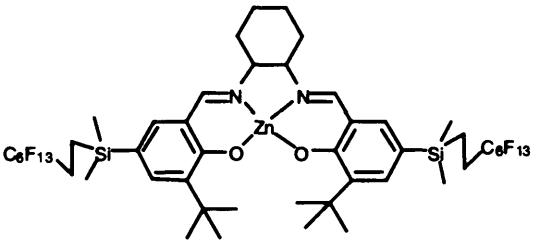
A solution of $ZnEt_2$ (3.18 mL, 1.0 M solution in hexane, 3.18 mmol) was added under nitrogen to a solution of H_2salen9 (4.00 g, 3.18 mmol) in dry THF (30 mL). The solution was heated at 70 °C for 16 h. After removing the solvent a powder was obtained that was purified by washing with ethanol to yield a yellow solid (3.11 g, 68%). $[\alpha]_D^{25}$: -50.48 (*c* 1.0 in $CHCl_3$). mp 210 °C (decomposed). m/z (ES^+) 1374 ($M.THF^+$, 40%). δ_H ($CDCl_3$): 1.40 (9H, s, ^tBu), 1.43- 2.13 (4H, m, $CH_{cyclohexyl}$), 3.70 (1H, m, $CH_{cyclohexyl}$), 7.31 (1H, m, ArH), 7.39 (1H, m, ArH), 8.40 (1H, s, HC=N). δ_F ($CDCl_3$): -80.81 (3F, t, $^4J_{FF}$ 10.3 Hz, CF_3), -109.32 (4F, t, $^4J_{FF}$ 14.4 Hz, 2 x CF_2), -121.84 to -122.71 (6F, m, 3 x CF_2), -126.07 (4F, m, 2 x CF_2). ν_{max} (solid):1605 cm^{-1} (C=N), 1544 cm^{-1} (CO), 1144 cm^{-1} (CF).

6.3.4.2 Synthesis of [Ni(salen9)] (45)



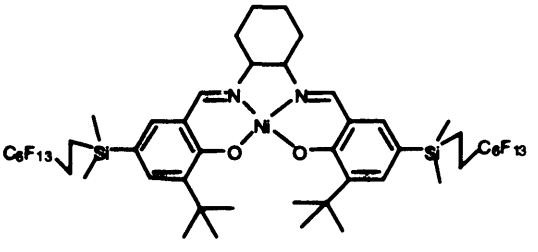
[Ni(AcO)$_2$.4H$_2$O] (0.020 g, 0.078 mmol) was added to a solution of H$_2$salen9 (0.100 g, 0.078 mmol) in EtOH (40 mL) and the solution was refluxed for 16 h. After removing the solvent, the residue was recrystallised with acetonitrile to yield an orange powder (0.079 g, 77 %). X-ray quality crystals were obtained by evaporation of $CHCl_3$. Found: C 39.89, H 2.64, N 2.09. Calc. for $C_{44}H_{34}F_{34}N_2NiO_2$: (1327.39) requires C 39.81, H 2.58, N 2.11. $[\alpha]_D^{25}$: -1.85 (*c* 0.25 in $CHCl_3$) mp 245 °C (decomposed). m/z (FAB$^+$): 1327 (M$^+$, 45%). δ_H (d$_6$-acetone): 1.29 (9H, s, ^{t}Bu), 1.73- 1.99 (4H, m, $CH_{cyclohexyl}$), 3.16 (1H, m, $CH_{cyclohexyl}$), 7.22 (1H, d, $^4J_{HH}$ 2.3 Hz, ArH), 7.51 (1H, d, $^4J_{HH}$ 2.5 Hz, ArH), 7.81 (1H, s, HC=N). δ_F: -81.62 (6F, t, $^4J_{FF}$ 10.5 Hz, CF_3), -109.41 (4F, t, $^4J_{FF}$ 13.9 Hz, 2 x CF_2), -120.84 to –125.21 (16F, m, 8 x CF_2), -126.69 (8F, m, 4 x CF_2). ν_{max} (solid): 1613 cm^{-1} (C=N), 1540 cm^{-1} (CO), 1146 cm^{-1} (CF).

6.3.4.3 Synthesis of [Zn(salen11)] (46)



A solution of $ZnEt_2$ (0.025 mL, 1.0 M in hexane, 0.025 mmol) was added to a solution of H$_2$salen11 (0.030 g, 0.025 mmol) in EtOH (30 mL). The solution was then refluxed for 16 h. After removing the solvent, the residue was recrystallised from chloroform to yield a yellow powder (0.015 g, 77%). $[\alpha]_D^{25}$: -1.09 (*c* 0.25 in Et_2O). mp 240 °C. m/z (FAB$^+$) 1304 (M$^+$, 40%). δ_H ($CDCl_3$): 0.16 (3H, s, $SiMe_2$), 0.19 (3H, s, $SiMe_2$), 0.82-0.97 (2H, m, $SiCH_2CH_2C_6F_{13}$), 1.38 (9H, s, ^{t}Bu), 1.83-2.10 (6H, m, $CH_{cyclohexyl}$, $SiCH_2CH_2C_6F_{13}$), 3.40 (1H, m, $CH_{cyclohexyl}$), 6.99-7.55 (3H, m, ArH, HCN). δ_F: -80.82 (3F, t, $^4J_{FF}$ 9.3 Hz, CF_3), -115.94 (2F, t, $^4J_{FF}$ 14.0 Hz, CF_2), -121.71 to –123.57 (6F, m, 3 x CF_2), -126.06 (2F, m, CF_2). ν_{max} (solid): 1591 cm^{-1} (C=N), 1528 cm^{-1} (CO), 1235 cm^{-1} (CF).

