The Synthesis and Applications of [2.2]Paracyclophane Derivatives

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The Synthesis and Applications of

[2.2]Paracyclophane Derivatives

By

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A thesis presented to

Dublin Institute of Technology for the award of Doctor of Philosophy

Prepared under the supervision of

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February 2016
Abstract:

This work concerns the preparation of novel [2.2]paracyclophane derivatives intended for use as asymmetric ligands and investigations into surface coatings prepared from [2.2]paracyclophanes. This begins with a general introduction to enantioselective synthesis, followed by a review of relevant reported ligands based on the [2.2]paracyclophane framework and their applications.

Next is described the preparation of novel ligands based on the [2.2]paracyclophane structure. Starting with the preparation of a range of mono and disubstituted [2.2]paracyclophanes, including several novel analogues, this moves on to investigating resolution procedures where a novel method for the preparation of enantiopure 4-bromo[2.2]paracyclophane is described. The coupling of prepared phenyl oxazoline analogues with the [2.2]paracyclophane moiety via the Buchwald-Hartwig amination is used to prepare several novel ligands and characterisation, along with a detailed investigation in the optimisation of their synthesis is presented. The focus of the work then moves to the analogous octafluoro[2.2]paracyclophane and several routes towards its preparation are investigated. The structure was functionalised and attempts at preparing analogous fluorinated ligands to those already detailed are discussed.

Protective surface coatings prepared from [2.2]paracyclophanes are known as parylenes and herein is presented methods for improved surface adhesion of these coatings. This was accomplished through the use of sol-gel coating pre-treatments. The pre-treatment formulations presented were characterised and ultimately proved superior to the current industrial benchmark. A number of fluorinated sol-gel additives were also prepared and characterised, two of which are novel, along with a brief study on the incorporation of organic dyes into sol-gel coatings.
The work concludes with a discussion of the outcomes and suggestions for future work. The most significant issue is the improvement of the synthesis of the new ligands which it is suggested may be enhanced by either the application of microwave synthesis or altering the coupling partners. Once this has been achieved the next steps would be examining the crystal structure of an isolated ligand-metal complex and then the application of this complex in model asymmetric transformations.
Declaration:

I certify that this thesis which I now submit for examination for the award of PhD is entirely my own work and has not been taken from the work of others, save and to the extent that such work has been cited and acknowledged within the text of my work.

This thesis was prepared according to the regulations for graduate study by research of the Dublin Institute of Technology and has not been submitted in whole or in part for another award in any other third level institution.

The work reported on in this thesis conforms to the principles and requirements of the DIT's guidelines for ethics in research.

________________________
Craig Hicks

Craig Hicks

3rd February 2016
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I would like to extend my sincerest thanks to my supervisors Dr. Gráinne Hargaden and Dr. Brendan Duffy for their invaluable assistance over the course of this work. I also gratefully acknowledge the contributions of Dr. Mohamed Oubaha, Mr. Martin Kitson and Ms. Annette Callaghan.

Finally I want to thank my mother Patricia, my sister Michelle, my brother Stephen and Caroline, for their patience and support over the years.
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Abbreviations:

AcOH  Acetic acid
AF4   Octafluoro[2.2]paracyclophane
AIBN  Azobisisobutyronitrile
BCl3  Boron trichloride
BF3   Boron trifluoride
BINAP 2,2’bis(diphenylphosphino)-1,1’-binaphthyl
BTF   Trifluorotoluene
CCl4  Carbon tetrachloride
CF3   Trifluoromethyl
CIP   Cahn-Ingold-Prelog
Cl2   Chlorine gas
COSY  Correlation spectroscopy
CsF   Caesium fluoride
CTAB  Cetyl trimethylammonium bromide
CVD   Chemical vapour deposition
DAST  Diethylaminosulfur trifluoride
DCM   Dichloromethane
DiPAMP (R,R)-1,2-Bis[(2-methoxyphenyl)(phenylphosphino)]ethane
DMA   Dimethylacetamide
DMF   Dimethylformamide
DMSO  Dimethylsulfoxide
DPPF  1,1’-bis(diphenylphosphino)ferrocene
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDX</td>
<td>Energy dispersive X-ray spectroscopy</td>
</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>FeBr₃</td>
<td>Iron (III) bromide</td>
</tr>
<tr>
<td>HBr</td>
<td>Hydrogen bromide</td>
</tr>
<tr>
<td>HCl</td>
<td>Hydrogen chloride</td>
</tr>
<tr>
<td>HF</td>
<td>Hydrogen fluoride</td>
</tr>
<tr>
<td>HNO₃</td>
<td>Nitric acid</td>
</tr>
<tr>
<td>HOOH</td>
<td>Hydrogen peroxide</td>
</tr>
<tr>
<td>H₂SO₄</td>
<td>Sulfuric acid</td>
</tr>
<tr>
<td>i-PrNEt</td>
<td>Ethyldiisopropylamine</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>KI</td>
<td>Potassium iodide</td>
</tr>
<tr>
<td>KOtBu</td>
<td>Potassium tert-butoxide</td>
</tr>
<tr>
<td>MAAH</td>
<td>Methacrylic acid</td>
</tr>
<tr>
<td>MAPTMS</td>
<td>3-Methacryloxypropyltrimethoxysilane</td>
</tr>
<tr>
<td>mCPBA</td>
<td>m-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>MeCN</td>
<td>Acetonitrile</td>
</tr>
<tr>
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</tr>
<tr>
<td>MPS</td>
<td>Mesoporous silicates</td>
</tr>
<tr>
<td>N₂</td>
<td>Nitrogen gas</td>
</tr>
<tr>
<td>NaBH₄</td>
<td>Sodium borohydride</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-Butyllithium</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
</tbody>
</table>
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NOESY Nuclear Overhauser effect spectroscopy

NO$_2$BF$_4$ Nitronium tetrafluoroborate

OPc Octafluoro[2.2]paracyclophane

Pc [2.2]Paracyclophane

PCl$_5$ Phosphorus pentachloride

Pd(dba)$_2$ Bis(dibenzylideneacetone)palladium(0)

PFOTS 1H,1H,2H,2H-Perfluorooctyltriethoxysilane

Phanephos (RP)-4,12-bis-diphenylphosphino[2.2]paracyclophane

pOPc Perfluoro[2.2]paracyclophane

PPh$_3$ Triphenylphosphine

rpm Rotations per minute

SEM Scanning electron microscopy

SF$_4$ Sulfur tetrafluoride gas

$S_{N}Ar$ Type of nucleophilic aromatic substitution

$S_{RN}I$ Radical nucleophilic aromatic substitution

SO$_2$ Sulfur dioxide gas

SOCl$_2$ Thionyl chloride

SO$_2$Cl$_2$ Sulfuryl chloride

TB Trypan blue

TBAB Tetrabutylammonium bromide

t-Bu $textit{tert}$-Butyl

t-BuLi $textit{tert}$-Butyllithium

TES Transmission electron microscopy
The Synthesis and Applications of [2,2]Paracyclophane Derivatives

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TEOS  Tetraethyl orthosilicate
THF  Tetrahydrofuran
TiCl₄  Titanium (IV) tetrachloride
TLC  Thin layer chromatography
TMS  Tetramethylsilane
Tol  Toluene
TsOH  p-Toluenesulfonic acid
UV-Vis  Ultraviolet-Visible
ZnCl₂  Zinc chloride
ZPO  Zirconium (IV) propoxide
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1.0 Introduction to Enantioselective Synthesis

1.1 Introduction

The first documented observation of stereochemistry was made by Louis Pasteur in 1849 when he observed that the salts of tartaric acid could rotate plane polarised light. Then in 1874, Jacobus Henricus van't Hoff and Joseph Le Bel attributed this optical activity to the tetrahedral arrangement of atoms about a carbon centre\(^1\) (Figure 1.1).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{enantiomers.png}
\caption{Both enantiomers of a simple chiral molecule.}
\end{figure}

Molecules of this nature are referred to as chiral, as it is not possible to superimpose the molecule onto its mirror image. These mirror images are called enantiomers. A simple natural analogy for this is the comparison between the right and left hand. In fact, nature demonstrates a consistent asymmetry with the vast majority of naturally occurring amino acids having an \(L\) configuration\(^2\). Enantiomers demonstrate identical physical and chemical properties in an achiral environment except in the direction that they rotate plane polarised light. The properties of enantiomers differ when they interact with other chiral molecules, receptors or enzymes within the body for example, which may result in different biological responses. This can be seen with simple compounds such as \((S)\)-limonene which smells like lemons and \((R)\)-limonene which smells like oranges. Another example is \((S, S)\)-aspartame which is used as an artificial sweetener while \((R, R)\)-aspartame has a bitter taste (Figure 1.2).
Perhaps the most famous example and the one which highlighted the importance of chirality and enantiopure substances is thalidomide, a compound prescribed to treat morning sickness in the 1960’s. \((R)\)-Thalidomide does indeed treat morning sickness however the \((S)\)-enantiomer was found to be teratogenic leading to foetal abnormalities (Figure 1.3). It was later found that thalidomide racemises \textit{in vivo} meaning that even an enantiopure form would not have averted this tragedy.\(^3\)

Currently, European and U.S. law dictates that all pharmaceutical products must be fully evaluated and for chiral compounds this includes testing both enantiomers.\(^4\) This means there is a need for effective enantioselective synthesis, which involves the preparation of chiral products with a specific preference for a single enantiomer. The compounds shown in Figure 1.4 are used to treat a variety of illnesses and have accounted for billions of dollars in sales.
This illustrates the possible commercial applications of improved enantioselective synthetic methods.

1.2 Synthesis of enantiopure compounds

The methods for producing enantiopure compounds may be categorised under three broad headings which are the chiral pool strategy, resolution of racemic mixtures and asymmetric synthesis (Figure 1.5).

*Figure 1.4: The structure of three successful chiral drug compounds.*

*Figure 1.5: The methods for preparing enantiopure compounds.*
1.2.1 Chiral pool strategy

The term chiral pool refers to readily available, naturally occurring enantiopure compounds such as amino acids, sugars, alkaloids and terpenoids. These may be used as starting materials to synthesise the desired enantiopure product by providing basic chiral centres which can be built upon. This may be an attractive approach if the desired product is structurally similar to the starting material so as to have a short synthetic sequence. However care must be taken to preserve the chirality of the starting material. This method has been used in the synthesis of prostaglandin F$_{2\alpha}$ and chiraphos (Scheme 1.1).

![Scheme 1.1: Chiral pool synthesis of prostaglandin F$_{2\alpha}$ and chiraphos.](image)

1.2.2 Resolution

Resolution is the process by which a racemic mixture is separated into its two enantiomers. It is the most widely used industrial method for obtaining enantiopure compounds. The disadvantage of this method is that the highest obtainable yield by definition is 50%. Resolution may be categorised under four headings which are classical resolution, kinetic resolution, enzymatic resolution and chromatographic resolution.

1.2.2.1 Classical resolution

Classical resolution involves derivatising a racemic mixture with an enantiopure reagent to yield a diastereomer. Diastereomers, unlike enantiomers, have different physical and
chemical properties which allow them to be separated by conventional techniques. The resolving agent is then removed to yield the desired material in an enantiopure form. This approach is applied extensively in industry such as the resolution of Naproxen (*Scheme 1.2*). This particular example is noteworthy as the unwanted (R)-enantiomer 1 can be efficiently racemised and recycled to give yields for (S)-Naproxen 2 above 95% along with over 98% recovery of the resolving agent *N*-propylglucosamine 3.\(^7\)

![Scheme 1.2: The resolution of (S)-Naproxen.](image)

### 1.2.2.2 Kinetic resolution

Kinetic resolution relies on the different rates of reaction of a pair of enantiomers with a chiral reagent or catalyst. Ideally, one enantiomer reacts while the other does not, making them readily separable. As with classical resolution, the unwanted enantiomer must be racemised and resolved to increase the yield. If these processes can occur concurrently the
process is referred to as dynamic kinetic resolution. Noyori et al. reported the preparation of (R)-1-phenylethanol using kinetic resolution facilitated by a ruthenium catalyst (Scheme 1.3).\(^8\)

\[ \text{Scheme 1.3: The kinetic resolution of (R)-1-phenylethanol.} \]

1.2.2.3 Chromatographic resolution

Chromatographic resolution relies on the different affinities of enantiomers between a chiral stationary phase and a mobile phase. This is an attractive method as it does not involve additional steps to derivatise enantiomers, separate them and then regenerate the desired compound. As an example, Li et al. reported the efficient resolution of a range of \(\alpha,\alpha'\)-dihydroxybiaryls using a modified silica prepared from readily available amino acid derivatives (Figure 1.6).\(^9\)

\[ \text{Figure 1.6: The structure of three successfully resolved biaryl compounds.} \]
1.2.2.4 Enzymatic resolution

Enzymes may also be used for the resolution of enantiomers. In the example shown in Scheme 1.4, resolution is achieved using the enzyme *Pseudomonas Stutzeri* lipase TL. A racmte of *cis*-5’-hydroxythalidomide 4 is selectively acylated to give enantiopure 5 while leaving the other enantiomer unchanged. These compounds can then be separated by conventional means and the initial compound regenerated using TsOH in MeOH.\(^{10}\)

![Scheme 1.4: Enzymatic resolution of a thalidomide derivative.](image)

1.2.3 Asymmetric synthesis

Asymmetric synthesis may be defined as a synthesis in which an achiral unit in a substrate molecule is converted to a chiral unit such that the possible stereoisomers are formed in unequal amounts.\(^7\) There are various ways this may be achieved and the approaches make use of chiral reagents, chiral auxiliaries or chiral catalysts to introduce the chirality into the substrate molecule.
1.2.3.1  Chiral reagents

This approach involves the conversion of an achiral substrate to a chiral substrate with the use of an appropriate chiral reagent which controls the asymmetry introduced. Chiral allylboranes are common reagents for this methodology (Scheme 1.5). For example, Hoffmann et al. developed allylboronate 6 for the preparation of a range of homoallylic alcohols 7. Brown et al. prepared a range of chiral lactones 8 using allylboronate 9. The obvious limitation of this methodology is the requirement for stoichiometric quantities of potentially expensive or difficult to prepare chiral reagent.

\[ \text{Scheme 1.5: The stereoselective allylation of carbonyl compounds using chiral allylboronates.} \]

1.2.3.2  Chiral auxiliaries

A chiral auxiliary is a reagent incorporated into the substrate molecule to influence the stereoselectivity of one or more subsequent reactions. The diastereomers produced are separated and the auxiliary is then removed from the products and, in ideal cases, recycled. Examples are shown in Figure 1.7 and include pseudoephedrine 10 used to produce enantiomerically pure carboxylic acids, alcohols, aldehydes and ketones. Other frequently
used chiral auxiliaries are the valine 11 and norephedrine 12 derived oxazolidinones developed by Evans.\textsuperscript{15,16}

![Common chiral auxiliaries.](image)

**Figure 1.7: Common chiral auxiliaries.**

1.2.3.3 Chiral catalysts

The third approach to asymmetric synthesis is the use of a chiral catalyst to facilitate an asymmetric transformation. This method is attractive because it does not require stoichiometric quantities of the chiral material which is one of the biggest disadvantages of using chiral reagents or chiral auxiliaries. Chiral catalysts may be categorised under four headings which are enzymes, catalytic antibodies, organocatalysts and metal catalysts.

1.2.3.3.1 Enzymes

Enzymes as catalysts are efficient, fast acting and usually give high levels of enantioselectivity. A successful use of an enzyme as a stereoselective catalyst is shown in Scheme 1.6 which is the synthesis of (S)-norcoclaurine 13. Tyrosine 14 is first decarboxylated and the subsequent aldehyde 15 coupled with dopamine 16 in the presence of the enzyme (S)-norcoclaurine synthase (NCS) to furnish the product.\textsuperscript{17} The limitations of enzymes are their pH sensitivity and limited solubility in organic solvents. They may also be less stable in these solvents than in aqueous solutions. Enzymes are natural materials designed to facilitate specific transformations so they tend to be substrate specific and not applicable as a general method.
1.2.3.3.2 Catalytic antibodies

Antibodies are used by the immune system to neutralise foreign objects such as bacteria and viruses. Like enzymes, they are proteins and operate in a similar fashion to enzymes in that they have an active site that will respond to a specific substrate. In recent years it has been shown that antibodies can be utilised as asymmetric catalysts. The example in Scheme 1.7 shows the conversion of the ketone 17 to the (S)-enantiomer of the Wieland-Miescher ketone 18 via the Robinson annulation using the antibody Ab38C2.18

**Scheme 1.7: The synthesis of enantiopure Wieland-Miescher ketone.**

1.2.3.3.3 Organocatalysts

An organocatalyst as the name suggests, is an organic molecule which does not contain a metal but which catalyses a chemical transformation. This is currently a major area of research and the advantages these materials offer are that they are easily accessible and robust, usually being stable towards moisture and oxygen. They also avoid the use of metals which makes them more environmentally friendly and cheaper to produce. Examples include
L-Proline 19\textsuperscript{19}, thioureas such as 20\textsuperscript{20} and alkaloids such as 21\textsuperscript{21}, which have all been used as organocatalysts for a variety of asymmetric transformations (Figure 1.8).

![Three compounds used as organocatalysts.](image)

1.2.3.3.4 Metal catalysts

Metal catalysts are the largest and most active area in asymmetric synthesis. These systems operate with a reactive metal centre coordinated to a chiral ligand. As such these ligands typically have donor atoms such as nitrogen, oxygen, phosphorus or sulfur. The metal activates the reagents allowing the reaction to proceed and the chirality of the products is translated from the chiral ligands around the metal centre. Figure 1.9 shows ligands which have been used in this methodology and these may possess axial chirality (BINAP 22)\textsuperscript{22}, central chirality (DiPAMP 23)\textsuperscript{23} or planar chirality (Phanephos 24)\textsuperscript{24}.