6.3.4.4 Synthesis of [Ni(salen11)] (47)



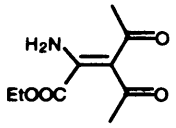
[Ni(AcO)$_2$.4H$_2$O] (0.044 g, 0.025 mmol) was added to a solution of H$_2$salen11 (0.030 g, 0.025 mmol) in EtOH (30 mL) and the solution was refluxed for 16 h. After removing the solvent, the residue was

recrystallised with acetonitrile to yield an orange powder (0.026 g, 80%). Found: C 44.41, H 4.19, N 2.16. Calc. for $C_{48}H_{54}F_{26}N_2NiO_2Si_2$: (1298.3) requires: C 44.35, H 3.99 N 2.07. $[\alpha]_D^{25}$: -7.62 (*c* 0.25 in $CHCl_3$). mp 225 °C. m/z (FAB$^+$) 1298, (M^+, 100%). δ_H ($CDCl_3$): 0.23 (3H, s, $SiMe_2$), 0.26 (3H, s, $SiMe_2$), 0.82-0.97 (2H, m, $SiCH_2CH_2C_6F_{13}$), 1.38 (9H, s, ^tBu), 1.85-2.04 (6H, m, $CH_{cyclohexyl}$, $SiCH_2CH_2C_6F_{13}$), 2.95 (1H, m, $CH_{cyclohexyl}$), 6.99-7.45 (3H, m, ArH, HCN). δ_F: -80.82 (3F, t, $^4J_{FF}$ 9.2 Hz, CF_3), -115.84 (2F, t, $^4J_{FF}$ 14.2 Hz, CF_2), -121.71 to -123.48 (6F, m, 3 x CF_2), -126.07 (2F, m, CF_2). ν_{max} (solid): 1585 cm^{-1} (C=N), 1524 cm^{-1} (CO), 1177 cm^{-1} (CF).

6.4 Catalysis

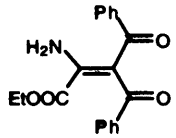
6.4.1 Synthesis of enaminodiones.[11]

6.4.1.1 Synthesis of β-enamino-β-ethoxycarbonyl-diketone[11] (48)



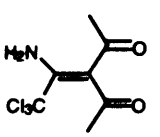
A mixture of the Lewis acid catalyst (0.01 mmol), ethyl cyanoformate (1.5 mL, 0.015 mol) and 2,4-pentanedione (1.0 mL, 0.01 mol) in dry DCM (5 mL) was stirred for 24 hours at room temperature under nitrogen. After removing the solvent, ethyl acetate (15 ml) was added and the solution was filtered through celite. Finally, the solvent was removed under vacuum to yield a white powder. δ_H ($CDCl_3$): 1.30 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 2.20 (3H, s, $COCH_3$), 2.40 (3H, s, $COCH_3$), 4.35 (2H, q, $^3J_{HH}$ 7.0 Hz, OCH_2), 6.10 (1H, br s, NH), 10.00 (1H, br s, NH).

6.4.1.2 Synthesis of β-enamino-β-ethoxycarbonyl-dibenzoylmethane[11] (49)



To a solution of dibenzoylmethane (1.39 g, 6.18 mmol) in dry DCM (2 mL), ethylcyanoformate (0.92 g, 9.28 mmol) and the Lewis acid catalyst (1 mol%) were added. After stirring the mixture for 24 h at room temperature under nitrogen, the suspension was filtered through celite and washed with further DCM (20 mL) to obtain a clear filtrate. The solvent was removed to yield β-enamino-β-ethoxycarbonyl-dibenzoylmethane as a pale crystalline solid. δ_H ($CDCl_3$): 1.10 (3H, t, $^3J_{HH}$ 6.0 Hz, CH_3), 4.20 (2H, q, $^3J_{HH}$ 6.0 Hz, CH_2), 7.20-8.10 (10H, um, ArH), 8.30 (2H, br s, NH_2).

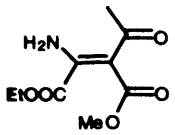
6.4.1.3 Synthesis of β-trichloromethylenaminodione[11] (50)



To a solution of 2,4-pentanedione (1.00 mL, 0.01 mmol) in dry DCM (2 mL), trichloroacetonitrile (2.16 g, 0.015 mmol) and the Lewis acid catalyst (1 mol%) were added. The mixture was then stirred at room temperature under nitrogen for 4 h. The suspension was filtered through celite and washed with DCM (20 mL) to give a clear

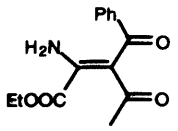
filtrate. After removing the solvent, the yellow residue was dissolved in Ligroin. After 5 h at 0 °C, the β-trichloromethylenaminodione was collected by suction filtration, as a pale cream crystalline solid. δ_H ($CDCl_3$): 2.20 (3H, s, CH_3), 2.75 (3H, s, CH_3), 8.70 (2H, br s, NH_2).

6.4.1.4 Synthesis of β-enamino-β-ethoxycarbonyl-methylketoester[11] (51)



Methylacetoacetate (1.1 mL, 10 mmol) and ethylcyanoformate (1.5 mL, 15 mmol) were added to the catalyst (1 mol %) in dry DCM (5 mL). The mixture was then stirred at room temperature for 24 h under nitrogen. After removing the solvent, ethylacetate was added and the solution was filtered through silica gel. The solvent was finally removed to obtain a white solid. δ_H ($CDCl_3$): 1.45 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 2.42 (3H, s, CH_3), 3.79 (3H, s, OCH_3), 4.45 (2H, q, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 6.16 (1H, br s, NH_2), 10.44 (1H, br s, NH_2).

6.4.1.5 Synthesis of β-enamino-β-ethoxycarbonyl-benzoylacetone[11] (52)



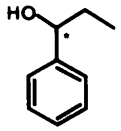
Benzoylacetone (1.1 mL, 10 mmol) and ethylcyanoformate (1.5 mL, 15 mmol) were added to a mixture of the catalyst (1 mol %) in dry DCM (5 mL). The mixture was then stirred at room temperature for 24 h under nitrogen. After removing the solvent, ethylacetate was added and the solution was filtered through silica gel. The solvent was finally removed to obtain a white solid. δ_H ($CDCl_3$): 1.10 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 2.25 (3H, s, CH_3), 4.25 (2H, q, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 6.50 (1H, br s, NH_2), 7.60-8.21 (5H, m, ArH), 10.44 (1H, br s, NH_2).

6.4.1.6 Recycling of the catalysts by filtration

A mixture of catalyst (0.1 mmol, 1 mol%), ethyl cyanoformate (1.5 mL, 0.015 mol) and 2,4-pentanedione (0.98 mL, 0.01 mol) in dry DCM (5 mL) was stirred for 24 hours at room temperature under nitrogen. After removing the solvent, acetonitrile (20 mL) was added and the suspension was cooled for 15 min at –20 °C. Finally, the suspension was filtered obtaining the catalyst as a powder and the product in solution. The solvent was removed to yield the product and the catalyst was dried for 5 h under oil pump vacuum after which it was ready to be used again.

6.4.2 Addition of diethylzinc to benzaldehyde

6.4.2.1 General catalysis procedure for the asymmetric addition of diethylzinc to benzaldehyde (53)



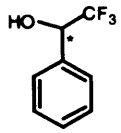
Benzaldehyde (0.107 mL, 1.02 mmol) was added to a mixture of the catalyst (0.12 mmol) in toluene (10 mL) under nitrogen. After cooling the reaction mixture to 0 °C, $ZnEt_2$ (3.12 mL, 1.0 M solution in hexane, 3.12 mmol) was added and the reaction mixture was stirred for 24 h. The reaction mixture was quenched with 1.0 M HCl (20 mL). Finally, the aqueous layer was extracted with Et_2O (2 x 10 mL), dried with $MgSO_4$ and the solvent was removed under vacuum to obtain a yellow oil. δ_H ($CDCl_3$)[12]: 0.84 (3H, t, $^3J_{HH}$ 7.4 Hz, CH_2CH_3), 1.66-1.89 (2H, m, CH_2CH_3), 2.00 (1H, s, OH), 4.61 (1H, m, CH), 7.18 (5H, m, ArH). Product enantioselectivity was determined using chiral GC (CYDEX-B 30 m, 90 °C for 24 min, ramp 45 °C/min to 135 °C, hold 5min. Injector: 220 °C, detector: 250 °C. Flow rate: 3 ml/min. R_t 25.3 minutes (S) enantiomer, R_t 25.9 minutes (R)-1-phenyl-propan-1-ol).

6.4.2.2 Experiments to recycle the catalyst

The product of the reaction was charged onto a short column of fluorous reverse phase silica gel (FRPSG) (1 g). MeOH (30 mL) was then added in order to recover the pure product which was then analysed by chiral GC. By elution with Et_2O (30 mL) the ligand was recovered pure.