![Three different chiral ligands used in asymmetric metal catalysis.](image)

Phanephos is an example of a [2.2]paracyclophane and since it was shown to be an effective compound for use in asymmetric catalysis, there has been a dramatic increase in research concerning [2.2]paracyclophanes.
1.3 Conclusion

This chapter has provided an introduction to enantioselective synthesis and will be followed by a review of relevant reported ligands based on the [2.2]paracyclophane framework and their applications in Chapter 2. Chapter 3 will describe the preparation of a novel class of asymmetric [2.2]paracyclophane ligands from commercially available starting materials. Chapter 4 contains a comprehensive review of the closely related octafluoro[2.2]paracyclophane. This is followed by Chapter 5 which is a description of progress towards the preparation of an analogous class of fluorinated [2.2]paracylophane ligands to complement those prepared in Chapter 3. Chapter 6 details protective surface coatings prepared from [2.2]paracyclophanes which are known as parylenes and here are presented methods for improved surface adhesion of these coatings. This was accomplished through the use of sol-gel pre-treatments on aluminium substrates, sol-gels themselves being another frequently used class of surface coatings. Chapter 7 discusses the preparation of a number of fluorinated sol-gel additives, along with a brief study on the incorporation of organic dyes into sol-gel coatings. Finally, Chapter 8 contains a brief conclusion along with suggestions for future work.
1.4 References


2.0 Review of [2.2]Paracyclophane Ligands: Preparation and Application

2.1 Introduction

The first report of [2.2]paracyclophane 1 was in 1949 with its isolation from a mixture of hydrocarbon polymers.\(^1\) The beginning of [2.2]paracyclophane (Pc) chemistry as a field of research however, is likely best credited to Cram and co-workers for their work commencing in 1951.\(^2\) Widespread industrial use of this compound and its derivatives are owed to Gorham for the development of a chemical vapour deposition (CVD) process to produce polymeric surface coatings\(^3\), commonly known as parylenes. The use of 1 and derivatives in this regard will be discussed in more detail in Chapter 7. The Pc framework has also been utilised in ligands for asymmetric catalysis. The advent of this area can be attributed to the preparation of enantiopure \((R_P)-4,12\text{-bis-diphenylphosphino}[2.2]\)paracyclophane 2 by Pye and Rossen in 1997 (Scheme 2.1), used for rhodium catalysed asymmetric hydrogenations.\(^4\)

\[\text{Scheme 2.1: The synthesis of } (R_P)-4,12\text{-bis-diphenylphosphino}[2.2]\text{paracyclophane.}\]
2.2 Preparation of [2.2]paracyclophane

1 and certain derivatives may be prepared via the Winberg dimerisation.\textsuperscript{5,6} This reaction proceeds through the formation of the 1,4-quinodimethane intermediate 3. An optimised Winberg dimerisation is shown in Scheme 2.2 and can be used to prepare some useful halide derivatives.\textsuperscript{7}

![Scheme 2.2: The preparation of [2.2]paracyclophane and simple derivatives.](image)

2.3 Assignment and stereochemical notation of [2.2]paracyclophane derivatives

Substituted Pc derivatives may possess no asymmetric carbon centres yet they may still be chiral molecules and this is because they exhibit planar chirality. This occurs due to two non-coplanar rings which are not symmetrical and rotation being restricted by the bonds connecting them, ethyl bridges in the case of Pc derivatives. Therefore, substituted Pc may exist as two enantiomers \(R_P\) and \(S_P\), where subscript \(P\) denotes planar chirality. A numbering scheme must be introduced which can be used to assign the various positions of the molecule and this is shown in Figure 2.1.\textsuperscript{8}
The plane with the highest level of substitution is considered the chiral plane. Position 1 is labelled as the closest out of plane atom to the chiral plane. This will be one of the ethyl bridge carbons in the case of Pc derivatives and the one chosen should lead to the lowest numbering for the highest priority substituent as per the Cahn-Ingold-Prelog (CIP) system.\textsuperscript{9,10} The adjacent atoms $a$, $b$ and $c$ will then show either a clockwise ($R_p$) or counter clockwise ($S_p$) orientation which provides a stereochemical assignment. When substituents are on the same ring this is readily assigned, when the substituents are on opposing rings the chiral

Figure 2.1: Numbering and assigning [2.2]paracyclophane derivatives.
plane is determined based on the highest priority substituent. To assign the tri-substituted enantiomers of 4-hydroxy-5-methyl-16-bromo[2.2]paracyclophane 4, the bromo substituent has the highest priority according to the CIP system however it does not reside on the chiral plane, as this has been defined as the most heavily substituted plane. Therefore the hydroxy substituent takes priority and is used as the basis to assign the stereochemistry. The development of more complex Pc structures has led to some ambiguity with nomenclature but the rules that have been presented here will be sufficient to assign all compounds described in this work.

The most commonly reported Pc regioisomers are shown in Figure 2.2. Bridge substituted analogues are quite rare but have been reported.

![Figure 2.2: Common regioisomers of disubstituted [2.2]paracyclophane.](image)

2.4 Resolution of [2.2]paracyclophane derivatives

Effective resolution protocols are a necessity if asymmetric ligands based on the Pc framework are to gain more attention. Various methods have been developed in classical resolution, kinetic resolution and enzymatic resolution, and examples are presented for key monosubstituted derivatives in Table 2.1. The chromatographic resolution approach is less common.
Table 2.1: Resolution protocols for key [2.2]paracyclophane derivatives.

<table>
<thead>
<tr>
<th>R</th>
<th>Resolution procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH₂</td>
<td>Crystallisation of diastereomeric salts of (1S)-(+)−10-camphorsulfonic acid.¹³</td>
</tr>
<tr>
<td>OH</td>
<td>Enzymatic kinetic resolution of OAc derivatives and subsequent hydrolysis,¹⁴,¹⁵,¹⁶,¹⁷ crystallisation of diastereomeric esters of (1S)-(−)−camphanic acid and subsequent hydrolysis,¹⁸ crystallisation of diastereomeric imines of methylbenzylamine and subsequent Dakin oxidation.¹⁹</td>
</tr>
<tr>
<td>CHO</td>
<td>Crystallisation of diastereomeric imines of methylbenzylamine and subsequent hydrolysis¹⁹,²⁰ and enzymatic kinetic resolution.²¹</td>
</tr>
<tr>
<td>COCH₃</td>
<td>Crystallisation of diastereomeric SAMP-hydrazones followed by reduction with NaBH₄.²²</td>
</tr>
<tr>
<td>CO₂H</td>
<td>Crystallisation of diastereomeric Brucine salts²³ and crystallisation of diastereomeric salts of α-methyl-4-nitrobenzylamine.²⁴</td>
</tr>
</tbody>
</table>

Other notable resolutions of monosubstituted Pc include that of phosphine derivatives via diastereomeric phosphine-palladacycle complexes²⁵ and 4-bromo[2.2]paracyclophane via kinetic resolution using a Buchwald-Hartwig amination.²⁶ Some success in the resolution of more heavily substituted derivatives has been reported with pertinent examples being the bis-phosphine oxide ⁵,⁴ the bis-phenol ⁶,²⁷ the bis-bromide ⁷²⁸ and a tetra-substituted derivative ⁸²⁹ (Figure 2.3).
Any endeavour in preparing enantiomerically pure Pc derivatives will likely require the use of one of these key intermediates presented in Table 2.1 or the development of an entirely new resolution protocol. Recent developments in the area have been focused on a single resolution protocol that could be used to prepare a range of Pc derivatives in enantiomerically pure form. The sulfoxide methodology is at present the most promising approach.

Sulfoxide derivatives of Pc were first prepared using Anderson reagent \( \text{9} \) and it was found that the resulting diastereomers could be separated \( \text{via} \) column chromatography (Scheme 2.3). Sulfoxides garnered from the thiosulfinate \( \text{10} \) were also found to be separable. The reaction proceeds with inversion of the sulfur centre but is stereospecific, the resulting diastereomers differ only in planar chirality. Both the toluene (Tol) and tert-butyl (t-Bu) moieties allow resolution however the different groups significantly alter the subsequent chemistry that can be carried out on the Pc framework.

\[
\text{Scheme 2.3: The resolution of diastereomeric sulfoxide derivatives.}
\]
Sulfoxide-metal exchange on the Tol derivative 11 using \( n \)-butyl lithium (\( n \)-BuLi) generates the 4-lithio[2.2]paracyclophane intermediate 12 and subsequent treatment with the appropriate electrophile yields a range of enantiopure monosubstituted Pc derivatives (Scheme 2.4).\(^{32,33}\)

\[
\begin{array}{ccc}
\text{Sulfoxide-} & \text{metal exchange} & \text{electrophile} \\
\text{on the Tol} & \text{using} & \text{yields} \\
\text{derivative} & \text{\( n \)-butyl lithium} & \text{a range} \\
11 & \text{(n-BuLi)} & \text{of enantiopure} \\
\text{of} & \text{the appropriate} & \text{monosubstituted} \\
\end{array}
\]

\( \text{Scheme 2.4: The preparation of enantiopure [2.2]paracyclophane derivatives.} \)

Bromination of 11 may allow access to enantiopure pseudo-geminal derivatives 13, but thus far selective substitution of the bromo group has proven problematic. Sulfide 14 and sulfone 15 analogues were also examined with mixed results (Scheme 2.5).\(^{33}\)

\[
\begin{array}{ccc}
\text{Bromination of} & \text{mixed results} & \text{Scheme 2.5: The preparation of sulfide and sulfone analogues.} \\
\text{enantiopure pseudo-geminal} & \text{of} & \text{20}\end{array}
\]
The sulfoxide methodology has been applied to *pseudo-ortho* derivatives allowing an alternative resolution approach to the phosphine oxide precursor of Phanephos 5 (Scheme 2.6).\(^3^4\)

![Scheme 2.6: The resolution of disubstituted sulfoxide derivatives.](image)

The use of the *t*-Bu derivative 16 allows selective *ortho*-lithiation of the *Pc* framework rather than substitution of the sulfoxide moiety. This is permissible only if the diastereomer has the *t*-Bu group orientated away from the ring as in Scheme 2.7.\(^3^5\)

![Scheme 2.7: Ortho-lithiation and derivatisation of sulfoxide derivatives.](image)

If the *t*-Bu group is orientated in towards the ring then lateral substitution of the C2 methylene carbon may occur as is the case in Scheme 2.8.\(^3^6\)
Scheme 2.8: Bridge functionalisation of sulfoxide derivatives.

The t-Bu derivative 16 is not amenable to pseudo-geminal substitution and its resistance to sulfoxide-metal exchange makes selective removal of the sulfoxide substituent problematic. The t-Bu sulfoxide may be converted to the thiol 17 if desirable via the pathway shown in Scheme 2.9.\textsuperscript{37,38}

Scheme 2.9: The synthesis of thiol derivatives.

The examples presented in this section provide an overview of the established resolution methodologies concerning Pc derivatives and the recent advances. This account is not exhaustive and there are other examples of resolutions of Pc derivatives presented in the literature. For further discussion of this area see reviews by Hopf\textsuperscript{39}, Gibson\textsuperscript{8} and Rowlands.\textsuperscript{36}

2.5 Oxazoline containing [2.2]paracyclophane derivatives

Oxazoline containing Pc derivatives have allowed the preparation of a versatile group of bidentate ligands. Examples to date encompass P,N, N,O, N,N, S,N and Se,N ligands and these have been applied to various asymmetric transformations.
2.5.1 As ligands in transition metal catalysis

The most common approach to preparing these derivatives is to begin with the carboxylic acid 18 and generate the corresponding amide 19 from an amino alcohol (Scheme 2.10). The oxazoline 20 is then formed via the Appel reaction. The stereochemistry and substitution of the oxazoline moiety is tuned by selecting the appropriate amino alcohol, so this method is widely applicable. In the example presented here by Hou et al., direct ortho-lithiation of 20 and treatment with diphenyl disulfide or diphenyl diselenide yielded three chromatographically separable stereoisomers 21a-c and 22a-c. The bridge substituted analogues 21c and 22c were not expected. The fact that only one bridge substituted diastereomer was detected indicates a steric effect from the oxazoline isopropyl group.40

Scheme 2.10: The preparation of N,S and N,Se ligands.

These ligands were applied in a palladium catalysed allylic alkylation (Table 2.2). It was found that the selenium derivatives 22a-c were slightly more selective than sulfur derivatives.
21a-c and the bridge substituted derivatives 21c and 22c were more efficacious than their aryl substituted counterparts. The stereochemistry of the products appears to be controlled by the planar chirality of the ligand in the case of the aryl analogues 21a-b and 22a-b. Both diastereomers of the bridge substituted derivatives were not prepared so it is not clear if this is the case with that substitution pattern.

Table 2.2: Asymmetric allylic alkylation of 1,3-diphenylallyl acetate.\textsuperscript{40}

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Solvent</th>
<th>Salt</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>(SpS)-21a</td>
<td>Tol</td>
<td>LiOAc</td>
<td>40</td>
<td>98</td>
<td>54</td>
<td>R</td>
</tr>
<tr>
<td>(SpS)-21a</td>
<td>DCM</td>
<td>LiOAc</td>
<td>24</td>
<td>98</td>
<td>50</td>
<td>R</td>
</tr>
<tr>
<td>(SpS)-21a</td>
<td>DCM</td>
<td>KOAc</td>
<td>36</td>
<td>98</td>
<td>53</td>
<td>R</td>
</tr>
<tr>
<td>(SpS)-21a</td>
<td>MeCN</td>
<td>KOAc</td>
<td>32</td>
<td>98</td>
<td>54</td>
<td>R</td>
</tr>
<tr>
<td>(RpS)-21b</td>
<td>MeCN</td>
<td>KOAc</td>
<td>21.5</td>
<td>98</td>
<td>63</td>
<td>S</td>
</tr>
<tr>
<td>(SpRS)-21c</td>
<td>MeCN</td>
<td>KOAc</td>
<td>1.5</td>
<td>98</td>
<td>94</td>
<td>S</td>
</tr>
<tr>
<td>(SpS)-22a</td>
<td>MeCN</td>
<td>KOAc</td>
<td>20</td>
<td>98</td>
<td>57</td>
<td>R</td>
</tr>
<tr>
<td>(RpS)-22b</td>
<td>MeCN</td>
<td>KOAc</td>
<td>30</td>
<td>98</td>
<td>73</td>
<td>S</td>
</tr>
<tr>
<td>(SpRS)-22c</td>
<td>MeCN</td>
<td>KOAc</td>
<td>2</td>
<td>98</td>
<td>93</td>
<td>S</td>
</tr>
</tbody>
</table>

Another report published at the same time detailed the preparation of a number of oxazoline containing pseudo-geminal derivatives. Standard bromination of amide 23 yielded 24 exclusively. The oxazoline 25 was furnished from 24 using the Appel reaction and this derivative gave access to useful analogues 26 and 27 (Scheme 2.11). None of these derivatives were prepared in optically pure form in this case.\textsuperscript{41}
Hou et al. then used an analogous method to that presented in Scheme 2.14, to prepare a series of pseudo-geminal precursors \textbf{28a-d} and \textbf{29a-d} which could be separated \textit{via} column chromatography (\textit{Scheme 2.12}). From these precursors was derived a series of ligands with varied groups on both the oxazoline moiety \textbf{30a-d}, \textbf{31a-d} and the phosphorus centre \textbf{32a-d}. \(^{42}\)
Scheme 2.12: The preparation of P,N ligands.

These ligands were also applied in a palladium catalysed allylic alkylation (Table 2.3). Contrary to the results presented in Table 2.2, in this case the central chirality of the oxazoline determined the configuration of the product. Altering the aryl substituents on the phosphorus centre had mixed results. The 4-methoxy derivative 32c showed a marked increase in selectivity and was the best reported ligand overall, while the 2-methyl derivative 32a showed very little selectivity and was the worst in the series.
Table 2.3: Asymmetric allylic alkylations of 1,3-diphenylallyl acetate.\textsuperscript{42}

![Chemical Reaction Image]

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R\textsubscript{p}S)-30a</td>
<td>20</td>
<td>98</td>
<td>37</td>
<td>S</td>
</tr>
<tr>
<td>(S\textsubscript{p}S)-31a</td>
<td>15</td>
<td>98</td>
<td>6</td>
<td>S</td>
</tr>
<tr>
<td>(R\textsubscript{p}S)-30a</td>
<td>10</td>
<td>98</td>
<td>49</td>
<td>S</td>
</tr>
<tr>
<td>(R\textsubscript{p}S)-30a</td>
<td>90</td>
<td>98</td>
<td>62</td>
<td>S</td>
</tr>
<tr>
<td>(R\textsubscript{p}S)-30b</td>
<td>210</td>
<td>98</td>
<td>11</td>
<td>S</td>
</tr>
<tr>
<td>(S\textsubscript{p}S)-31b</td>
<td>90</td>
<td>98</td>
<td>41</td>
<td>S</td>
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<td>98</td>
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<tr>
<td>(S\textsubscript{p}S)-31c</td>
<td>60</td>
<td>98</td>
<td>29</td>
<td>S</td>
</tr>
<tr>
<td>(R\textsubscript{p}R)-30d</td>
<td>60</td>
<td>98</td>
<td>73</td>
<td>R</td>
</tr>
<tr>
<td>(S\textsubscript{p}R)-31d</td>
<td>90</td>
<td>98</td>
<td>54</td>
<td>R</td>
</tr>
<tr>
<td>(R\textsubscript{p}R)-32a</td>
<td>180</td>
<td>98</td>
<td>6</td>
<td>R</td>
</tr>
<tr>
<td>(R\textsubscript{p}R)-32b</td>
<td>60</td>
<td>98</td>
<td>69</td>
<td>R</td>
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<tr>
<td>(R\textsubscript{p}R)-32c</td>
<td>20</td>
<td>98</td>
<td>90</td>
<td>R</td>
</tr>
<tr>
<td>(R\textsubscript{p}R)-32d</td>
<td>240</td>
<td>98</td>
<td>49</td>
<td>R</td>
</tr>
</tbody>
</table>

Hou \textit{et al.} subsequently prepared a series of N,O ligands again utilising the precursors 28a-d and 29a-d. Bromo-lithium exchange and treatment with benzophenone furnished ligands 33a-d and 34a-d (Scheme 2.13).\textsuperscript{43}
Scheme 2.13: The preparation of N,O ligands.

These ligands were applied in the addition of diethyl zinc to a variety of aldehydes (Table 2.4). It was found that matched planar and central chirality was optimal for appreciable selectivity. The benzyl ligand 33c proved to be particularly efficacious over a range of substrates.

**Table 2.4: Asymmetric addition of diethyl zinc to benzaldehyde.**

<table>
<thead>
<tr>
<th>Ar</th>
<th>Ligand</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>(SpS)-33a</td>
<td>9</td>
<td>96</td>
<td>93</td>
<td>R</td>
</tr>
<tr>
<td>Ph</td>
<td>(RpS)-34a</td>
<td>24</td>
<td>35</td>
<td>5</td>
<td>S</td>
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<tr>
<td>Ph</td>
<td>(SpS)-33b</td>
<td>24</td>
<td>37</td>
<td>32</td>
<td>R</td>
</tr>
<tr>
<td>Ph</td>
<td>(RpS)-34b</td>
<td>24</td>
<td>13</td>
<td>7</td>
<td>S</td>
</tr>
<tr>
<td>Ph</td>
<td>(SpS)-33c</td>
<td>7</td>
<td>93</td>
<td>93</td>
<td>R</td>
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</tbody>
</table>
The final report from Hou et al. also examined N,O ligands with a series which varied in steric bulk about the hydroxyl substituent. 33a-c and 34a-c were examined previously and were now compared to ligands with less steric bulk. 35a-c and 36a-c represent the least hindered hydroxyl group and then an intermediate series in 37a-b and 38 (Figure 2.4).\textsuperscript{44}
These ligands were also applied in the addition of diethyl zinc to aromatic aldehydes (Table 2.5). The less hindered ligands 35a-c and 36a-c gave improved or comparable yields and selectivity in all cases compared to 33a-c and 34a-c. Again the results showed that matched planar and central chirality was optimal. The methylated derivative 37b was shown to be slightly more selective than its phenyl counterpart 33c over a range of substrates.

Table 2.5: Asymmetric addition of diethyl zinc to benzaldehyde.\(^{44}\)

<table>
<thead>
<tr>
<th>Ar</th>
<th>Ligand</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>(S&lt;sub&gt;p&lt;/sub&gt;S)-35a/((S&lt;sub&gt;p&lt;/sub&gt;S)-33a)</td>
<td>5 (9)</td>
<td>94 (96)</td>
<td>91 (93)</td>
<td>R (R)</td>
</tr>
</tbody>
</table>
Using a ligand with an achiral oxazoline moiety 39a-b afforded excellent yields and selectivity, comparable to 37a and 37b which also possessed central chirality (Scheme 2.14). This clearly demonstrates that the planar chirality is crucial in the selectivity of the ligand. It is of note that 38, which possessed opposing planar and central chirality was an ineffective ligand.

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>$\text{(R}_1\text{P}_1\text{S}_1)\text{-36a}[(\text{R}_1\text{P}_1\text{S}_1)-\text{34a}]$</td>
<td>24 (24)</td>
<td>49 (35)</td>
<td>25 (5)</td>
<td>$\text{S} (\text{S})$</td>
</tr>
<tr>
<td>Ph</td>
<td>$\text{(S}_1\text{P}_1\text{S}_1)\text{-35b}[(\text{S}_1\text{P}_1\text{S}_1)-\text{33b}]$</td>
<td>7 (24)</td>
<td>93 (37)</td>
<td>94 (32)</td>
<td>$\text{R} (\text{R})$</td>
</tr>
<tr>
<td>Ph</td>
<td>$\text{(R}_1\text{P}_1\text{S}_1)\text{-36b}[(\text{R}_1\text{P}_1\text{S}_1)-\text{34b}]$</td>
<td>24 (24)</td>
<td>46 (13)</td>
<td>36 (7)</td>
<td>$\text{S} (\text{S})$</td>
</tr>
<tr>
<td>Ph</td>
<td>$\text{(S}_1\text{P}_1\text{S}_1)\text{-35c}[(\text{S}_1\text{P}_1\text{S}_1)-\text{33c}]$</td>
<td>5 (7)</td>
<td>94 (93)</td>
<td>91 (93)</td>
<td>$\text{R} (\text{R})$</td>
</tr>
<tr>
<td>Ph</td>
<td>$\text{(R}_1\text{P}_1\text{S}_1)\text{-36c}[(\text{R}_1\text{P}_1\text{S}_1)-\text{34c}]$</td>
<td>24 (24)</td>
<td>51 (12)</td>
<td>45 (7)</td>
<td>$\text{S} (\text{S})$</td>
</tr>
<tr>
<td>Ph</td>
<td>$\text{(S}_1\text{P}_1\text{S}_1)\text{-37a}$</td>
<td>3.5</td>
<td>93</td>
<td>97.9</td>
<td>$\text{R}$</td>
</tr>
<tr>
<td>Ph</td>
<td>$\text{(S}_1\text{P}_1\text{S}_1)\text{-37b}$</td>
<td>1.5</td>
<td>95</td>
<td>98.4</td>
<td>$\text{R}$</td>
</tr>
<tr>
<td>Ph</td>
<td>$\text{(R}_1\text{P}_1\text{S}_1)\text{-38}$</td>
<td>48</td>
<td>&lt;5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$p-$ClC$_6$H$_4$</td>
<td>$\text{(S}_1\text{P}_1\text{S}_1)\text{-37b}[(\text{S}_1\text{P}_1\text{S}_1)-\text{33c}]$</td>
<td>2 (8)</td>
<td>96 (96)</td>
<td>97.6 (94)</td>
<td>$\text{R} (\text{R})$</td>
</tr>
<tr>
<td>$p-$BrC$_6$H$_4$</td>
<td>$\text{(S}_1\text{P}_1\text{S}_1)\text{-37b}[(\text{S}_1\text{P}_1\text{S}_1)-\text{33c}]$</td>
<td>2 (9)</td>
<td>95 (95)</td>
<td>96.8 (93)</td>
<td>$\text{R} (\text{R})$</td>
</tr>
<tr>
<td>$p-$MeOC$_6$H$_4$</td>
<td>$\text{(S}_1\text{P}_1\text{S}_1)\text{-37b}[(\text{S}_1\text{P}_1\text{S}_1)-\text{33c}]$</td>
<td>3.5 (24)</td>
<td>94 (86)</td>
<td>96 (82)</td>
<td>$\text{R} (\text{R})$</td>
</tr>
<tr>
<td>$o-$MeOC$_6$H$_4$</td>
<td>$\text{(S}_1\text{P}_1\text{S}_1)\text{-37b}[(\text{S}_1\text{P}_1\text{S}_1)-\text{33c}]$</td>
<td>1 (4)</td>
<td>96 (94)</td>
<td>96 (81)</td>
<td>$\text{R} (\text{R})$</td>
</tr>
</tbody>
</table>
Scheme 2.14: The synthesis and application of N,O ligands in the addition of diethyl zinc. These ligands were also utilised in the nickel catalysed asymmetric addition of diethyl zinc to a range of chalcones (Table 2.6). The reaction yields were uniformly excellent and the selectivity was moderate to high. The configurations were not assigned for the majority of cases but for those that were the product matched the configuration of the planar chirality of the catalysts. Again mismatched planar and central chirality was observed to reduce selectivity.

**Table 2.6: Asymmetric addition of diethyl zinc to chalcones.**

<table>
<thead>
<tr>
<th>Ar₁</th>
<th>Ar₂</th>
<th>Ligand</th>
<th>Ligand (mol%)</th>
<th>ee (%)</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>33-34</td>
<td>10</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>(SₚS)-37a</td>
<td>10</td>
<td>8</td>
<td>S (-)</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>(SₚS)-35a [(RₚS)-36a]</td>
<td>10</td>
<td>52 (0)</td>
<td>S (-)</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>(SₚS)-35b [(RₚS)-36b]</td>
<td>10</td>
<td>63 (0)</td>
<td>S (R)</td>
</tr>
</tbody>
</table>
The majority of the ligands presented thus far have been pseudo-geminal structures however Bolm et al. have reported pseudo-ortho ligands. The precursor series $40$ was functionalised with varying imidazole groups. The subsequent ligands $41a-d$ and $42b,d$ were used to prepare catalytic iridium carbene complexes $43a-c$ and $44b$ (Scheme 2.15).$^{45}$
These iridium complexes were then applied to the asymmetric hydrogenation of a variety of alkenes 45a-e. Substrates 45a and 45b were tested at both 25 °C and 50 °C (Table 2.7). The higher temperature afforded higher yields but generally reduced selectivity. 43c which possessed only planar chirality was found to be the best performing ligand and was extended to substrates 45c-e. Yields were uniformly excellent except when using only 1 bar of H₂. The configuration of the products when using catalyst 43b and 44b were the same indicating that in this case central chirality may be more dominant than planar chirality.
Table 2.7: Asymmetric hydrogenation of alkenes.\(^{45}\)

Table 2.7: Asymmetric hydrogenation of alkenes.\(^{45}\)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Catalyst</th>
<th>Time</th>
<th>Temp</th>
<th>H(_2) (bar)</th>
<th>Yield</th>
<th>ee (%)</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>45a</td>
<td>((S_p))-43a</td>
<td>6-24</td>
<td>25/50</td>
<td>50</td>
<td>-/40</td>
<td>-/0</td>
<td>-</td>
</tr>
<tr>
<td>45a</td>
<td>((S_p)S)-43b</td>
<td>6-24</td>
<td>25/50</td>
<td>50</td>
<td>17/61</td>
<td>12/4</td>
<td>(R)</td>
</tr>
<tr>
<td>45a</td>
<td>((R_{p}S))-44b</td>
<td>6-24</td>
<td>25/50</td>
<td>50</td>
<td>15/59</td>
<td>11/10</td>
<td>(R)</td>
</tr>
<tr>
<td>45a</td>
<td>((S_p))-43c</td>
<td>6-24</td>
<td>25/50</td>
<td>50</td>
<td>35/76</td>
<td>28/15</td>
<td>(R)</td>
</tr>
<tr>
<td>45b</td>
<td>((S_p))-43c</td>
<td>6-24</td>
<td>25/50</td>
<td>50</td>
<td>25/100</td>
<td>11/4</td>
<td>-</td>
</tr>
<tr>
<td>45c</td>
<td>((S_p))-43c</td>
<td>2</td>
<td>25</td>
<td>50</td>
<td>100</td>
<td>9</td>
<td>(R)</td>
</tr>
<tr>
<td>45c</td>
<td>((S_p))-43c</td>
<td>6-24</td>
<td>25</td>
<td>10</td>
<td>100</td>
<td>13</td>
<td>(R)</td>
</tr>
<tr>
<td>45c</td>
<td>((S_p))-43c</td>
<td>48</td>
<td>25</td>
<td>1</td>
<td>46</td>
<td>46</td>
<td>(R)</td>
</tr>
<tr>
<td>45d</td>
<td>((S_p))-43c</td>
<td>6-24</td>
<td>25</td>
<td>50</td>
<td>99</td>
<td>38</td>
<td>(R)</td>
</tr>
<tr>
<td>45e</td>
<td>((S_p))-43c</td>
<td>6-24</td>
<td>25</td>
<td>50</td>
<td>100</td>
<td>21</td>
<td>(R)</td>
</tr>
</tbody>
</table>

Bolm et al. produced a later report detailing a series of N,O ligands. A variety of regioisomers were prepared including pseudo-geminal 46-47, pseudo-ortho 48-49 and ortho 50-51 derivatives (Figure 2.5).\(^{46}\)
Figure 2.5: The preparation of N,O ligands.

These ligands were applied in the addition of diethyl zinc to benzaldehyde (Table 2.8). 

*Pseudo-geminal* ligands 46a-b demonstrated the highest selectivity while 47 showed the lowest. Opposing planar and central chirality was optimal and an increase in steric bulk on the oxazoline as with 46b increased yield and selectivity. The planar chirality seems to determine the configuration of products with *pseudo-geminal* ligands 46-47 and *ortho* ligands 50-51. In the case of *pseudo-ortho* ligands 48-49 however the central chirality appears to be the deciding factor.

Table 2.8: Asymmetric addition of diethyl zinc to benzaldehyde.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Time</th>
<th>Yield (%)</th>
<th>ee(%)</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R&lt;sub&gt;pS&lt;/sub&gt;)-46a</td>
<td>2</td>
<td>78</td>
<td>78</td>
<td>R</td>
</tr>
<tr>
<td>(S&lt;sub&gt;pS&lt;/sub&gt;)-47</td>
<td>24</td>
<td>93</td>
<td>11</td>
<td>S</td>
</tr>
</tbody>
</table>
The final report from Bolm et al. details the preparation of a series of P,N ligands. Again pseudo-geminal 52-53, pseudo-ortho 54-55 and ortho derivatives 56-57 were prepared. There was also variation around the phosphorus centre and the oxazoline moiety 54a-c and 55a-c (Figure 2.6).\(^{47}\)

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>54</th>
<th>55</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S(_P)S)-48</td>
<td>4</td>
<td>96</td>
<td>51</td>
<td>S</td>
</tr>
<tr>
<td>(R(_P)S)-49</td>
<td>24</td>
<td>74</td>
<td>35</td>
<td>S</td>
</tr>
<tr>
<td>(R(_P)S)-50</td>
<td>48</td>
<td>72</td>
<td>44</td>
<td>R</td>
</tr>
<tr>
<td>(S(_P)S)-51</td>
<td>24</td>
<td>79</td>
<td>62</td>
<td>S</td>
</tr>
<tr>
<td>(R(_P)S)-46b</td>
<td>4</td>
<td>93</td>
<td>87</td>
<td>R</td>
</tr>
</tbody>
</table>

**Figure 2.6: The preparation of N,P ligands.**

These ligands were applied in a palladium catalysed allylic alkylation (*Table 2.9*). The *pseudo-geminal* ligands 52-53 with matched planar and central chirality provided the
Optimum selectivity and the central chirality appears to determine the configuration of the product. This is also the case for the ortho ligands 56-57. The pseudo-ortho ligands 54a and 55a in contrast perform best with mismatched planar and central chirality and the product configuration appears to be determined by the planar chirality. Replacing the phenyl groups on the phosphorus centre with Tol groups increased selectivity, markedly so in the \((S_P S)\) derivative 54b. Interestingly, changing the oxazoline substituent from an isopropyl to a phenyl group reversed the situation and the mismatched analogue 54c outperforms the matched analogue 55c.

**Table 2.9: Asymmetric allylic alkylation of 1,3-diphenylallyl acetate.**

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>((R_P S))-52</td>
<td>8</td>
<td>96</td>
<td>30</td>
<td>(S)</td>
</tr>
<tr>
<td>((S_P S))-53</td>
<td>6</td>
<td>&gt;98</td>
<td>56</td>
<td>(S)</td>
</tr>
<tr>
<td>((S_P S))-54a</td>
<td>10</td>
<td>&gt;98</td>
<td>28</td>
<td>(R)</td>
</tr>
<tr>
<td>((R_P S))-55a</td>
<td>10</td>
<td>&gt;98</td>
<td>82</td>
<td>(S)</td>
</tr>
<tr>
<td>((R_P S))-56</td>
<td>8</td>
<td>&gt;98</td>
<td>23</td>
<td>(S)</td>
</tr>
<tr>
<td>((S_P S))-57</td>
<td>7</td>
<td>&gt;98</td>
<td>47</td>
<td>(S)</td>
</tr>
<tr>
<td>((S_P S))-54b</td>
<td>20</td>
<td>&gt;98</td>
<td>63</td>
<td>(R)</td>
</tr>
<tr>
<td>((R_P S))-55b</td>
<td>5</td>
<td>&gt;98</td>
<td>89</td>
<td>(S)</td>
</tr>
<tr>
<td>((S_P R))-54c</td>
<td>5</td>
<td>&gt;98</td>
<td>89</td>
<td>(R)</td>
</tr>
<tr>
<td>((R_P R))-55c</td>
<td>20</td>
<td>&gt;98</td>
<td>62</td>
<td>(S)</td>
</tr>
</tbody>
</table>
2.5.2 As organocatalysts

The last report discussing oxazoline containing Pc ligands is more unusual as a rather different approach has been taken in the preparation of the target compound. Firstly the unusual aza derivative 58 has been utilised as a precursor. The oxazolines 59a-d were prepared from the cyano moiety of 58 via the Witte Seeliger reaction. This is in contrast to previous examples which all relied on some variation of amide formation followed by cyclisation via the Appel reaction. The final step to yield organocatalysts 60a-d is treatment with the oxidant mCPBA (Scheme 2.16).