6.4.3 Asymmetric trifluoromethylation

6.4.3.1 Asymmetric trifluoromethylation[13] (54)

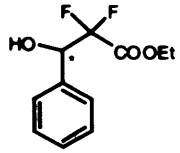


TBAF (10 µl, 1.0 M solution in THF) and $TMSCF_3$ (1.2 mL, 0.5 M solution in THF, 0.6 mmol) were added to a solution of the catalyst (0.033 g, 0.05 mmol) and benzaldehyde (0.5 mL, 0.5 mmol) in THF (5 mL) at 0 °C under nitrogen. After stirring for 24 h, the reaction was quenched with 1N HCl (5 mL) and extracted with Et_2O (3 x 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and finally the solvent was removed to yield a clear oil. δ_H ($CDCl_3$): 2.99 (1H, br s, OH), 4.89 (1H, q, $^3J_{HF}$ 6.8 Hz, CH), 7.34 (5H, m, ArH). δ_F ($CDCl_3$): -79.23 (3F, s, CF_3). Product ee was determined using chiral GC (CYDEX-B 30 m, 90 °C for 30 min, ramp 45 °C/min to 135 °C, hold 5min. Injector: 220 °C, detector: 250 °C. Flow rate: 3 ml/min. 35.05 minutes for the (S) enantiomer, 35.24 minutes for the (R)-1-phenyl-2,2,2-trifluoroethan-1-ol.

6.4.4 Asymmetric addition of ethyl bromodifluoroacetate to benzaldehyde.

6.4.4.1 Asymmetric addition of ethyl bromodifluoroacetate to benzaldehyde[14] (55)

Me_3SiCl (10 µl, 0.08 mmol) was added to a mixture of Zn powder (261 mg, 4 mmol) in THF (2 mL) under nitrogen at room temperature. After 30 min ethyl bromodifluoroacetate (0.13 mL, 1 mmol) was added and the mixture was stirred for 1h at room temperature. This mixture was added *via* canula to a flask containing benzaldehyde (26 µl, 0.25 mmol) and the corresponding catalyst in THF (4 mL) at 0 °C and the mixture was then stirred for 24 h. After quenching the reaction mixture with HCl 1N (10 mL), it was extracted with Et_2O (3x 20 mL). The organic phases were combined, dried over $MgSO_4$ and the solvent was removed to yield a dark oil, which was purified by column chromatography ($CHCl_3$/MeOH, 97/3) to yield a clear oil. δ_H ($CDCl_3$): 1.09 (3H, t, $^3J_{HH}$ 7.2 Hz, OCH_2CH_3), 4.11 (2H, q, $^3J_{HH}$ 6.9 Hz, OCH_2CH_3), 5.01 (1H, dd, $^3J_{HF}$ 15.8 Hz, $^3J_{HF}$ 8.2 Hz, C*H*), 7.15-7.41 (5H, m, ArH). δ_F ($CDCl_3$): -113.68 (1F, d, $^2J_{FF}$ 260 Hz, C*F*F), -120.12 (1F, d, $^2J_{FF}$ 260 Hz, C*F*F).



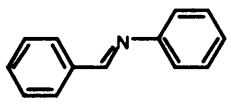
6.4.4.2 Measurement of the enantiomeric excess by capillary ^{19}F NMR[15]

The substrate (at least 0.01 mmol) was added to an NMR tube and diluted with a premixed solution (0.35 mL) of diisopropyl *L*-tartrate (1.25 g, 5.3 mmol) in HPLC grade chloroform (1.55 g, 13.0 mmol). After solution has been achieved, a sealed capillary tube containing $CDCl_3$ was added and the ^{19}F NMR spectrum was recorded. The signals from chiral molecules have split into two peaks (one for each enantiomer) and the enantiomeric excess can therefore be calculated.

6.4.5 Asymmetric addition of $ZnEt_2$ to imines

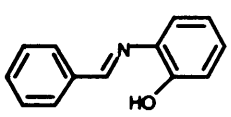
6.4.5.1 Synthesis of *N*-Benzylideneaniline[16] (56)

Aniline (1.74 g, 20 mmol) was added to a solution of benzaldehyde (2.01 mL, 20 mmol) in EtOH (50 mL) and the solution was refluxed for 16 h. After removing the solvent, the residue was recrystallised from hexane (40 mL) to yield white crystals (3.40 g, 93 %). m/z (ES^+) 182, (MH^+, 100%). δ_H ($CDCl_3$): 7.13 (3H, m, ArH), 7.29 (2H, m, ArH), 7.38 (3H, m, ArH), 7.82 (2H, m, ArH), 8.34 (1H, s, HCN).



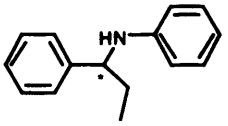
6.4.5.2 Synthesis of 2-(benzylideneamino)phenol[17] (57)

2-Aminophenol (2.18 g, 20 mmol) was added to a solution of benzaldehyde (2.01 mL, 20 mmol) in EtOH (50 mL) and the solution was refluxed for 16 h. After removing the solvent, the residue was recrystallised from hexane (40 mL) to yield cream



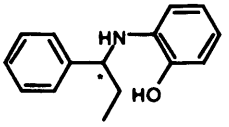
crystals (3.35 g, 85%). m/z (ES^+) 198, (MH^+, 100%). δ_H ($CDCl_3$): 6.83 (1H, td, $^3J_{HH}$ 7.3 Hz $^4J_{HH}$ 1.4 Hz, ArH), 6.97 (1H, dd, $^3J_{HH}$ 8.1 Hz $^4J_{HH}$ 1.4 Hz, ArH), 7.12 (1H, td, $^3J_{HH}$ 7.3 Hz $^4J_{HH}$ 1.5 Hz, ArH), 7.23 (1H, dd, $^3J_{HH}$ 7.8 Hz $^4J_{HH}$ 1.5 Hz, ArH), 7.42 (3H, m, ArH), 7.84 (2H, m, ArH), 8.62 (1H, s, HCN).

6.4.5.3 Synthesis of *N*-(1-phenylpropyl)aniline[16] (58)



N-Benzylideneaniline (0.09 g, 0.5 mmol) was added to a mixture of the catalyst in toluene (10 mL) under nitrogen. After cooling the mixture to 0 °C, $ZnEt_2$ (1.12 mL 1.0 M solution in hexane, 1.12 mmol) was added and the reaction was stirred for 24h. The mixture was quenched with 1.0 M HCl (20 mL). Finally, the aqueous layer was extracted with DCM (2 x 20 mL), dried with $MgSO_4$ and the solvent was removed under vacuum to obtain a yellow oil which was purified by column chromatography (hexane/ $CHCl_3$, 80:20) to yield a clear pure oil. δ_H ($CDCl_3$): 0.85 (3H, t, $^3J_{HH}$ 7.4 Hz, CH_2CH_3), 1.66-1.89 (2H, m, CH_2CH_3), 4.05 (1H, t, $^3J_{HH}$ 6.9 Hz, CH), 5.71 (1H, br s, NH), 6.54 (2H, d, $^3J_{HH}$ 7.6 Hz, ArH), 6.60 (1H, t, $^3J_{HH}$ 7.3 Hz, ArH), 6.95 (2H, t, $^3J_{HH}$ 7.3 Hz, ArH), 7.04-7.24 (5H, m, ArH). Product enantioselectivity was determined using chiral HPLC (CHIRALCEL OD-H column, hexane/^{i}Pro 91.5/8.5, flow rate 0.80 mL/min: R_t 5.21 min, R_t 5.85 min).

6.4.5.4 Synthesis of 2-(1-phenylpropylamino)phenol[17] (59)



2-(Benzylideneamino)phenol was added (0.094 g, 0.5 mmol) to a mixture of the catalyst in toluene (10 mL) under nitrogen. After cooling the mixture to 0 °C, $ZnEt_2$ (1.12 mL 1.0 M solution in hexane, 1.12 mmol) was added and the reaction was stirred for 24 h. The mixture was quenched with 1.0 M HCl (20 mL). Finally, the aqueous layer was extracted with DCM (2 x 20 mL), dried with $MgSO_4$ and the solvent was removed under vacuum to obtain a yellow oil which was purified by column chromatography (hexane/ $CHCl_3$, 80/20) to yield a clear pure oil. δ_H ($CDCl_3$): 0.65 (3H, t, $^3J_{HH}$ 7.3 Hz, CH_2CH_3), 2.01 (1H, s, OH), 2.15 (1H, m, CH_2CH_3), 2.45 (1H, m, CH_2CH_3), 4.05 (1H, dd, $^3J_{HH}$ 10.7 Hz, $^3J_{HH}$ 4.7 Hz, CH), 6.95-7.45 (9H, m, ArH), 9.27 (1H, br s, NH). Product enantioselectivity was determined using chiral HPLC (CHIRALCEL OD-H column, hexane/ ^{i}Pro, 91.5/ 8.5, flow rate 0.80 mL/min: R_t 3.56 min, R_t 3.80 min).

6.15 References.

1 Aldrich Catalogue, 2003- 2004.

2 E. T. G. Cavalheiro, F. C. D. Lemos, J. Z. Schpector, E. R. Dockal. *Thermochim. Acta.* 2001, **370**, 129.

3 N. U. Hofsløkken, L. Skkatebøl, *Acta Chem. Scand.*, 1999, **53**, 258.

4 S. Mizukami, H. Houjou, Y. Nagawa, M. Kanesato, *Chem. Comm.*, 2003, 1148.

5 P. J. Pospisil, D. H. Cartsen, E. N. Jacobsen. *Chem. Eur. J.*, 1996, **2**, 974.

6 G. Pozzi, M. Cavazzini, F. Cinato, F. Montanari, S. Quici. *Eur. J. Org. Chem.*, 1999, 1947

7 M. Cavazzini, A. Manfredi, F. Montanari, S. Quici, G. Pozzi, *Eur. J. Org. Chem.*, 2001, 4639.

8 J. Berthelot, C. Guette, P. L. Desbene, J. J. Basselier, P. Chaquin, D. Masure, *Can. J. Chem.* 1989, **67**, 2061.

9 V. Andrushko, D. Schwinn, C. Ch. Tzschucke, F. Michalek, J. Horn, Ch. Mössner, W. Bannwarth, *Helvetica Chim. Acta*, 2005, **88**, 936.