![Scheme 2.16: The preparation of N-oxide organocatalysts.](image)

The catalysts were applied in the allylation of 4-methoxybenzaldehyde (Table 2.10). The choice of solvent and base had a significant impact on the yield and selectivity of the reaction. MeCN and i-Pr₂NEt were found to be the optimal solvent and base respectively. The configuration of the product appears to be controlled by the planar rather than central chirality. The t-Bu derivative 60a provided the highest ee of 90%.
Table 2.10: Asymmetric allylation of 4-methoxybenzaldehyde.\(^{49}\)

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>((R_pS)-60a)</td>
<td>(i)-Pr(_2)NEt</td>
<td>THF</td>
<td>83</td>
<td>47</td>
<td>(S)</td>
</tr>
<tr>
<td>((R_pS)-60a)</td>
<td>(i)-Pr(_2)NEt</td>
<td>Toluene</td>
<td>61</td>
<td>48</td>
<td>(S)</td>
</tr>
<tr>
<td>((R_pS)-60a)</td>
<td>(i)-Pr(_2)NEt</td>
<td>DCM</td>
<td>82</td>
<td>86</td>
<td>(S)</td>
</tr>
<tr>
<td>((R_pS)-60a)</td>
<td>(i)-Pr(_2)NEt</td>
<td>MeCN</td>
<td>91</td>
<td>90</td>
<td>(S)</td>
</tr>
<tr>
<td>((R_pS)-60a)</td>
<td>Et(_3)N</td>
<td>MeCN</td>
<td>67</td>
<td>38</td>
<td>(S)</td>
</tr>
<tr>
<td>((R_pS)-60b)</td>
<td>(i)-Pr(_2)NEt</td>
<td>MeCN</td>
<td>83</td>
<td>75</td>
<td>(S)</td>
</tr>
<tr>
<td>((R_pS)-60c)</td>
<td>(i)-Pr(_2)NEt</td>
<td>MeCN</td>
<td>92</td>
<td>37</td>
<td>(S)</td>
</tr>
<tr>
<td>((R_pR)-60d)</td>
<td>(i)-Pr(_2)NEt</td>
<td>MeCN</td>
<td>85</td>
<td>43</td>
<td>(S)</td>
</tr>
</tbody>
</table>

The catalysts were then applied to a variety of aromatic aldehydes using the optimised conditions (Table 2.11). This series further confirmed that the planar chirality was the determining factor in the configuration of the products. \(60a\) was again found to be the most selective catalyst across all substrates with the exception of 4-nitrobenzaldehyde where it was slightly outperformed by \(60b\).
Table 2.11: Asymmetric allylation of aromatic aldehydes.\(^{49}\)

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Ar</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>((R_P S)-60a)</td>
<td>95</td>
<td>93</td>
<td>S</td>
</tr>
<tr>
<td>Ph</td>
<td>((R_P S)-60b)</td>
<td>90</td>
<td>87</td>
<td>S</td>
</tr>
<tr>
<td>Ph</td>
<td>((R_P R)-60c)</td>
<td>93</td>
<td>47</td>
<td>S</td>
</tr>
<tr>
<td>Ph</td>
<td>((R_P R)-60d)</td>
<td>89</td>
<td>53</td>
<td>S</td>
</tr>
<tr>
<td>4-CH(_3)C(_6)H(_4)</td>
<td>((R_P S)-60a)</td>
<td>87</td>
<td>88</td>
<td>S</td>
</tr>
<tr>
<td>4-CH(_3)C(_6)H(_4)</td>
<td>((R_P S)-60b)</td>
<td>91</td>
<td>67</td>
<td>S</td>
</tr>
<tr>
<td>4-CH(_3)C(_6)H(_4)</td>
<td>((R_P R)-60c)</td>
<td>84</td>
<td>36</td>
<td>S</td>
</tr>
<tr>
<td>2-CH(_3)C(_6)H(_4)</td>
<td>((R_P R)-60d)</td>
<td>85</td>
<td>41</td>
<td>S</td>
</tr>
<tr>
<td>2-CH(_3)C(_6)H(_4)</td>
<td>((R_P S)-60a)</td>
<td>88</td>
<td>85</td>
<td>S</td>
</tr>
<tr>
<td>2-CH(_3)C(_6)H(_4)</td>
<td>((R_P R)-60c)</td>
<td>86</td>
<td>31</td>
<td>S</td>
</tr>
<tr>
<td>3,4-(OCH(_3))(_2)C(_6)H(_3)</td>
<td>((R_P S)-60a)</td>
<td>93</td>
<td>96</td>
<td>S</td>
</tr>
<tr>
<td>3,4-(OCH(_3))(_2)C(_6)H(_3)</td>
<td>((R_P R)-60c)</td>
<td>90</td>
<td>12</td>
<td>S</td>
</tr>
<tr>
<td>4-ClC(_6)H(_4)</td>
<td>((R_P S)-60a)</td>
<td>91</td>
<td>91</td>
<td>S</td>
</tr>
<tr>
<td>4-ClC(_6)H(_4)</td>
<td>((R_P S)-60b)</td>
<td>90</td>
<td>82</td>
<td>S</td>
</tr>
<tr>
<td>4-ClC(_6)H(_4)</td>
<td>((R_P R)-60c)</td>
<td>88</td>
<td>27</td>
<td>S</td>
</tr>
<tr>
<td>4-ClC(_6)H(_4)</td>
<td>((R_P R)-60d)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2-ClC(_6)H(_4)</td>
<td>((R_P S)-60a)</td>
<td>89</td>
<td>93</td>
<td>S</td>
</tr>
<tr>
<td>2-ClC(_6)H(_4)</td>
<td>((R_P S)-60b)</td>
<td>92</td>
<td>83</td>
<td>S</td>
</tr>
<tr>
<td>4-N(_2)OC(_6)H(_4)</td>
<td>((R_P S)-60a)</td>
<td>96</td>
<td>87</td>
<td>S</td>
</tr>
</tbody>
</table>
### 2.6 Conclusion

This review introduces [2.2]paracyclophane beginning with its discovery and details the advent of its application in asymmetric catalysis. The methods of assigning stereochemical configuration to planar chiral Pc structures have been detailed along with the established protocols and current research trends in the resolution of this class of compounds. Oxazoline containing Pc derivatives have been discussed in detail, both their preparation and application in asymmetric catalysis. Although these ligands have proved versatile in their own right, they represent only a subset of Pc ligands which have been investigated. For a broader discussion of the area see reviews by Hopf, Gibson, Paradies, David and Rowlands.
2.7 References

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1998, 1441.


529.


(49) Chai, Q.; Song, C.; Sun, Z.; Ma, Y.; Ma, C.; Dai, Y.; Andrus, M. B. *Tetrahedron Lett.* **2006**, *47*, 8611.

(50) Paradies, J. *Synthesis (Stuttg).* **2011**, No. 23, 3749.


3.0 Preparation of Asymmetric Ligands Based on [2.2]Paracyclophane

3.1 Introduction

This chapter describes the synthetic work carried out towards the preparation of novel Pc ligands. This begins with the preparation of a variety of mono and disubstituted derivatives of [2.2]paracyclophane 1. A selection of these derivatives were then utilised in preparing novel oxazoline containing derivatives of 1 via the Buchwald-Hartwig amination. Various conditions and substrates were examined for these amination reactions and these are discussed in detail.

The general design and structure of these Pc ligands is shown in Scheme 3.1. This specific design was chosen for a number of reasons. Firstly, no ligands have been reported with this type of arrangement. The structurally closest examples are discussed in Chapter 2. Secondly, it was envisaged that the ligand would act as a bidentate N,N ligand forming a six membered system with a metal centre. Finally, it was proposed that a high level of stereo control could be obtained due to having two separate chiral moieties on the ligand, planar chirality from the Pc group and central chirality from the oxazoline substituent.

*Scheme 3.1: A general outline for the preparation of novel oxazoline containing [2.2]paracyclophane ligands and the proposed binding of a metal atom.*
3.2 Synthesis of monosubstituted [2.2]paracyclophane derivatives

A range of monosubstituted Pc derivatives were prepared from the precursor 1 using various methodologies (Scheme 3.2).

Scheme 3.2: The preparation of monosubstituted [2.2]paracyclophanes.

3.2.1 Synthesis of 4-bromo[2.2]paracyclophane

4-bromo[2.2]paracyclophane 2 is synthesised directly from 1 using a combination of bromine and iron in DCM. The reaction was heated at reflux for 20 hours and 2 may be isolated by a standard aqueous workup in 96% yield (Scheme 3.3). No further purification is required.

Scheme 3.3: The synthesis of 4-bromo[2.2]paracyclophane.
The proposed mechanism shown in Scheme 3.4, is an electrophilic aromatic substitution with the iron (III) bromide (FeBr$_3$) catalyst formed in situ from elemental bromine and iron. This catalyst facilitates the electrophilic addition of bromine which forms a resonance stabilised carbocation. Aromaticity is restored by the abstraction of a proton to give the product, hydrogen bromide (HBr) and regenerate the catalyst.

\[ \text{Br} - \text{Br} \xrightarrow{\text{FeBr}_3} \text{Br} - \text{H} \xrightarrow{\text{FeBr}_3} \text{Br}_2 \]

Scheme 3.4: The proposed mechanism for the formation of 4-bromo[2.2]paracyclophane.

3.2.2 Synthesis of 4-formyl[2.2]paracyclophane

4-Formyl[2.2]paracyclophane 3 may be synthesised directly from 1 by Rieche formylation$^2$ in reported quantitative yield.$^{3,4}$ It may also be produced from the corresponding sulfoxides.$^5$ Here 3 was prepared by the Rieche formylation but it was found the reported conditions were not optimal. Using the reported conditions which involved a reaction time of 6 hours and
isolation by standard aqueous workup\(^4\), it was found that the resulting product was not pure and contained significant amounts of 1. Using an extended reaction time of 20 hours and purifying the product using flash column chromatography pure product was isolated in a 63% yield (Scheme 3.5).

![Scheme 3.5: The synthesis of 4-formyl[2.2]paracyclophe](image)

The proposed mechanism shown in Scheme 3.6 begins with the generation of the electrophile from dichloromethoxymethane and titanium tetrachloride (TiCl\(_4\)). This electrophile attacks the aromatic ring and forms a resonance stabilised carbocation. The proton is abstracted to form HCl and regenerates the catalyst. Finally, treatment with water results in the loss of the chloro and methyl groups as HCl and MeOH respectively, yielding the product.
Scheme 3.6: The proposed mechanism for the formation of 4-formyl[2.2]paracyclophane.

### 3.2.3 Synthesis of 4-hydroxy[2.2]paracyclophane

4-Hydroxy[2.2]paracyclophane 4 is most readily prepared from 3 via an acid catalysed Dakin oxidation. Alternatively it may be synthesised from the bromo derivative 2 using a three step protocol beginning with lithiation, transmetallation onto boron and subsequent hydrolysis of the borate ester to yield the title compound. Here the Dakin oxidation was utilised to give 4 in 55% yield (Scheme 3.7).
Scheme 3.7: The synthesis of 4-hydroxy[2.2]paracyclophane.

The proposed mechanism shown in Scheme 3.8 begins with the formation of a resonance stabilised oxonium ion by protonation with H$_2$SO$_4$. Hydrogen peroxide (HOOH) then attacks the carbocation resulting in another oxonium species. There is a hydrogen transfer and a loss of water, forming a carbonyl oxonium ion. The carbonyl carbon is attacked by MeOH followed by another hydrogen transfer. This yields the desired product, regenerates the catalyst and produces methyl formate as a by-product.
3.2.4 Synthesis of 4-nitro[2.2]paracyclophane

4-Nitro[2.2]paracyclophane 5 was originally synthesised from 1 by nitration using a mixture of AcOH and HNO₃ yielding 5 in yields of 33%. A more recent report detailed a modified procedure which gave an improved yield of 5 at 48%. The low yields are attributed to the oxidation sensitivity of 1 which, under these conditions, leads to the formation of tars. Yields
above 95% have been achieved using an acidic ion exchange resin called Nafion.\textsuperscript{9} Using a modified version of the procedure reported by Paradies et al.\textsuperscript{8}, 5 was prepared in quantities above 5 g in 27% yield (Scheme 3.9). The time this reaction is allowed to proceed for is crucial and it was found that 30-60 seconds was optimal. If the reaction was allowed to proceed any longer yields were significantly reduced.

\textit{Scheme 3.9: The synthesis of 4-nitro[2.2]paracyclophane.}

The proposed mechanism shown in Scheme 3.10, begins with the electrophilic addition of the nitronium ion to the aromatic ring. The resulting carbocation is resonance stabilised and aromaticity is restored by loss of an aromatic proton.
Scheme 3.10: The proposed mechanism for the formation of 4-nitro[2.2]paracyclophane.

3.2.5 Synthesis of 4-amino[2.2]paracyclophane

4-Amino[2.2]paracyclophane 6 was initially synthesised via the reduction of 5 using MeOH and Platinum oxide in 89% yield. A later report utilises a similar procedure with hydrogen gas as the hydrogen source instead of methanol. 6 was also prepared using a phase transfer catalysis procedure which furnished the compound in 95% yield. A two-step procedure beginning with metalation and subsequent amination of bromo derivative 2 has also been reported. Here, 6 was prepared from 5 using HCl with iron as a catalyst in yields of up to 83% (Scheme 3.11). Although a standard procedure for the reduction of nitro compounds, this method does not appear to have been applied to 5. This compares well to the other reported procedures and has the benefit of avoiding expensive materials such as platinum and crown.
ethers. Furthermore, the product may be isolated by standard aqueous workup and requires no further purification.

![Scheme 3.11: The synthesis of 4-amino[2.2]paracyclophane.](image)

The proposed mechanism shown in Scheme 3.12 is facilitated by acid and electrons from the iron catalyst. First the nitro group is reduced to a hydroxylamine which is reduced again to yield the amine.

![Scheme 3.12: The proposed mechanism for the reduction of 4-nitro[2.2]paracyclophane.](image)

### 3.3 Synthesis of disubstituted [2.2]paracyclophane derivatives

A range of disubstituted [2.2]paracyclophane analogues were also prepared (Scheme 3.13). Analysis of these analogues required a close examination of the ^1^H NMR spectra to elucidate at which position substitution had occurred and this will be discussed in detail.
Preparation of Asymmetric Ligands Based on [2.2]Paracyclophane

Chapter 3


3.3.1 Synthesis of 4-bromo-13-nitro[2.2]paracyclophane

4-Bromo-13-nitro[2.2]paracyclophane 7 is prepared from 5 using bromine and iron in reported yields of up to 70%. Here, 7 was isolated in yields up to 28% (Scheme 3.14).


The mechanism for this reaction is proposed to be similar to that shown in Scheme 3.4, however the regioselectivity is explained by the formation of a complex between the nitro
group and the hydrogen atom at the 4’ position as shown in Scheme 3.15. This effect has also been documented to occur with methyl ester, methyl ketone and carboxy Pc derivatives and is termed the pseudo-geminal effect.\textsuperscript{14}

Scheme 3.15: The proposed mechanism for the bromination of 4-nitro[2.2]paracyclophane.

The low yield for the desired product is attributed to the formation of two distinct trisubstituted by-products which were isolated here. Surprisingly no mention of this issue appears in the literature. The by-products can be readily identified as trisubstituted by having only five aromatic protons in their \textsuperscript{1}H NMR spectra (Figure 3.1). They therefore must differ in the addition of two bromine atoms from the starting material 5. They also share the same splitting pattern of 2 singlets, 2 doublets and a doublet of doublets (dd). The two doublets and the dd indicate a monosubstituted ring with the doublet displaying the small coupling constant being ortho to the substituent, in this case a nitro group. The dd is then in the para position and the other doublet, with the larger coupling constant, being in the meta position. The opposing ring is responsible for the two singlets and these indicate disubstitution in a para orientation.
Figure 3.1: A segment of the $^1$H NMR spectra of trisubstituted by-products.
It would be likely for the two bromo substituents to be on the opposing ring to the nitro substituent. The initial investigation into directing effects by Cram et al\textsuperscript{13} would support this inference as they have not identified any \textit{homo}-annular bromination of 5. Although it is reported that the vast majority of product (70\%) is the \textit{pseudo-geminal} configuration, \textit{pseudo-meta} is the next most abundant isomer (8\%). On this basis and in consideration of the splitting pattern only two structures are possible which are 4,7-dibromo-13-nitro[2.2]paracyclophane 8 and 4,7-dibromo-12-nitro[2.2]paracyclophane 9. These are presented in Figure 3.2 and it is suggested both have been isolated here. However with the available information it is not possible to definitively assign which one is which.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{structures.png}
\caption{The structures of the by-products in the Bromination of 4-nitro[2.2]paracyclophane.}
\end{figure}

\textbf{3.3.2 Synthesis of 4-bromo-13-amino[2.2]paracyclophane}

4-Bromo-13-amino[2.2]paracyclophane 10 has been prepared by reduction using hydrogen and platinum\textsuperscript{15,16} and with HCl and Iron\textsuperscript{8} in yields up to 91\%. The latter approach was carried out here to give 10 in 68\% yield (Scheme 3.16). The mechanism for this reaction is proposed to be analogous with that shown in Scheme 3.12. The $^1$H NMR data for this compound is in agreement with the published values for this regioisomer.
3.3.3 Synthesis of 4-nitro-13-formyl[2.2]paracyclophane

This compound has not been previously reported. The Reich formylation was extended to 5 to garner 4-nitro-13-formyl[2.2]paracyclophane 11 in 18% yield (Scheme 3.17). The mechanism for this reaction is analogous with that proposed in Scheme 3.6 but again with the pseudo-geminal effect responsible for the regioselectivity.


The $^1$H NMR spectrum shows the characteristic formyl proton at 9.94 ppm along with the presence of six aromatic protons. This confirms that 5 has been substituted with the formyl moiety. Furthermore it can be readily elucidated that the substitution pattern is hetero-annular due to the splitting pattern of the aromatic protons shown in Figure 3.3. The two doublets with small coupling constants are the ortho protons, the 2 dd's are the para protons and the remaining two doublets are the meta protons, relative to each functional group.
Figure 3.3: A segment of the $^1$H NMR spectrum of 4-nitro-13-formyl[2.2]paracyclophane.

At this point the structure could be assigned as a *pseudo-geminal*, *pseudo-ortho*, *pseudo-meta* or *pseudo-para* regioisomer. The nitro and formyl functional groups cause the closest alkyl proton to be shifted downfield so it would be expected to observe two alkyl protons clearly separated from the remaining six. This is what is observed and the COSY spectrum shows coupling between these two indicating they are on position 1’ and 2’ or the same side of the system (*Figure 3.4*).
This then eliminates the pseudo-ortho and pseudo-para configurations. The remaining possibilities are then the pseudo-geminal and pseudo-meta isomers and as stated previously the pseudo-geminal effect of the nitro group should lead to specificity. However the COSY spectrum does not allow assignment of these two alkyl protons as cis or trans to one another. This required examination of through-space coupling by nuclear Overhauser effect spectroscopy (NOESY) analysis. Coupling between these protons would confirm the product as the pseudo-geminal isomer while no interaction would indicate the pseudo-meta isomer. This was attempted but a clear spectrum could not be obtained. It is on the basis of the pseudo-geminal effect that the product is tentatively assigned as the pseudo-geminal isomer however the spectroscopic evidence presented here is not sufficient for unambiguous assignment.
3.3.4 Synthesis of 4-amino-7-formyl[2.2]paracyclophane

This compound has not been previously reported. Initially reduction of 11 was attempted using HCl and iron to prepare 12 however it was found that the starting material degraded and no product was detected (Scheme 3.18). Reaction times as short as 15 minutes and lower temperatures still resulted in degradation.


In light of this it was then attempted to extend the Reiche formylation to 6. It was expected that in this case homo-annular substitution would be observed due to the activating effect of the amino substituent. This was found to be the case and the para isomer 4-amino-7-formyl[2.2]paracyclophane 13 was isolated in 26% yield (Scheme 3.19). It was expected that the ortho isomer may be produced but likely in lower quantities as this position is not as sterically favourable however no such material was isolated.

Scheme 3.19: The synthesis of 4-amino-7-formyl[2.2]paracyclophane.

Homo-annular analogues prove much simpler to assign than hetero-annular analogues. Firstly the presence of the formyl moiety is confirmed by a singlet at 9.76 ppm in the $^1$H NMR spectrum. The aromatic splitting shows 4 $dd$’s which correspond to an unsubstituted ring
(Figure 3.5). The two singlets indicate a para orientation. The ortho isomer would present two doublets as would the meta isomer however these would be readily distinguishable by the coupling constant.

![NMR spectrum](image)

*Figure 3.5: A segment of the $^1$H NMR spectrum of 4-amino-7-formyl[2.2]paracyclophane.*

### 3.4 Resolution of [2.2]paracyclophane derivatives

#### 3.4.1 Resolution of 4-amino[2.2]paracyclophane

$(R_P)$-4-amino[2.2]paracyclophane 6 was resolved using a previously reported procedure.$^{11}$ Resolution was achieved by recrystallisation of diastereomeric salts formed from (1S)-(+)10-camphorsulfonic acid. Yields of 24% were reported however only yields up to 6% were achieved here (Scheme 3.20).
3.4.2 Resolution of 4-bromo[2.2]paracyclopnone

Resolution of [2.2]paracyclophane derivatives via the use of diastereomeric sulfoxides has been discussed in detail in Section 2.4. The method was utilised here and proceeded as reported garnering both the **14**-(R,S) and **14**-(S,S) derivatives in 25% and 26% yield respectively (Scheme 3.21).

From these resolved sulfoxides Rowlands *et al.* prepared an impressive variety of useful enantiopure derivatives. However they were not successful in preparing any halide derivatives. Attempts to do so using electrophiles such as bromine and iodine resulted in protonation of the intermediate lithio species yielding only the parent compound **1**. In this work, bromobenzene was added to the lithio species generated *in-situ* with the aim of a
bromo-lithio exchange occurring. This proved to be the case and 2-(S<sub>p</sub>) was isolated in 35% yield (Scheme 3.22). This represents a novel method for the preparation of both enantiomers of 2.

![Scheme 3.22: The resolution of 4-bromo[2.2]paracyclophane.](image)

### 3.5 Synthesis of phenyl-oxazoline derivatives

As mentioned in Section 2.5, oxazolines are usually prepared from the cyclisation of the appropriate amino alcohol and carboxylic acid. The carboxylic acid is normally activated by generating the corresponding acid chloride via thionyl chloride (SOCl<sub>2</sub>) or a modification of the Appel reaction which uses triphenylphosphine (PPh<sub>3</sub>). Oxazolines are also readily prepared using the Witte Seeliger reaction. This is the cyclisation of nitriles and amino alcohols using zinc chloride (ZnCl<sub>2</sub>) as a catalyst. This procedure was utilised here to prepare a range of compounds, two of which have not been previously reported (Table 3.1). A mechanism for this reaction has not been reported.
Table 3.1: The preparation of phenyl-oxazoline derivatives via the Witte Seeliger reaction.

<table>
<thead>
<tr>
<th></th>
<th>R_1</th>
<th>R_2</th>
<th>R_3</th>
<th>R_4</th>
<th>R_5</th>
<th>Yield</th>
<th>Reported yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH_2</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>24%</td>
<td>72%_{21}</td>
</tr>
<tr>
<td>NH_2</td>
<td>H</td>
<td>H</td>
<td>iPr</td>
<td>H</td>
<td>H</td>
<td>82%</td>
<td>72%_{21}</td>
</tr>
<tr>
<td>NH_2</td>
<td>H</td>
<td>H</td>
<td>Bn</td>
<td>H</td>
<td>H</td>
<td>58%</td>
<td>65%_{21}</td>
</tr>
<tr>
<td>NH_2</td>
<td>H</td>
<td>H</td>
<td>tBu</td>
<td>H</td>
<td>H</td>
<td>40%</td>
<td>77%_{21}</td>
</tr>
<tr>
<td>NH_2</td>
<td>OMe</td>
<td>OMe</td>
<td>iPr</td>
<td>H</td>
<td></td>
<td>45%</td>
<td>----</td>
</tr>
<tr>
<td>Br</td>
<td>H</td>
<td>H</td>
<td>iPr</td>
<td>H</td>
<td></td>
<td>42%</td>
<td>78%_{21}</td>
</tr>
<tr>
<td>I</td>
<td>H</td>
<td>H</td>
<td>iPr</td>
<td>H</td>
<td></td>
<td>48%</td>
<td>----</td>
</tr>
</tbody>
</table>

3.6 Synthesis of phenyl-oxazoline [2.2]paracyclophane ligands

It was envisaged that the prepared phenyl-oxazolines could be linked to the Pc moiety using the Buchwald-Hartwig amination. This reaction forms a carbon-nitrogen bond via the palladium catalysed cross-coupling of an amine and a halide. To begin, 2 and the oxazoline 15 were selected. Along with these components Buchwald-Hartwig reactions also require an appropriate ligand and base to proceed. Hence a series of conditions were examined to determine the optimum reagents for the synthesis. This included different palladium sources and bases and three ligands which were triphenylphosphine (PPh_3), 2,2’bis(diphenylphosphino)-1,1’-binaphthyl (BINAP) and 1,1’-
bis(diphenylphosphino)ferrocene (DPPF). The results of these experiments are given in Table 3.2.

**Table 3.2: Buchwald-Hartwig reaction of 4-bromo[2.2]paracyclophane with (S)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)aniline.**[^a][^b]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd source</th>
<th>Base</th>
<th>Ligand</th>
<th>Time (days)</th>
<th>Yield</th>
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<td>CsCO$_3$</td>
<td>PPh$_3$</td>
<td>5</td>
<td>----</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>CsCO$_3$</td>
<td>BINAP</td>
<td>5</td>
<td>12%</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>CsCO$_3$</td>
<td>DPPF</td>
<td>5</td>
<td>----</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>tBuOK</td>
<td>PPh$_3$</td>
<td>5</td>
<td>----</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$</td>
<td>tBuOK</td>
<td>BINAP</td>
<td>5</td>
<td>13%</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)$_2$</td>
<td>tBuOK</td>
<td>DPPF</td>
<td>5</td>
<td>----</td>
</tr>
<tr>
<td>7</td>
<td>Pd(dba)$_2$</td>
<td>CsCO$_3$</td>
<td>PPh$_3$</td>
<td>5</td>
<td>----</td>
</tr>
<tr>
<td>8</td>
<td>Pd(dba)$_2$</td>
<td>CsCO$_3$</td>
<td>BINAP</td>
<td>5</td>
<td>13%</td>
</tr>
<tr>
<td>9</td>
<td>Pd(dba)$_2$</td>
<td>CsCO$_3$</td>
<td>DPPF</td>
<td>5</td>
<td>----</td>
</tr>
<tr>
<td>10</td>
<td>Pd(dba)$_2$</td>
<td>tBuOK</td>
<td>PPh$_3$</td>
<td>5</td>
<td>----</td>
</tr>
<tr>
<td>11</td>
<td>Pd(dba)$_2$</td>
<td>tBuOK</td>
<td>BINAP</td>
<td>5</td>
<td>14%</td>
</tr>
<tr>
<td>12</td>
<td>Pd(dba)$_2$</td>
<td>tBuOK</td>
<td>DPPF</td>
<td>5</td>
<td>----</td>
</tr>
<tr>
<td>13</td>
<td>Pd(dba)$_2$</td>
<td>tBuOK</td>
<td>BINAP</td>
<td>5</td>
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<td>tBuOK</td>
<td>BINAP</td>
<td>7</td>
<td>20%[^c]</td>
</tr>
</tbody>
</table>
Based on the results of this series of reactions several conclusions can be drawn. The selection of palladium source and base do not appear to significantly impact the reaction. The choice of ligand is essential and no product was observed when DPPF or PPh$_3$ was used. Higher loadings of palladium and BINAP increased the yield by approximately 5% (Entry 13) while longer reaction times had little effect (Entry 14). Even after 7 days significant amounts of starting material remain in the mixture and it was found that 45-50% of the starting material could be retrieved.

The $^1$H NMR spectra of the isolated mixture shows two peaks at approximately 10.21 and 10.33 ppm. These have been identified as the NH peaks for the diastereomers 16-(R$_P$S) and 16-(S$_P$S) respectively, based on a crystal structure obtained of 16-(S$_P$S). This region of the spectra is generally clean so it provides a convenient way of assessing the diastereomeric ratio (d.r.) of the products. In all cases here there was no excess and an equal distribution of diastereomers was observed. However on lowering the reaction temperature to 70 °C a change in the product distribution is observed, with 16-(R$_P$S) produced in 62:38 d.r. (Figure 3.6).
Using the established conditions but changing the solvent to benzene gave 16-(R_P_S) in 90:10 d.r. which is a very significant increase in selectivity and surprising given the only change is the solvent. Unfortunately this diastereomer could not be recrystallised to purify the material further.

It was found that using the appropriate solvent system 16-(S_P_S) and 16-(R_P_S) had small differences in their \( R_f \) values and could be separated by careful flash column chromatography. The products were not completely pure after separation and required recrystallisation. This was successful with the 16-(S_P_S) diastereomer which was isolated as white crystals. Again the 16-(R_P_S) diastereomer could not be recrystallised. Further, attempting to recrystallize from a 1:1 mixture of diastereomers could not be achieved and enriching the 16-(S_P_S) isomer by column chromatography first was necessary. Crystals of the
16-(S$_P$S) isomer suitable for X-ray crystallography were obtained and the structure is presented in Figure 3.7.

![Figure 3.7: The crystal structure of (S$_P$S)-N-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-[2.2]paracyclophane-4-amine.](image)

Full details of the crystallographic data including bond lengths and bond angles are presented in Appendix 106. This compound is expected to act as a bidentate N,N ligand that will bond to a metal centre. A hypothetical model of 16-(R$_P$S) bonded to a zinc atom has been prepared and this is shown in Figure 3.8.
Using this purification protocol the preparation of other derivatives was attempted (Table 3.3). The isopropyl derivative was ultimately prepared in only 6% yield while the benzyl derivative was prepared in 7% yield. The t-Bu derivative was detected in the reaction mixture however ultimately none could be isolated. While the yields are poor it is important to note that this method represents a one pot synthesis and resolution procedure. This is significant as
resolving [2.2]paracyclophane precursors is arguably the most laborious aspect of dealing with this class of ligands.

Table 3.3: The synthesis of phenyl-oxazoline-[2.2]paracyclophane ligands using the Buchwald-Hartwig amination.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>iPr</td>
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</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>7%</td>
</tr>
<tr>
<td>3</td>
<td>tBu</td>
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</tbody>
</table>

[a] 1 mmol oxazoline, 1.2 eq. 2, 10% Pd, 20% ligand, 2 eq. base, 20 ml toluene at 120 °C, 5 days.

3.7 Attempted optimisation of ligand synthesis

Although a procedure for the preparation and resolution of novel ligands had been demonstrated the yields were extremely poor. The limits of catalyst and ligand loadings as well as reaction time and temperature were at the practical limits so it was decided to investigate changes to the synthetic routes (Table 3.4). Switching to an amino Pc and a bromo oxazoline (Entry 1) showed no increase in the yield at 18% as 19% was achieved under these conditions with the initial reagents. Using an iodo oxazoline (Entry 2) there was a marked increase in yield to 29%.
Furthermore, an oxazoline derivative containing aryl methoxy groups was examined (Entry 3). It was hoped this electron rich system would couple more readily however it was found to perform less effectively than the original system garnering only 10% product. Furthermore the resulting diastereomers could not be separated chromatographically as was the case with the original ligands.

_table: Attempted optimisation of phenyl-oxazoline-[2.2]paracyclophane synthesis._\(^\text{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>X^1</th>
<th>X^2</th>
<th>X^3</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH₂</td>
<td>Br</td>
<td>H</td>
<td>18%</td>
</tr>
<tr>
<td>2</td>
<td>NH₂</td>
<td>I</td>
<td>H</td>
<td>29%</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>NH₂</td>
<td>OCH₃</td>
<td>10%</td>
</tr>
</tbody>
</table>

\(^{[a]}\) 1 mmol oxazoline, 1.2 eq. cyclophane, 10% Pd, 20% ligand, 2 eq. base, 20 ml toluene at 120 °C, 5 days.

A linear synthetic sequence was also considered where the aryl nitrile is coupled to the Pc moiety and the subsequent product utilised in the Witte Seeliger reaction to give the final ligands (Table 3.5). Using the bromo Pc and an amino nitrile no product was detected (Entry 1). Switching the functionalities, using amino Pc and halo nitriles yielded no detectable product either (Entry 2 and 3). It is suggested that the deactivating nitrile in the _ortho_ position is the cause for this lack of reactivity. Using the more electron rich dimethoxy derivative, the resulting product 2-(4-amino-[2.2]paracyclophane)-4,5-dimethoxybenzonitrile _17_ was isolated in 32% yield (Entry 4).
Table 3.5: Buchwald-Hartwig reaction of substituted [2.2]paracyclophanes with aryl nitriles.\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>(R^3)</th>
<th>(R^4)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>NH(_2)</td>
<td>H</td>
<td>H</td>
<td>----</td>
</tr>
<tr>
<td>2</td>
<td>NH(_2)</td>
<td>Br</td>
<td>H</td>
<td>H</td>
<td>----</td>
</tr>
<tr>
<td>3</td>
<td>NH(_2)</td>
<td>I</td>
<td>H</td>
<td>H</td>
<td>----</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>NH(_2)</td>
<td>OCH(_3)</td>
<td>OCH(_3)</td>
<td>32(^{[b]})</td>
</tr>
</tbody>
</table>

\(^{[a]}\) 1 mmol nitrile, 1.2 eq. Pc, 10% Pd, 20% ligand, 2 eq. base, 20 ml toluene at 120 °C, 5 days \(^{[b]}\) 2 days.

17 was then used in the Witte Seeliger reaction where it proceeded in only 16% yield (Scheme 3.23). This result indicates that the linear synthetic approach is not superior to the initial convergent synthesis.

Scheme 3.23: The synthesis of \((S\_P\_S)\)-N-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)4,5-dimethoxy-phenyl)-[2.2]paracyclophane-4-amine.
3.8 Conclusion

A series of monosubstituted Pc were prepared including bromo, formyl, hydroxy, nitro and amino derivatives. Using a number of these compounds, additional functionality was added to prepare a range of disubstituted derivatives including two novel materials. The resolution of two Pc derivatives was investigated and a novel procedure for preparing enantiopure 4-bromo[2.2]paracyclophane was reported. Following this, a series of phenyl-oxazolines were prepared via the Witte Seeliger reaction, including two novel derivatives, for use in Buchwald-Hartwig aminations intended to prepare novel asymmetric ligands. Initial studies were aimed at optimising conditions and two novel asymmetric ligands were isolated in enantiopure form and characterised. The yields however were under 10% so further work was aimed at an alternative synthetic route that would be more efficacious. Attempts at different combinations of amines and halides provided a mild improvement in the case of iodides. A more electron rich phenyl-oxazine system prepared by introducing aryl methoxides failed to improve the coupling efficiency. Finally a linear synthetic sequence was investigated but again this did not provide a more effective route over the initial preparation. Further work is needed to optimise this synthesis and the most likely avenues will be the use of microwave synthesis or some redesign of the oxazoline component to make it more amenable to Buchwald-Hartwig coupling.
3.9 References


4.0 Review of the Synthesis and Modification of Octafluoro[2.2]paracyclophane

4.1 Introduction

Octafluoro[2.2]paracyclophane (OPc) 1, commonly referred to industrially as AF4, is a fluorinated analogue of [2.2]paracyclophane with the alkyl hydrogen atoms replaced by fluorine (Figure 4.1). This compound finds widespread application in industry for preparing surface coatings. These coatings offer superior thermal and UV stability, a low dielectric constant and excellent barrier properties in comparison to their hydrocarbon counterparts.1,2 However a facile and high yielding synthesis of 1 has proven difficult and the following details the advances to date in its preparation and modification.

![Figure 4.1: The structure of octafluoro[2.2]paracyclophane.](image)

4.2 Preparation of octafluoro[2.2]paracyclophane

The initial procedures for the preparation of 1 were developed in the early 1960’s when a number of 1,4-bis-alkylsulfonyls 2 were pyrolysed at high temperatures (600-800 °C) to yield 1.3 Around the same time, a similar high temperature procedure in the presence of copper was developed using 1,4-bis-alkylhalo analogues 3 and 4 from derivative 5 (Scheme 4.1).4 These methods did not exclusively yield 1 and a variety of cyclic and linear oligomers were also formed contributing to a yield of approximately 30% by either method. Subsequent research focused on pathways which would lead exclusively to 1.5
Scheme 4.1: The synthesis of 1,4-bis-alkylsulfonyl and 1,4-bis-alkylhalo precursors for the high temperature synthesis of octafluoro[2.2]paracyclophane.

The high temperature synthesis optimised by Wheelright et al. remained the only route to produce 1 for almost 30 years. It was not until the early 1990’s that a new method was presented. Dolbier et al. attempted to extend the Hoffman elimination of an amino tetrafluoroborate salt 6 to yield 1, based on a previous synthesis of the parent hydrocarbon paracyclophane (Scheme 4.2). This proved unsuccessful as did an attempt to use a carboxylic acid salt 7. It was found that treatment of compound 4 with a combination of titanium tetrachloride and lithium aluminium hydride afforded 1 in a 32% yield.