10 C. S. Marvel, S. A. Aspey, E. A. Dudley. *J. Am. Chem. Soc.*, 1956, 4905.

11 B. Croxtall, Ph. D. Thesis, Univ. of Leicester, 2003.

12 C. W. Edwards, D. M. Haddleton, D. Morsley, M. R. Shipton, M. Wills. *Tetrahedron*, 2003, **59**, 5823.

13 R. Krishnamurti, D. R. Bellew, G. K. S. Prakash. *J. Org. Chem.*, 1991, **56**, 984.

14 J. M. Andres, M. A. Martinez, R. Pedrosa, A. Perez-Encabo. *Synthesis*, 1996, **9**, 1070.

15 R. Roig, Ph. D. Thesis, Univ. of Leicester, 2003.

16 D. Tsvelikhovsky, H. Schemann, J. Blum, *Synthesis*, 2006, **11**, 1819.

17 J. R. Porter, J. F. Traverse, A. H. Hoveyda, M. L. Snapper, *J. Am. Chem. Soc.*, 2001, **123**, 984.

Appendix

A 1

Crystal Data and Structure Refinement for 4-bromo-1-benzyloxy-2-*tert*-butyl-benzene

Identification code	06055	
Empirical formula	C17 H19 Br O	
Formula weight	319.23	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.479(7) Å	α = 76.600(13)°.
	b = 8.551(7) Å	β = 82.597(13)°.
	c = 10.517(8) Å	γ = 88.765(13)°.
Volume	735.6(10) $Å^3$	
Z	2	
Density (calculated)	1.441 Mg/m^3	
Absorption coefficient	2.784 mm^{-1}	
F(000)	328	
Crystal size	0.25 x 0.22 x 0.18 mm^3	
Theta range for data collection	2.01 to 26.00°.	
Index ranges	-10<=h<=10, -10<=k<=10, -12<=l<=12	
Reflections collected	5759	
Independent reflections	2855 [R(int) = 0.0299]	
Completeness to theta = 26.00°	98.8 %	
Absorption correction	Empirical	
Max. and min. transmission	0.928 and 0.634	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2855 / 0 / 175	
Goodness-of-fit on F^2	0.994	
Final R indices [I>2sigma(I)]	R1 = 0.0327, wR2 = 0.0816	
R indices (all data)	R1 = 0.0363, wR2 = 0.0828	
Largest diff. peak and hole	0.510 and -0.545 $e.Å^{-3}$	

A2

Crystal Data and Structure Refinement for 4-(1*H*,1*H*,2*H*,2*H*-perfluorooctyldimethylsilane)-2-*tert*-butyl-benzyloxybenzene

Identification code	06064a	
Empirical formula	C27 H29 F13 O Si	
Formula weight	644.59	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 5.8039(17) Å	α= 99.182(6)°.
	b = 13.039(4) Å	β= 94.976(6)°.
	c = 19.954(6) Å	γ= 96.099(6)°.
Volume	1474.0(7) $Å^3$	
Z	2	
Density (calculated)	1.452 Mg/m^3	
Absorption coefficient	0.182 mm^{-1}	
F(000)	660	
Crystal size	0.18 x 0.12 x 0.06 mm^3	
Theta range for data collection	2.05 to 25.00°.	
Index ranges	-6<=h<=6, -15<=k<=15, -23<=l<=23	
Reflections collected	10704	
Independent reflections	5145 [R(int) = 0.1012]	
Completeness to theta = 25.00°	99.2 %	
Absorption correction	Empirical	
Max. and min. transmission	0.969 and 0.392	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5145 / 156 / 384	
Goodness-of-fit on F^2	1.017	
Final R indices [I>2sigma(I)]	R1 = 0.1314, wR2 = 0.3307	
R indices (all data)	R1 = 0.2403, wR2 = 0.3973	
Largest diff. peak and hole	1.486 and -0.412 $e.Å^{-3}$	

A3

Crystal data and structure refinement for [Ni(salen9)]

Identification code	06076	
Empirical formula	C44 H34 F34 N2 Ni O2	
Formula weight	1327.44	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 19.1697(19) Å	α = 90°.
	b = 10.3875(11) Å	β = 95.599(2)°.
	c = 24.714(3) Å	γ = 90°.
Volume	4897.7(9) $Å^3$	
Z	4	
Density (calculated)	1.800 Mg/m^3	
Absorption coefficient	0.568 mm^{-1}	
F(000)	2648	
Crystal size	0.14 x 0.10 x 0.08 mm^3	
Theta range for data collection	1.66 to 26.00°.	
Index ranges	-23<=h<=23, -12<=k<=12, -29<=l<=30	
Reflections collected	37583	
Independent reflections	9610 [R(int) = 0.1194]	
Completeness to theta = 26.00°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.983 and 0.653	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9610 / 0 / 760	
Goodness-of-fit on F^2	1.057	
Final R indices [I>2sigma(I)]	R1 = 0.1081, wR2 = 0.2700	
R indices (all data)	R1 = 0.1788, wR2 = 0.3018	
Largest diff. peak and hole	1.332 and -0.533 $e.Å^{-3}$	

A3

Crystal data and structure refinement for [Ni(salen9)]

Identification code	06076	
Empirical formula	C44 H34 F34 N2 Ni O2	
Formula weight	1327.44	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 19.1697(19) Å	α = 90°.
	b = 10.3875(11) Å	β = 95.599(2)°.
	c = 24.714(3) Å	γ = 90°.
Volume	4897.7(9) $Å^3$	
Z	4	
Density (calculated)	1.800 Mg/m^3	
Absorption coefficient	0.568 mm^{-1}	
F(000)	2648	
Crystal size	0.14 x 0.10 x 0.08 mm^3	
Theta range for data collection	1.66 to 26.00°.	
Index ranges	-23<=h<=23, -12<=k<=12, -29<=l<=30	
Reflections collected	37583	
Independent reflections	9610 [R(int) = 0.1194]	
Completeness to theta = 26.00°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.983 and 0.653	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9610 / 0 / 760	
Goodness-of-fit on F^2	1.057	
Final R indices [I>2sigma(I)]	R1 = 0.1081, wR2 = 0.2700	
R indices (all data)	R1 = 0.1788, wR2 = 0.3018	
Largest diff. peak and hole	1.332 and -0.533 $e.Å^{-3}$	

A4

Organic/Inorganic Seminar Programme (Autumn/Winter 2003)

Date	Title	Speaker
6th Oct.	*Palladium and Platinum Metallocycles for Organic Chemistry*	**Dr. Chris Richards** ***Queen Mary, University of London***
8th Oct.	*NMR and Proteins*	**Prof. Ian Campbell** ***University of Oxford***
20th Oct.	*Unusual Complex Oxides and Sulphides*	**Dr. Sandie Dann** ***University of Loughborough***
27th Oct.	*Natural and Non-natural Products: Total Synthesis And Biological Applications*	**Dr. Chris Hayes** ***University of Nottingham***
3rd Nov.	*Controlling Electrons and Molecules Using Light*	**Prof. Helen Fielding** ***U.C.L***
14th Nov.	*Green Solvents for Catalysis- From Molecular Understanding to Process Design*	**Prof. Dr. Walter Leitner** ***Greiss Lecture***
24th Nov	*Scope and Potential of Chiral Eletrophiles in Stereoselective Synthesis*	**Prof. Thomas Wirth** ***University of Oxford***

A5

Organic/Inorganic Seminar Programme (Spring/Summer 2004)

Date	Title	Speaker
12th Jan.	*Exploiting Silicon Reagents in Asymmetric Reactions*	**Dr. Liam Cox** ***University of Brimingham***
12th Jan.	*Recent Developments in the Chemistry of Antimony Ligands*	**Prof. Bill Levason** ***University of Southampton***
2nd Feb.	*Synthesis of Biologically Active Compounds*	**Dr. Adam Nelson** ***University of Leeds***
9th Feb.	*Stoichiometric and Catalytic Ruthenium Carbene Species*	**Dr. Michael Whitlesey** ***University of Bath***
23rd Feb.	*3rd Leicester Half-Day Catalysis Symposium*	**Prof. P. Braunstein** **Prof. Sue Gibson** **Dr. P. Kamer** **Dr. Gregory Solan**
1st March	*Stereoselective Synthesis of Cyclic Amines using Chiral Organolithium Species*	**Dr. Ian Coldham** ***University of Sheffield***
15th March	*Connectivity of Functionalised Nanoparticles and their Arrays*	**Prof. David Schiffrin** ***University of Liverpool***

A6

Date	**Title**	**Speaker**
29th March	*Synthesis and Reactivity of Organometallic Complexes*	**Dr. Polly Arnold** ***University of Nottingham***
26th April	*Polyfunctional Heterocycles and Macrocycles*	**Dr. Graham Sandorf** ***University of Durham***
10th May	*Torocyclic Ligands*	**Dr. Dominic Wright** ***University of Cambridge***
17th May	*Ion Mobility Spectrometry-a Little-known Technique*	**Dr. Andy Bell** ***DSTL, Porton Down***
31st May	*New Asymmetric Routes to Chiral Heterocycles*	**Dr. Steve Allin** ***University of Loughborough***
7th June	*Catalysis with Chiral metal Complexes*	**Dr. Peter Scott** ***University of Warwick***

A7

Organic/Inorganic Programme (Autumn/ Winter 2004)

Date	Title	Speaker
4th Oct.	*Templates and Tentacles*	**Dr. Stuart Warrimer** ***University of Leeds***
15th Oct.	*The Chemistry of Interstellar Space*	**Prof. Eric Hebst,** ***Ohio State University***
18th Oct.	*Continuous Flow Homogeneous Catalysis*	**Prof. David Cole-Hamilton,** ***University of St. Andrews***
25th Oct.	*New Methods and Synthetic Applications of Asymmetric Heteroatom Transfer*	**Prof. Alan Armstrong** ***Imperial College, London***
8th Nov.	*Chiral Lanthanide Complexes for Organic Synthesis*	**Dr. Helen Aspinall,** ***University of Liverpool***
15th Nov.	*New Routes to Heterocyclic Systems for Vinylcyclopropanes*	**Dr. Gareth Pritchard** ***Loughborough University***
29th Nov.	*Polymer Imprintig: Metal Clusters That Make Lasting Impression*	**Prof. Paul Walton** ***University of York***