Scheme 4.2: Development of a low temperature preparation of octafluoro[2.2]paracyclophane.

Although this work removed the necessity for high temperatures, it presented a new issue. An appreciable yield was only obtained when the reaction was carried out under highly dilute conditions, 1.5L of solvent yielded 1.7g of 1 (32%) and extremely slow addition of reactants
was necessary. This limitation is explained by consideration of the reaction mechanism which proceeds via formation of the reactive tetrafluoro-p-xylene 8, as evidenced by a small amount of the trimer 9 in the reaction mixture (Scheme 4.3). There is an increase in the concentration of 8 as the dilution factor is decreased so it must be maintained to limit the collisions with the di-radical intermediate 10. This dilution also provides the optimal kinetic environment to minimise the bimolecular oligomerisation of the extended conformer 11.

Scheme 4.3: The possible reaction pathways of the intermediate tetrafluoro-p-xylene.

Dolbier et al. reported an improved method several years later which obviated the need for high dilution. Based on a study into Diels-Alder reactions by Mori et al.,\(^8,9\) it was found that a combination of trimethylsilyl tributyltin and caesium fluoride (CsF) could affect the required debromination of 4 to yield 1 in 40% yield (Scheme 4.4). It was found that a solvent system of 4:1 THF:DMSO was crucial for this to proceed. A mechanistic reasoning explains the need for this and the formation of 8. CsF has limited solubility in this solvent system so it impedes the rate of formation of the necessary intermediate such that at any one time its concentration is low. This essentially presents the same favourable kinetic environment that high dilution facilitates, but without the increased solvent volume.\(^{10}\)
Scheme 4.4: A tin catalysed debromination to prepare octafluoro[2.2]paracyclophane.

This synthesis allowed production of 1, did not require high dilution technology and was industrially feasible to produce the material on a kilogram scale, but some issues remained. The reaction was still low yielding at 40%, there is significant cost associated with the reagents, and the use of stochiometric quantities of an organostannane is undesirable.

In a subsequent report by Dolbier et al., it was shown that 1 could be produced in a 60% yield without the use of stannanes. Treating the chloro analogue 3 with zinc dust in dimethylacetamide (DMA) yielded the product without needing high dilution conditions (Scheme 4.5). The mechanism is not fully understood but it is believed that the coupling occurs on the metal surface. Not requiring high dilution would imply that the pathway does not involve generation of free intermediate 8.\(^{11}\)

Scheme 4.5: The zinc catalysed coupling of 1,4-bis-chlorodifluoromethylbenzene to prepare octafluoro[2.2]paracyclophane.

A year following this report, Uneyama et al. presented a new carbon-fluorine bond cleavage route to 1 from the inexpensive starting material 1,4-bis-trifluoromethyl benzene 12 (Scheme 4.6). A magnesium-promoted defluorinative silylation of one of the trifluoromethyl (CF₃) groups was used to yield the corresponding trimethylsilyl compound 13. This was then heated
at reflux in anisole in the presence of catalytic amounts of CsF and Pd$_3$(dba)$_3$ providing 1 in yields of 53\%.$^{12}$

![Scheme 4.6](image)

Scheme 4.6: The preparation of octafluoro[2.2]paracyclophane via the formation of an organosilane and a subsequent Pd/CsF catalysed coupling.

This procedure, along with the previously mentioned zinc catalysed method, represent the current leading technology for the synthesis of 1. The yields of both procedures are comparable so when deciding which route is best it would be prudent to consider the precursor compounds required. While 12 is inexpensive and readily available in bulk commercially, 3 is not commercially available and its preparation from an inexpensive precursor could prove laborious.

There are two pathways presented in the literature to this end and these will now be considered. The first is described in a patent from the mid 1990s$^{13}$ and is summarised in Scheme 4.7. Terephthalaldehyde 14 is fluorinated using sulfur tetrafluoride (SF$_4$) to yield 1,4-bis-difluormethyl benzene 5$^{14}$ and this is subsequently chlorinated (or brominated if desired) by a photo halogenation process to yield the desired precursor 3. SF$_4$ is a highly corrosive gas which liberates HF on contact with moisture. Such a material is undesirable industrially. However, the use of this material can be circumvented in two steps, by chlorinating 14 with boron trichloride (BCl$_3$) to yield 1,4-bis-dichloromethyl benzene 15$^{15}$, and a subsequent solid state halogen exchange process with CsF to give 5$^{16}$ or the use of phase transfer agents.$^{17}$

Thionyl chloride (SOCl$_2$) may be utilised in place of BCl$_3$ to yield 15.$^{18}$ The second approach to this precursor was published in 2007 by Dolbier et al. and describes its production from
1,4-bis-trichloromethyl benzene 16 (readily produced itself via photochlorination of p-xylene) using anhydrous HF with reported yields of 79% for 3.\(^\text{16}\)

\[ \text{CHO} \xrightarrow{\text{BCl}_3, \text{hexane}} \text{CHO} \]

**Scheme 4.7: Two chemical pathways to the precursor 1,4-bis-chlorodifluoromethyl benzene.**

### 4.3 Preparation of substituted octafluoro[2.2]paracyclophane derivatives

There have been numerous reports to date examining analogues of 1 and they range from the preparation of commercially useful substituted analogues to studies of chiral di-paracyclophanes which are of academic interest. Pc systems have elicited much academic interest due to their unique chemical behaviours such as unusual reactivities, \textit{trans}-annular communication and spectroscopic abnormalities\(^1\). It is worth noting that the reports discussed in the following were all carried out by Dolbier’s group. Work published in 1999 details procedures for the electrophilic aromatic substitution of 1. Methods were developed to introduce an impressive variety of functionalities, beginning with nitratin using nitronium tetrafluoroborate (NO\(_2\)BF\(_4\)) in sulfolane (\textit{Scheme 4.8}).\(^19\) This work is particularly relevant because these additional groups can act as linkers for the attachment of other chemical entities to the precursors or the subsequent coating they generate.
Scheme 4.8: The preparation of a variety of monosubstituted octafluoro[2.2]paracyclophane derivatives.\(^{19}\)

It was subsequently shown that utilising harsher nitrating conditions could yield a di-nitro analogue of 1 in 81% yield, again using NO\(_2\)BF\(_4\) in sulfolane but at a higher temperature. The product was found to be an equivalent mixture of three hetero-annularly substituted isomers which were pseudo-ortho 17, pseudo-meta 18 and pseudo-para 19 (Scheme 4.9). No pseudo-geminal or homo-annular substitution was detected. Interestingly the pseudo-ortho isomer could be readily separated by column chromatography (along with any mono-nitrated or starting material). These isomers could all be reduced to the corresponding amines and
converted to bromo or chloro derivatives by substitution. Attempts at the reduction of a single nitro group were achieved but were found to be low yielding at 11%.\textsuperscript{20}


Direct bromination was also carried out on 1 using N-bromosuccinimide and H$_2$SO$_4$ and gave an unexpected result. The reaction proceeded in 55\% yield and the product was exclusively a homo-annular $p$-dibromide which is unusual given the deactivating nature of halo substituents.\textsuperscript{20} This provides a method for the synthesis of novel homo-annularly and hetero-annularly disubstituted analogues of 1. Such compounds may prove superior to their hydrocarbon counterparts as ligands for asymmetric synthesis because they show a significantly higher resistance to thermal isomerisation.\textsuperscript{20,21}

As shown previously, the CF$_3$ derivative of 1 could be produced in 5 steps (\textit{Scheme 4.8}). Attempts were made to extend Sawada’s free radical trifluoromethylation procedure to 1 which utilises decomposition of trifluoroacetyl peroxide in DCM.\textsuperscript{22} Although the CF$_3$ radical
added to one of the rings, no rearomatisation was observed. Instead the resulting cyclohexadienyl radical 20 proved stable enough to dimerise to one of the isomers 21 or 22 (Scheme 4.10). The value of these isomers is in the generation of CF$_3$ radicals.\(^{23}\) Usually these are generated using trifluoroacetyl peroxide which is thermally unstable even at room temperature or by the use of Scherer’s radical which is considered an excellent clean source.\(^{24}\) The isomers shown here are stable crystalline compounds which produce CF$_3$ radicals at temperatures above 150 °C with the only by product being the essentially chemically inert 1.

\[
\text{Scheme 4.10: The preparation of trifluoromethyl substituted bis-octafluoro[2.2]paracyclophane analogues.}
\]

Following this was the first report of a di-octafluoro[2.2]paracyclophane produced via the palladium catalysed reductive homo-coupling of the iodo analogue 23 (Scheme 4.11). The result was again an isomeric mixture of 24 and 25. Low temperature $^{19}$F NMR studies showed that the meso compound 25 is a rotamer. The introduction of a CF$_3$ group as in 26 yielded only the meso compound 27 by a similar procedure.\(^{25}\)
Facile access to the iodo analogue 23 also allowed an investigation into the use of Suzuki cross couplings (Scheme 4.12). The reactions proved very effective when using non-hindered boronic acids and pinacol esters. A method was also developed for the production of boronic acid derivative 28. This novel material showed comparable yields under the same conditions when coupled with non-hindered aryl iodides.26


It was found that phenyl spacer groups could be introduced between the OPc units under appropriate conditions to yield novel compounds 29 and 30 (Scheme 4.13).

An examination of the $S_{RN1}$ reactivity of 23 showed that it reacts with certain aryl thiylates and stabilised enolates (Scheme 4.14). This result was promising because it indicated that many novel OPc derivatives may be produced from $S_{RN1}$ nucleophiles. These reactions did however require photochemical initiation and did not proceed via thermal methods alone.27

![Scheme 4.14: The preparation of substituted octafluoro[2.2]paracyclophe derivatives by an $S_{RN1}$ pathway.](image)

An unusual product of nucleophilic attack of the nitro analogue 31 led to the discovery of a novel ring cleaving reaction of OPc (Scheme 4.15).28 Although there were reports of opening the [2.2]paracyclophane system with the parent hydrocarbon,29,30 this occurred via the alkyl bridge carbons whereas in this case the cleavage occurs at the alkyl-aryl bond. It is suggested that this occurs via an $S_{NAr}$ pathway.
Scheme 4.15: The ring cleaving reaction of nitro OPc with a nucleophile.

4.4 Preparation of substituted octafluoro[2.2]paracyclophane analogues by Diels-Alder reactions

Arynes (or benyznes) are a highly reactive intermediary species that are known to readily take part in Diels-Alder reactions. It was shown in a report from 2002 that benyznes 32 and 33 can be produced from mono and di-iodo substituted analogues of 1 (Figure 4.2).\(^{31,32}\)

Figure 4.2: The structure of 4,5-dehydrooctafluoro[2.2]paracyclophane and 4,5,15,16-bis-dehydrooctafluoro[2.2]paracyclophane.

Prior to this report in 1969, Longone et al. had used [2.2]paracyclophane in the presence of anthracene to produce the Diels-Alder adduct, however the yield was only 15%.\(^{33}\) In the same year Cram et al. also reported a bis Diels-Alder product via the dehalogenation of 4,5,15,16 tetrabromo[2.2]paracyclophane.\(^{34}\) Longone generated the necessary aryne using KO\textit{t}Bu a method normally avoided since its original reporting.\(^{35}\) This is because arynes typically react with the nucleophilic \textit{t}-Bu ion leading to significant amounts of by-product. In the case of arynes generated from 1 however this method is ideal giving excellent yields with virtually none of this by-product detected. As an example, Scheme 4.16 shows the Diels-Alder products produced from iodo analogues of 1 (which occur via the formation of the
Review of the Synthesis and Modification of Octafluoro[2.2]paracyclophane  Chapter 4

corresponding arynes 32 and 33) with anthracene as a substrate which gave excellent yields. Other substrates employed were benzene, naphthalene, t-butylbenzene, furan and [2.2]paracyclophane, each of which demonstrated comparable yields with anthracene.


As a continuation of this synthesis it was found that the Diels-Alder adduct 34, amongst others, could be used to prepare novel OPc derivatives such as the anthraceno analogue 35 (Scheme 4.17). This compound is of note because it was found to form a dimer when exposed to UV light. The structure is unusual in that the anthracene ring directly involved in the OPc system breaks aromaticity to form a cyclobutane ring.36
Scheme 4.17: The preparation of 1,4-anthraceno-octafluoro[2.2]paracyclophane and its dimerisation.

The approach used thus far in this area was the Cram methodology but Diels-Alder adducts may also be produced using the Cadogan method.\textsuperscript{37} This method generates the aryne by reaction of an $N$-nitroacetanilide, produced \textit{in-situ} by the reaction of acetanilide \textsuperscript{36} and 4-chlorobenzoyl nitrite \textsuperscript{37}, which proceeds to react with the desired arynophile. This method is typically low yielding with the reaction of acetanilide and anthracene for example, yielding only 16\% of the Diels-Alder adduct. When extended to the acetanilide derivative \textsuperscript{38} the yield was 90\% (Scheme 4.18). The increased efficiency of the reaction is ascribed to the bridge fluorine atoms because they increase the ring hydrogen acidity and produce a more electron deficient aryne.

The Cadogan methodology was also found to be very effective for reactions with alkenes. For example, the reaction with oct-1-ene yielded 91% of the ene product 39 (Scheme 4.19). Interestingly, the same reaction under Cram conditions yielded no product, only reduction of the aryl iodide. No alkene utilised was shown to produce any ene product under Cram conditions.
Scheme 4.19: Ene reactivity of octafluoro[2.2]paracyclophane derivatives under Cadogan and Cram conditions.

The final report relating to this area details a sequential ene reaction followed by a Diels-Alder reaction with cyclohepta-1,3,5-triene. The ene adduct 40 produced via the Cadogan method reacts further with an additional aryne to yield a Diels-Alder adduct (Scheme 4.20). The product was synthesised as a diastereomeric 2:1 mixture 41 and 42 in a yield of 25%. It was possible to fully characterise the mixture solely by NMR. 38
Scheme 4.20: Sequential ene and Diels-Alder reaction of OPc-acetamide and cyclohepta-1,3,5-triene.

4.5 Preparation and modification of perfluoro[2.2]paracyclophane

A logical progression from the preparation of 1 was the synthesis of perfluoro[2.2]paracyclophane (pOPc) 43 (Scheme 4.21). The initial preparation of this compound detailed two synthetic routes; a five step procedure beginning with 2,3,5,6-tetrachloroterphthalonitrile 44, and a second refined pathway beginning with 1,2,4,5-tetrachlorobenzene 45. Although a zinc-catalysed homo-coupling is again utilised to produce pOPc, the presence of aromatic fluorine instead of hydrogen meant a different approach was required to make the necessary precursor 46. It was determined that ultimately 43 may be produced in a 39% yield when the coupling is carried out in MeCN at 100 °C for 38 hours.39
Following the preparation of 43, an investigation was carried out to examine the reactivity of this compound to nucleophilic aromatic substitution.\(^{40}\) It was found that 43 could indeed be modified in this manner and several examples were reported using both mono and bi-dentate nucleophiles. The presence of such significant amounts of fluorine produces an extremely electron deficient aromatic system which is then quite reactive to nucleophiles (Scheme 4.22).

No disubstitution is observed in the phenol derivative 47 and this is likely due to the strongly electron donating ability of the phenoxide. It is noteworthy that this effect is transmitted to the other ring of the system. This then explains why the more weakly donating methoxy derivative 48 shows some disubstitution exclusively in the form of the pseudo-para isomer 49. The reaction of 43 with sodium thiophenoxide yielded no monosubstituted product but gave a para isomer 50, indicating that this group had an activating effect. This is in agreement with a previous study of the reaction of sodium thiophenoxide and 2,3,5,6-tetrafluorobenzene.\(^ {41}\) The most successful bi-dentate ligand class were found to be catechols followed closely by bis-amines. In a reaction with ethylene glycol no cyclisation product was

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**Scheme 4.21:** Two synthetic pathways for the synthesis of perfluoro[2.2]paracyclophanes.
observed. Competition experiments showed that 43 was in fact much more reactive than hexafluorobenzene under these conditions. It was determined that the most likely mechanistic pathway for these reactions is an S$_{N}$Ar mechanism.

Mono-substituted analogues of 43 constitute a break in the symmetry and this allowed a detailed study of the spectral and conformational properties of these new analogues. Examination of the $^{19}\text{F}$ coupling constants, particularly long range four and five bond couplings, allowed a detailed characterisation of the system and any disubstituted products could be differentiated. It was found that substitution skews the geometry of the system such that the unsubstituted ring may be drawn toward or away from the new substituent (Figure 4.3). The results showed that this was not just due to the size of the substituent but is likely to be heavily dependent on the electronic environment of the aromatic rings. The experimental data was found to be in good agreement with computational models.\textsuperscript{42}

![Figure 4.3: Possible conformations of the perfluoro[2.2]paracyclophane system with respect to the new substituent.](image)

The most recent report concerning 43 is the atropoisomerism of the acetoacetic ester produced by the reaction of 43 and ethyl acetoacetate.\textsuperscript{43} Atropisomers are stereoisomers resulting from restricted rotation about a single bond where the barrier of rotation is sufficiently high that both isomers can be isolated. In this case the isomers were produced as a mixture 51 and 52 (Scheme 4.23) in the form of a crystalline solid and it was determined that the compound exists purely in the enol form with no keto tautomer detected by $^1\text{H}$ NMR. In solution the energy barrier to rotation was found to be 23.5 Kcal mol$^{-1}$ and it is suggested this is due to interference from the close fluorinated methylene bridge. The ester was then cyclised under basic conditions to a furan product 53.
Scheme 4.23: The preparation of the acetoacetic ester derivative of perfluoro[2.2]paracyclophane and its subsequent cyclisation under basic conditions.

4.6 Conclusion

This review has discussed the history and development of OPc and subsequent investigations into its chemistry. The development of facile synthetic pathways to the compound and the subsequent functionalisation of its structure have demonstrated that it is amenable to a broad variety of chemistry. Its unusual electronic properties, ascribed to the highly fluorinated structure, have led to it being surprisingly efficacious under a range of conditions. At present it is a highly desirable material in industry for protective coatings. Research to date has demonstrated that it would be an ideal precursor to a new generation of multifunctional coatings as it can be readily modified. The chirality of the substituted Pc framework, along
with its unique electronic properties, means that it could have applications as a scaffold in asymmetric synthesis and catalyst design, areas which have not yet been fully explored.
Review of the Synthesis and Modification of Octafluoro[2.2]paracyclophane

Chapter 4

4.7 References


5.0 Preparation of Asymmetric Ligands Based on Octafluoro[2.2]paracyclophane

5.1 Introduction

This chapter details the investigation into the synthetic routes to octafluoro[2.2]paracyclophane (OPc) 1. Mono-substituted derivatives of 1 were also prepared and interpretation of their NMR spectra is discussed in detail. Finally, the Buchwald-Hartwig amination was used in attempts to couple the OPc framework with a phenyl-oxazoline to prepare analogous ligands to those reported in Chapter 3.

5.2 Preparation of octafluoro[2.2]paracyclophane

Two synthetic routes to 1 were investigated and these are presented in Scheme 5.1.

Scheme 5.1: Synthetic routes for the preparation of octafluoro[2.2]paracyclophane.
5.2.1 Synthesis of 1,4-bis-dichloromethylbenzene

Terephthaldehyde 2 was selected as an inexpensive and readily available starting material for the synthesis of 1. It was intended that the initial step would involve the conversion of 2 to the geminal dichloride 1,4-bis-dichloromethylbenzene 3. To this end four options were available, chlorination via chlorine gas (Cl₂), phosphorus pentachloride (PCl₅), boron trichloride (BCl₃) or thionyl chloride (SOCl₂). Due to availability and ease of handling, it was decided to utilise the BCl₃ and SOCl₂ routes (Scheme 5.2).

Scheme 5.2: The synthesis of 1,4-bis-dichloromethylbenzene.

BCl₃ was purchased as a 1M solution in pentane. This was added to a solution of dry hexane and 2 which was heated at reflux for 4 hours. The product was isolated in 45% yield (98% reported) by a standard work-up followed by flash column chromatography. In addition, the intermediate 4-dichloromethylbenzaldehyde 4 was isolated in a yield of 11%.

In the alternative procedure, SOCl₂ was used neat with a catalytic amount of dimethyl formamide (DMF). After a 3 hour reflux, the reaction mixture was poured onto cold water and the product was immediately precipitated and collected by filtration. The yield was 70% (94% reported) and no further purification was required. Using SOCl₂ provided a simpler, higher yielding procedure and has the additional advantage of being significantly cheaper than BCl₃.
The reaction involving BCl$_3$ is proposed to proceed via the formation of an alkoxyboron dichloride and presumably the migration of a second chlorine atom to the carbon centre to yield the product (Scheme 5.3). The SOCl$_2$ reaction then follows the same pathway differing only in producing sulphur dioxide (SO$_2$) as a by-product.

Scheme 5.3: The proposed mechanisms for the formation of 1,4-bis-dichloromethyl benzene.

5.2.2 Synthesis of 1,4-bis-difluoromethylbenzene

Two general routes were considered to prepare 1,4-bis-difluoromethylbenzene 5 (Scheme 5.4), a halogen exchange process beginning with 3, or direct fluorination of 2. 5 has been synthesised by both routes with examples shown of solid phase exchange processes,$^{5,6}$ exchange processes via phase transfer catalysis$^{5,7}$ and direct fluorination using various fluorinating reagents.$^{8-10}$

Scheme 5.4: The synthesis of 1,4-bis-difluoromethylbenzene.
5.2.2.1 Fluoride exchange processes

The halogen exchange process relies on the nucleophilic displacement of chlorine by fluorine via an S_N2 mechanism (Figure 5.1). However, to achieve this, there must be an interaction between 3 and the fluoride generated from CsF. Solubility is the main issue as 3 is insoluble in water and the ionic salt CsF is insoluble in most organic solvents. Phase transfer catalysis offers a solution to this problem by allowing the reaction to be carried out with a mixture of two immiscible solvents, in this case benzene and water. The reaction is mediated by the use of a phase transfer catalyst. Such catalysts are usually ammonium salts or phosphonium salts if strongly basic conditions or very high temperatures are required.\textsuperscript{11,12} Tetrabutyl ammonium bromide (TBAB) is a widely used catalyst and was used in this work. The tetrabutyl ammonium cation forms a complex with the fluoride anion resulting in a neutral species capable of passing from the aqueous phase into the organic phase, thus delivering the fluoride. The nucleophilicity of the fluoride anion should also be increased without the stabilising effect of the hydration shell provided by the aqueous solvent. It was also envisaged that the carbon centre would be more susceptible to nucleophilic attack due to the electron withdrawing chlorine atoms. This process is similar to the Finkelstein reaction which involves the substitution of alkyl chlorides and bromides for iodides and has been further extended to encompass α-carbonyl, allyl and benzyl halides.\textsuperscript{13,14}
Figure 5.1: The proposed mechanism for the synthesis of 1,4-bis-difluoromethylbenzene via phase transfer catalysis.

On performing this procedure in a mixture of benzene and water with temperatures up to 100 °C, no product was detected by $^{19}$F NMR. The reaction was then attempted in dry DMF in which CsF has limited solubility. TBAB was again added to aid the delivery of the fluoride ion and the reaction was carried out for 24 hours at reflux. Again no product was detected. Finally, the starting material and CsF were mixed together and heated as a solid melt. There were practical issues with mixing a sealed melt so the reaction could not be stirred which likely hindered the progress significantly. $^{19}$F NMR showed traces of product but no material was isolated from the mixture.

5.2.2.2 Direct fluorination of terephthaldehyde

The failure of the halogen exchange processes meant considering alternative routes. Direct fluorination of 2 was the obvious choice because if successful it would remove one step in the synthetic sequence. Due to the success of BCl$_3$ in yielding 3, boron trifluoride (BF$_3$) seemed a
logical choice. However when the reaction was carried out no product was formed. This is likely due to BF$_3$ being a weaker Lewis acid.

The boron trihalides shown in Figure 5.2 are trigonal planar molecules with sp$^2$ hybridisation where the boron atom has an empty p-orbital, allowing it to act as a Lewis acid. It would be expected that because of the relative electronegativity of the different halides that BF$_3$ would yield the most electron deficient boron atom of the boron trihalides and hence be the strongest Lewis acid. However, the trend in Lewis acidity goes in the opposite direction with BBr$_3$ being the most acidic. This is because there is an orbital overlap between the empty p-orbital of boron and the full p-orbitals of the halides. This overlap is most efficient with fluorine and decreases going down the group. Therefore the boron p-orbital in BF$_3$ actually has the most electron density of the boron trihalides making it the weakest Lewis acid. On forming the appropriate adduct this π contribution would be lost as the molecular geometry switches from trigonal planar to tetrahedral, thus forming the alkoxyboron intermediate would not be favoured.$^{15}$

![Diagram of boron trihalides](image)

*Figure 5.2: The relative Lewis acidity of the boron trihalides.*

Diethylaminosulfur trifluoride (DAST) was selected as an alternative fluorinating agent. It is quite similar in reactivity to SF$_4$ from which it is synthesised but much more easily handled.
DAST was added to a dry solution of 2 in DCM along with a catalytic amount of ethanol (EtOH). The reaction was heated at reflux for 16 hours and quenched with water. An aqueous workup and subsequent flash column chromatography allowed isolation of 5 in a 67% yield (94% reported⁹).

The proposed mechanism for this reaction, shown in Scheme 5.5, begins with the generation of hydrofluoric acid (HF) in the presence of EtOH. This reduces the carbonyl to an alcohol nucleophile which subsequently attacks the sulfur atom of the DAST reagent. This leads to regeneration of the initial HF and the formation of an S-O bond which then rearranges with loss of another fluorine atom to the carbon centre to yield the product and an amino sulfoxide by product.

**Scheme 5.5: The proposed mechanism for the preparation of 1,4-bis-difluoromethyl benzene.**

5.2.3 Synthesis of 1,4-bis-chlorodifluoromethylbenzene

Only two methods are presented for the preparation of 1,4-bis-chlorodifluoromethylbenzene 6. The first is chlorination of 5 which can be achieved using either chlorine gas (Cl₂) in tetrachloromethane¹⁶ (CCl₄) or sulfuryl chloride (SO₂Cl₂) and a radical initiator (Scheme 5.6). The latter process is more suitable to carry out on laboratory scale due to the toxicity of
chlorine gas and the difficulty in handling harmful gases. The second method is fluoration of 1,4-bis-trichloromethylbenzene using anhydrous HF in DCM.$^6$

Initially CCl$_4$ and benzene were selected as possible solvents for the reaction on the basis that they have no alkyl hydrogen atoms which would compete with the desired transformation. The radical initiator utilised was azobisisobutyronitrile (AIBN). Benzene was chosen as the solvent on the basis of availability however the reaction was found to proceed poorly. Even at extended periods heating at reflux (up to 9 days) and at higher catalyst loadings, no product was formed by TLC. It was noted that AIBN was soluble in SO$_2$Cl$_2$ so the reaction was run neat and it was found to proceed much more efficiently. After 5 days heating at reflux the mixture was diluted with DCM and quenched with slow additions of ice water. The organic layer was extracted and the solvent removed in vacuo. The resulting oil was purified by flash column chromatography affording 5 in 20% yield along with the intermediate 1-(chlorodifluoromethyl)-4-(difluoromethyl)benzene 7 in 34% yield.

AIBN is thermally decomposed to form two radicals with the elimination of nitrogen gas (N$_2$). This radical abstracts a chlorine atom from SO$_2$Cl$_2$ which in turn rearranges to form sulfur dioxide (SO$_2$) and a chlorine radical. This initiates the radical chain reaction. The chlorine radical abstracts an alkyl hydrogen atom from the starting material generating hydrogen chloride and a new radical species. This radical then follows the same pathway as the initiation step which yields the product and regenerates the chlorine radical in the process.
This process repeats until one of three termination steps occurs. The reaction ends in the formation of Cl₂, the desired product or a diarylfluoroethane type product (Scheme 5.7).

**Scheme 5.7: The proposed mechanism for the formation of 1,4-bis-chlorodifluoromethylbenzene.**

### 5.2.4 Synthesis of 1-(trimethylsilyl)difluoromethyl-4-trifluoromethylbenzene

1-(Trimethylsilyl)difluoromethyl-4-trifluoromethylbenzene 9 can be prepared from 1,4-bis-trifluoromethylbenzene 8, and is known to be another precursor to 1 which may be synthesised via two routes, both of which are defluorinative silylations. The first method is photo promoted¹⁷ while the second utilises magnesium¹⁸ (Scheme 5.8). The second method
was chosen due to a higher reported yield. In addition, the photochemical method is hampered by formation of polymeric by-products.

Scheme 5.8: The synthesis of 1-(trimethylsilyl)difluoromethyl-4-trifluoromethylbenzene.

The reaction was carried out under anhydrous conditions with the precursor 8 being added to the mixture dropwise. The reaction is highly exothermic so the precursor was added over 30 minutes. Standard workup and flash column chromatography afforded the product in 32% yield (48% reported\textsuperscript{18}). The literature indicated that the product was contaminated with a small amount of side product where an additional fluorine atom has been substituted with hydrogen (protodesilylation). However none of this by-product was detected by \textsuperscript{1}H or \textsuperscript{19}F NMR.

The reaction is proposed to begin with a magnesium promoted defluorination shown in Scheme 5.9. Normally this would be unlikely due to the strength of the C-F bond (approximately 550KJ mol\textsuperscript{-1}) but in this case the resulting benzylic anion is stabilised by its resonance contributors. Nucleophilic attack of this anion on the silicon centre with the loss of chloride then yields the product.
Scheme 5.9: *The proposed mechanism for the formation of 1-(Trimethylsilyl)difluoromethyl-4-trifluoromethylbenzene.*

5.2.5 **Synthesis of octafluoro[2.2]paracyclophane**

For details of the available synthetic routes to octafluoro[2.2]paracyclophane 1 see Section 4.2. The methods selected here were the fluoride catalysed 1,6 elimination reaction beginning with 9\(^{18}\) and the zinc catalysed coupling of 6\(^{19}\) (*Scheme 5.10*).

Scheme 5.10: *The synthesis of octafluoro[2.2]paracyclophane.*

5.2.5.1 **Zinc catalysed homo-coupling**

In this procedure 6 was added to a dispersion of zinc in dry DMA. The reported conditions detail maintaining the reaction at 100°C for 4 hours however in this case no product was detected. Further modifications were attempted (*Table 5.1*) but even at reflux and reaction times of 2 days no product was detected (*Entry 1*). On the advice of the authors of the
procedure, it was indicated that the zinc or the zinc washing procedure may have been the issue. Two different batches of zinc were used with various washing procedure and in each case no product was isolated.

Table 5.1: Reaction conditions for the zinc catalysed coupling of 1,4-bis-chlorodifluoromethylbenzene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (h)</th>
<th>Temperature (°C)</th>
<th>Zinc purity</th>
<th>Zinc washing</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4, 24, 48</td>
<td>100, reflux</td>
<td>&gt;99</td>
<td>N/A</td>
<td>----</td>
</tr>
<tr>
<td>2</td>
<td>4, 24, 48</td>
<td>100, reflux</td>
<td>&gt;99</td>
<td>2% HCl, H₂O, EtOH, Et₂O</td>
<td>----</td>
</tr>
<tr>
<td>3</td>
<td>4, 24, 48</td>
<td>100, reflux</td>
<td>&gt;99</td>
<td>H₂O, EtOH, Me₂CO, Et₂O</td>
<td>----</td>
</tr>
<tr>
<td>4</td>
<td>4, 24, 48</td>
<td>100, reflux</td>
<td>98</td>
<td>N/A</td>
<td>----</td>
</tr>
<tr>
<td>5</td>
<td>4, 24, 48</td>
<td>100, reflux</td>
<td>98</td>
<td>2% HCl, H₂O, EtOH, Et₂O</td>
<td>----</td>
</tr>
<tr>
<td>6</td>
<td>4, 24, 48</td>
<td>100, reflux</td>
<td>98</td>
<td>H₂O, EtOH, Me₂CO, Et₂O</td>
<td>----</td>
</tr>
</tbody>
</table>

5.2.5.2 Fluoride catalysed 1,6 elimination

The fluoride catalysed method involved heating 9 at reflux in dry anisole in the presence of catalytic amounts of fluoride from CsF and Pd₂(dba)_3. The product was isolated by flash column chromatography in 18% yield (53% reported). It is proposed that the method suffers from an unwanted protodesilylation reaction which attributes to the low yield (Scheme 5.11) and this species 10 was observed by ¹⁹F NMR but was not isolated.
Scheme 5.11: The protodesilylation of 1-(Trimethylsilyl)difluoromethyl-4-trifluoromethylbenzene.

The mechanism proposed for this reaction begins with loss of the silicon moiety via the addition of fluoride (Scheme 5.12). This process is thought to proceed due to the stable F-Si bond. The resulting benzylic anion loses fluoride from the trifluoromethyl group at the 4 position. This generates the reactive p-xylylene, and homo-coupling yields the product. The palladium is thought to facilitate this coupling but the exact role it plays in the mechanism is not clear.

Scheme 5.12: The proposed mechanism for the synthesis of octafluoro[2,2]paracyclophane via fluoride catalysed 1,6 elimination.
5.3 Preparation of octafluoro[2.2]paracyclophane derivatives

5.3.1 Synthesis of 4-nitro-octafluoro[2.2]paracyclophane

1 was nitrated using a mixture of nitric acid (HNO₃) and sulfuric acid (H₂SO₄) and the product 11 was isolated in 26% yield (56% reported)²⁰. Along with 11, the di-nitro product 12 was isolated in 19% yield as a mixture of 3 isomers, pseudo-ortho, pseudo-meta and pseudo-para. 1 was also retrieved in 22% (Scheme 5.13). The mechanism of this reaction is discussed in Section 3.2.4.

![Scheme 5.13: The synthesis of 4-nitro-octafluoro[2.2]paracyclophane.]

5.3.2 Synthesis of 4-amino-octafluoro[2.2]paracyclophane

4-Amino-octafluoro[2.2]paracyclophane 13 was produced by reduction of 11 using a mixture of HCl and iron (Scheme 5.14)²⁰. The product was isolated by filtration in a yield of 80% (82% reported) and did not require any further purification. The mechanism of this reaction is discussed in Section 3.2.5.

![Scheme 5.14: The synthesis of 4-amino-octafluoro[2.2]paracyclophane.]

120
The amino analogue has been selected for discussion because of the clear resolution in the $^1$H NMR spectrum (Figure 5.3). The amino protons H4 were assigned at 5.6 ppm based on the broad peak, chemical shift and integration. The adjacent peak was assigned as H5 based on it being a doublet with a small coupling constant attributed to long range coupling with H7. Once H5 was assigned the COSY allowed ready identification of H7 and H8 (Figure 5.4). The COSY allows assignment of the adjacent ring if one of the four protons is assigned first. A single proton is shifted significantly downfield with respect to the others at 8.0 ppm and this was assigned H13 due to its pseudo-geminal position which brings it closest spatially to the electron withdrawing nitrogen atom. Knowing this the pseudo-ortho, pseudo-meta and pseudo-para positions can be readily assigned from the COSY.

![Figure 5.3: The assigned $^1$H NMR spectrum of 4-amino-octafluoro[2,2]paracyclophane.](image)
Figure 5.4: The assigned COSY spectrum of 4-amino-octafluoro[2,2]paracyclophane.

5.3.3 Preparation of oxazoline-octafluoro[2,2]paracyclophane derivatives

The amino derivative 13 was utilised along with the iodo phenyl-oxazoline 14 in the Buchwald-Hartwig amination. The successful conditions outlined in Chapter 3 were used (10% Pd and 20% ligand) however no product was detected. A second attempt was made increasing the reaction time to 7 days and delivering two portions of ligand and catalyst, a second quantity at 4 days reaction time. Even at these extended reaction times and loadings still no product was detected.
Scheme 5.15: The attempted synthesis of the diastereomers of $N$-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-octafluoro[2.2]paracyclophane-4-amine.