A8

Organic/Inorganic Seminar Programme (Spring/Summer 2005)

Date	Title	Speaker
17th Jan.	*Non-Innocent N-Heterocyclic Carbene and Phosphine Ligands: Computational Studies*	**Dr. Stuart Macgregor** ***Heriot-Watt University***
7th Feb.	*Molecular Catalysis with Group 2 Metals*	**Dr. Mike Hill** ***Imperial College, London***
14th Feb.	*Fiddling with Phosphorous*	**Dr. Simon Jones** ***University of Sheffield***
7th March	*New Strategies for the Synthesis of Pyran Containing Natural Products*	**Dr. Paul Clark** ***University of Nottingham***
4th April	*s-Electron Deficiency Chemistry*	**Prof. P. P. Power** ***University of California***
25th April	*Metal Helicates and Pacman Complexes- Topological Control of Bimetallic Reaction Sites Using Polypyrrolic Ligands*	**Dr. Jason Love** ***University of Nottingham***
4th May	*The Synthesis of Marine Natural Products*	**Prof. Christine Willis,** ***University of Bristol***
6th June	*Fixed Configuration Macrocyclic Chelators: Chemokine Receptor Antagonists and Radiopharmaceuticals*	**Dr. Steve Archibald** ***University of Hull***

A9

Date	Title	Speaker
13th June	*Combining Two-Directional Synthesis and Tandem Reactions: Developing Efficient Strategies For Chemistry*	**Dr. Robert Stockmann,** ***University of East Anglia***
31st August	*Development of Enantioselective Fluorination Reaction and its Application to the Synthesis of Biologically Compounds*	**Prof. Norio Shibata** ***Nagoya Institute of Technology, Japan***

A10

Organic/Inorganic Seminar Programme (Autumn/Winter 2005)

Date	Title	Speaker
31st Oct.	*Metal and non-Metal Phenolates: Catalysts, Sensors and Surprises*	**Prof. Mathew *Davidson, University of Bath***
14th Nov.	*Harnessing Reactive Intermediates for Organic Synthesis*	**Dr. Richard Grainger *University of Birmingham***
21st Nov.	*Synergic Effects in Catalysis with Phosphorus (III) Ligands*	**Prof. Paul Pringle *University of Bristol***
5th Dec.	*Fungal Polyketides: Tales of the Unexpected*	**Prof. Tom Simpson *University of Bristol***
7th Dec.	*Studies on Solute-Solvent Interactions in Supercritical CO_2 by Using Raman Spectroscopy*	**Prof. Yasukisa Ikeda *Tokyo Institute of Technology***
7th Dec.	*Applications of Ionic Liquids to Pyrochemical Reprocessing Methods*	**Prof. Yasukisa Ikeda *Tokyo Institute of Technology***

A11

Organic/Inorganic Seminar Programme (Spring/Summer 2006)

Date	Title	Speaker
22nd Feb.	*Chiral water from Chiral Relays: Stereocontrol in The oxy-Michael and Related Reactions*	**Dr. Darren Dixon** ***University of Manchester***
22nd Feb.	*Novel Approaches for the Enantioselective Total Synthesis of Steroids*	**Dr. Bruno Linclau** ***University of Southampton***
22nd Feb.	*Recent Advances in Methods for Parallel Synthesis*	**Prof. Tony Barrett** ***Imperial College, London***
6th March	*Enantioselective Catalysis Based on Palladium Enolate Chemistry*	**Prof. Mikiko Sodeoka** ***Tohoku University***

A12

Conferences Attended

Date	Conference	Location
Oct. 2003	*Organic Synthesis Symposium*	**Loughborough**
June 2004	*Coordination Chemistry Discussion Group*	**Leicester**
Sept. 2004	*4th Postgrad. Fluorine Subject Group Meeting*	**Durham**
Oct. 2004	*Organic Synthesis Symposium*	**Loughborough**
April 2005	*5th Bristol Synthesis Meeting*	**Bristol**
April 2005	*Fluorination Technologies-Applications and Challenges*	**Syngenta, Jealott's Hill, Bracknell**
Sept. 2006	*6th Postgrad. Fluorine Subject Group Meeting*	**Manchester**

Presentations

Coordination Chemistry Discussion Group, Leciester, July 2004:
Poster entitiled "Synthesis and Coordination Chemistry of Fluorous Salen Salts and Their Use as Catalysts in the Synthesis of Enaminodiones."

4th Postgrad. Fluorine Subject Group Meeting, Durham, September 2004:
Poster entitled "Salen Coordination Compounds as Catalysts"

6th Postgrad. Fluorine Subject Group Meeting, Manchester, September 2006:
Poster entitled "Salen Coordination Compounds as Catalysts."

A13

Lecture Courses Attended (2003-2004)

Title	Lecturer	Term	Credits
Retrosynthetic Analysis	Dr. P. Jenkins	1	5
Organic Strategies	Dr. P. Jenkins/ Dr. S. Handa	2	10