5.4 Conclusions

The synthetic routes to 1 were investigated and it was prepared using a fluoride catalyst 1,6 elimination in 18\% yield. The reported zinc catalysed method could not be reproduced even after extensive attempts using various conditions. 1 was successfully derivativised to prepare the monosubstituted nitro OPc 11 which was then reduced to give the amino OPc 13. Attempts to couple 13 to an iodo phenyl-oxazoline 14 using the Buchwald-Hartwig amination were not successful.
5.5 References


6.0 Parylene Coating Pre-Treatment and Adhesion Promotion

6.1 Introduction

A series of sol-gel formulations were applied as pre-treatments to aluminium panels in an attempt to improve the adhesion of parylene N surface coatings. These pre-treatments were characterised by IR and $^{29}\text{Si}$ NMR spectroscopy. The aluminium panels were subsequently coated in parylene N and their adhesion promotion was evaluated using the cross hatch measurement.

6.1.1 Parylene coatings

Parylene is a commonly used industrial term to describe a number of vapour deposited poly(p-xylylene) polymers. Since their development in the late 1940’s\(^1\) these materials have garnered attention as protective coatings due to their attractive physical and chemical properties and are widely used by the electronic and medical device industries.\(^2,3\) The conformal coating can be applied at ambient temperatures with tailored thickness, and specific properties of the coating can be altered by adjusting the chemistry of the precursors by the addition of various chemical substituents. The precursors used to produce these coatings are [2.2]paracyclopahes and a variety have been reported (Scheme 6.1).

![Scheme 6.1: Examples of different parylene coatings.](image-url)
The development by Gorham\(^4\) of a deposition process in 1966 ultimately led to the widespread industrial use of these coatings. The precursors are pyrolysed at temperatures of approximately 650 °C in a vacuum chamber resulting in the formation of the reactive \(p\)-xylylene monomers which are deposited and begin chain growth polymerisation on the substrate (Scheme 6.2). Typical chain lengths are of the order of 2000-4000 units. This is considered to be a green process as no initiators or terminators are used and the process produces no by-products. As a result, the coatings are free of contaminants and chemically pure.

\[
\text{Pyrolysis} \quad \begin{array}{c}
\text{Pyrolysed} \\
\text{at 650°C} \\
\text{50 Pa}
\end{array} \rightarrow \begin{array}{c}
\text{Deposition} \\
\text{25°C} \\
\text{10 Pa}
\end{array} \rightarrow \begin{array}{c}
\text{Cold Trap} \\
\text{-200°C} \\
\text{1 Pa}
\end{array} \rightarrow \text{Pump} \\
\text{0.1 Pa}
\]

\text{Scheme 6.2: The vapour deposition process for parylene coatings.}

However, some substrates can prove more difficult than others to properly coat in parylene due to the difference in surface adhesion of the coating. A practical example is shown in Figure 6.1. This is a medical device wire composed of a nickel-chromium alloy. Thermal treatment has caused the parylene coating to fail and very extensive delamination has occurred. Only small amounts of the coating remain.
Figure 6.1: SEM image of a wire coated in parylene C which has heavily delaminated.

A typical metal surface will have a number of free hydroxyl groups present. The concentration of hydroxyl groups depends on how the metal has been treated, for example plasma or acid treatment can increase this concentration. The mechanism by which parylene polymerises is a radical reaction so there will be no chemical bonding occurring between the metal surface (hydroxyl groups) and the growing polymer, resulting in poor adhesion. To improve adhesion, adhesion promoters are used and the adhesion promoter of choice for parylene coatings is 3-methacryloxypropyltrimethoxysilane (MAPTMS). This organosilane contains two reactive sites, a methoxysilane group that can react with the metal surface and a methacryloxy group that can be used in radical organic polymerisation. This dual functionality makes MAPTMS an excellent candidate as an adhesion promoter for parylene on metal surfaces, the principle of which is shown in Scheme 6.3. The standard industrial approach for the pre-treatment of aluminium 2024 panels to be coated in parylene N is to add MAPTMS directly into the chamber. This is done by placing an absorbent which has soaked up MAPTMS in with the panels and when the chamber is placed under vacuum the MAPTMS is dispersed.
6.1.2 Sol-gels and their use as pre-treatments

The sol-gel method is a frequently used way of applying surface coatings to a material. In this process the sol (or solution) gradually moves towards the formation of a gel network which contains both a liquid and solid phase. This process can be used for several applications such as making coatings, ceramics, fibres, gels and powders as shown in Figure 6.2.

Figure 6.2: Different applications of the sol-gel process.\textsuperscript{6}
The process begins with the growth of discrete particles from a monomeric material by a series of hydrolysis and condensation reactions as shown in Figure 6.3. This results in a colloidal suspension which is an evenly dispersed phase (the particles) within a continuous phase or dispersion medium (the solvent). These particles continue to grow and link together to form a polymeric network and the sol may then be applied in conjunction with a curing treatment to remove the solvent leaving a solid surface coating. The polymer will have a complex randomly branched structure meaning the final solid coating will be a non-crystalline material.

![Diagram of sol-gel process](image)

*Figure 6.3: General hydrolysis and condensation reactions of a silicon alkoxide that lead to the formation of polymer networks from sol-gel precursors.*

The next aspect of the sol-gel process to consider is selecting the appropriate materials. Invariably these materials are metal or metalloid atoms surrounded by ligands, some of which must be labile to facilitate polymerisation. The most common compounds used in sol-gel chemistry are metal alkoxides and metal chlorides particularly of silicon, aluminium, titanium and zirconium. These are readily hydrolysed in water with the reaction being catalysed by...
the addition of acid or base. Specific compounds used depend on the desired application and properties such as hardness, resistance to chemical erosion or hydrophobicity. To achieve this, additives may be added to the sol-gel preparation or the monomers themselves can be chemically modified.

6.2 Sol-gel pre-treatment formulation and coating preparation

To investigate the optimisation of surface adhesion using sol-gel coatings, a series of formulations were prepared (Table 6.1). These formulations vary two parameters, the concentration of MAPTMS and the acidity of the solution via the addition of nitric acid (HNO$_3$) solution.

Table 6.1: Sol-gel pre-treatment formulations.

<table>
<thead>
<tr>
<th>Sample</th>
<th>MAPTMS (ml)</th>
<th>IPA (ml)</th>
<th>H$_2$O (ml)</th>
<th>HNO$_3$ (ml)</th>
<th>HNO$_3$ (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>1.25</td>
<td>45</td>
<td>5.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S2</td>
<td>2.50</td>
<td>45</td>
<td>5.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S3</td>
<td>5.00</td>
<td>45</td>
<td>5.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S4</td>
<td>10.00</td>
<td>45</td>
<td>5.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S5</td>
<td>1.25</td>
<td>45</td>
<td>4.5</td>
<td>0.5</td>
<td>0.01</td>
</tr>
<tr>
<td>S6</td>
<td>2.50</td>
<td>45</td>
<td>4.5</td>
<td>0.5</td>
<td>0.01</td>
</tr>
<tr>
<td>S7</td>
<td>5.00</td>
<td>45</td>
<td>4.5</td>
<td>0.5</td>
<td>0.01</td>
</tr>
<tr>
<td>S8</td>
<td>10.00</td>
<td>45</td>
<td>4.5</td>
<td>0.5</td>
<td>0.01</td>
</tr>
<tr>
<td>S9</td>
<td>1.25</td>
<td>45</td>
<td>4.5</td>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>S10</td>
<td>2.50</td>
<td>45</td>
<td>4.5</td>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>S11</td>
<td>5.00</td>
<td>45</td>
<td>4.5</td>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>S12</td>
<td>10.00</td>
<td>45</td>
<td>4.5</td>
<td>0.5</td>
<td>0.1</td>
</tr>
</tbody>
</table>
After stirring for 24 hours, the sol-gel formulations were applied to aluminium alloy 2024 panels by a spin coating deposition process. The spin coating process relies on centrifugal force to coat the substrate and provides high quality uniform coatings. Using higher spin rates thinner coatings are produced so this method allows control over the coating thickness. The sol-gels were applied at a speed of 500 rpm for 40 seconds and cured for 1 hour at 100 °C. Another set of samples were prepared using the same condition but a higher spin rate of 1000 rpm.

Aluminium 2024 has a composition which roughly includes 4.3-4.5% copper, 0.5-0.6% manganese, 1.3-1.5% magnesium and less than 0.5% of silicon, zinc, nickel, chromium, lead and bismuth. Immediately prior to spin coating, the panels were treated with the cleaning process shown in Figure 6.4 to prepare the surface. This process removes any dirt or grease and activates the surface by formation of reactive hydroxyl groups that will enable the immobilisation of the hydrolysed and oligomeric MAPTMS species.

The sol-gel coated panels were subsequently coated with a layer of parylene N via the vapour deposition process outlined in Scheme 6.2.
6.3 Analysis

6.3.1 $^{29}\text{Si NMR spectroscopy}$

The $^{29}\text{Si}$ NMR method allows the level of hydrolysis and condensation of silicon containing species such as MAPTMS to be determined semi-quantitatively. Similar to the $^{13}\text{C}$ nuclei, $^{29}\text{Si}$ has a low isotopic abundance, approximately 4.7%. It also has a lower susceptibility to the technique because of its gyromagnetic ratio which is approximately five times lower than the hydrogen nuclei. The chemical shift of the silicon nuclei is dependent on the substituents around it so the various different stages in the sol-gel polymerisation can be identified. The chemical shifts of the $^{29}\text{Si}$ nuclei, as they relate to hydrolysis and condensation are presented in Table 6.2.\(^9\)

*Table 6.2: The relevant chemical shifts of the $^{29}\text{Si}$ species in sol-gel formulations.*\(^9\)

<table>
<thead>
<tr>
<th>Species</th>
<th>Notation</th>
<th>Chemical shift (ppm) $\pm$0.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSi(OMe)$_3$</td>
<td>$T_0^0$</td>
<td>-42.3</td>
</tr>
<tr>
<td>RSi(OMe)$_2$OH</td>
<td>$T_0^1$</td>
<td>-41.4</td>
</tr>
<tr>
<td>RSiOMe(OH)$_2$</td>
<td>$T_0^2$</td>
<td>-40.6</td>
</tr>
<tr>
<td>RSi(OH)$_3$</td>
<td>$T_0^3$</td>
<td>-40.1</td>
</tr>
<tr>
<td>RSi(OMe)$_2$O-Si</td>
<td>$T_1^0$</td>
<td>-49.9</td>
</tr>
<tr>
<td>RSi(OMe)OH-O-Si</td>
<td>$T_1^1$</td>
<td>-50.5</td>
</tr>
<tr>
<td>RSi(OH)$_2$O-Si</td>
<td>$T_2^0$</td>
<td>-49.3</td>
</tr>
<tr>
<td>RSi(OMe) – (O-Si)$_2$</td>
<td>$T_2^1$</td>
<td>-59.1</td>
</tr>
<tr>
<td>RSiOH-(O-Si)$_2$</td>
<td>$T_2^2$</td>
<td>-58.5</td>
</tr>
<tr>
<td>RSi(OSi)$_3$</td>
<td>$T_3$</td>
<td>-67.4</td>
</tr>
</tbody>
</table>
The formulations tested using this technique were S4, S8 and S12 as these had the highest concentration of MAPTMS and would provide the clearest spectra (Figure 6.5). The spectra were taken 24 hours after preparation of the sol-gel solutions and the chemical shifts are calibrated to the internal standard tetramethylsilane (TMS) at 0 ppm. S4 was prepared using no HNO₃ and the lack of an acidic environment should lead to little or no hydrolysis and no condensation. This is what is observed in the $^{29}$Si NMR spectrum with the single peak at -42.2 ppm indicating only the $T_0^0$ species. S8 in contrast, prepared with 0.01M HNO₃, shows no $T_0^0$ but a dominant signal at -40.6 ppm indicating the hydrolysed species $T_0^2$. This sample also presents a signal at -49.7 ppm indicating the oligomeric $T_1^0$ species. The signal at -43.4 ppm was not identified. The final sample S12, prepared with 0.1M HNO₃, has its most significant signal at -49.7 ppm, again indicative of the $T_1^0$ species. The signal at -59.0 ppm indicates the more heavily condensed $T_2^0$ species and the $T_0^2$ species appears again at -40.7 ppm. This data agrees with the expected trend in that an increase in acidity leads to more advanced degrees of hydrolysis and then condensation.
6.3.2 Infrared spectroscopy

IR spectra were recorded for selected sol-gels as applied to the aluminium 2024 panels before the parylene N coating was applied (Figure 6.6). An increase in absorption band intensities in the 800-1100 cm\(^{-1}\) region is indicative of a thicker coating, as seen most prominently in S12. This area represents the silicate network and contains several species such as various silanol stretches (Si-OH, 950 cm\(^{-1}\)) and the Si-O-Si stretches (1000-1100 cm\(^{-1}\)). This is what is expected as higher concentrations of acid lead to increased hydrolysis and condensation of alkoxy silanes, resulting in more condensed, thicker coatings.
6.3.3 Adhesion Testing

Adhesion testing is used in industry to determine if a coating will adhere efficiently to a given substrate. The most common method for adhesion testing is the cross hatch measurement. This measurement is taken by making 12 equally spaced cuts into the coating, down to the substrate, in a crosshatch pattern. At this point any detached fragments of the coating are removed with light brushing and a single piece of pressure sensitive tape is applied across the incisions. The tape is removed in one rapid motion and can then be discarded. The adhesion of the coating is then graded from 0B to 5B based on the level of delamination as shown in Figure 6.7.10

Figure 6.6: IR spectra of applied sol-gel formulations before parylene N deposition.
As mentioned previously, the standard industrial approach for the pre-treatment of aluminium 2024 panels to be coated in parylene N is to add MAPTMS directly into the chamber. This is done by placing an absorbent which has soaked up MAPTMS in with the panels and when the chamber is placed under vacuum the MAPTMS is dispersed. This approach can give coatings which score 3B using the cross hatch measurement. However there may be significant batch variation based on the location the absorbent is placed indicating that the distribution of MAPTMS is not reliable.

The adhesion results of the pre-treatment formulations shown in Table 6.3 indicate that thinner sol-gel pre-treatments are better adhesion promoters than their thicker counterparts. In all cases the adhesion promoters applied at 1000 rpm, which result in thinner coating layers, perform the same or better than their thicker counterparts deposited at 500 rpm. A general trend is also observed in increasing the acid concentration. Samples S1-S4 perform better than S5-S8 which in turn perform better than S9-S12. The concentration of MAPTMS in the sol affects the adhesion in some cases such as S1-S4 at 500rpm and S9-S12 at 1000rpm. However in S5-S8 at 500 rpm and S1-S4 at 1000 rpm it shows no apparent effect on the adhesion, hence no clear conclusion can be drawn about the effect of varying the MAPTMS concentration. In comparison to the standard industrial method every sample, with the exception of S12 performed as well or better.
Table 6.3: The cross hatch test results of the pre-treatment formulations used on aluminium 2024 panels coated with parylene N.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Classification (500 rpm)</th>
<th>Classification (1000 rpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>4B</td>
<td>5B</td>
</tr>
<tr>
<td>S2</td>
<td>5B</td>
<td>5B</td>
</tr>
<tr>
<td>S3</td>
<td>3B</td>
<td>5B</td>
</tr>
<tr>
<td>S4</td>
<td>3B</td>
<td>5B</td>
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<td>S5</td>
<td>3B</td>
<td>5B</td>
</tr>
<tr>
<td>S6</td>
<td>3B</td>
<td>4B</td>
</tr>
<tr>
<td>S7</td>
<td>3B</td>
<td>5B</td>
</tr>
<tr>
<td>S8</td>
<td>3B</td>
<td>4B</td>
</tr>
<tr>
<td>S9</td>
<td>3B</td>
<td>4B</td>
</tr>
<tr>
<td>S10</td>
<td>3B</td>
<td>3B</td>
</tr>
<tr>
<td>S11</td>
<td>3B</td>
<td>3B</td>
</tr>
<tr>
<td>S12</td>
<td>1B</td>
<td>2B</td>
</tr>
</tbody>
</table>

6.4 Conclusion

A series of sol-gel formulations were prepared and applied to aluminium 2024 panels as pre-treatments for the application of parylene N coatings. The formulations were designed to yield successively more hydrolysed and condensed sol-gel systems and this was supported by the $^{29}$Si NMR analysis. The pre-treatments also showed a successive increase in thickness and this was shown by IR spectroscopy. The adhesion capability of the coatings was assessed by the cross hatch measurement and the general trend showed that thinner sol-gels coatings were
better pre-treatments than their thicker counterparts. Of the 24 samples prepared 22 showed comparable or better adhesion performance in comparison to the industrial benchmark.
6.5 References


7.0 Sol-gel Coating Additives

7.1 Introduction

The preparation of a range of additives for sol-gel coatings was briefly investigated. The additives are intended to be used in the production of hydrophobic sol-gel coatings. Two distinct classes of materials were prepared for this purpose, fluorinated triethoxysilane precursors and fluorinated mesoporous silicate particles. Following this there was also a brief investigation into the addition of organic dyes to hybrid sol-gel formulations. These hybrid sol-gels are prepared with a mixture of silicon and zirconium alkoxides. Molecular interactions between these materials and a dye molecule can impact the physicochemical properties of the dye and this was explored here.

7.2 Hydrophobic surfaces and fluorocarbons

Surface hydrophobicity is the property of a surface which makes it water repellent or difficult to wet. This property has long been recognised as important in self-cleaning technologies and was initially observed in nature, called the Lotus effect, in reference to the leaves of the Lotus flower. When water comes into contact with the Lotus leaf surface it remains in a spherical bead rather than spreading out evenly to wet the surface. This is a measurable property based on the angle of the water bead to the surface, known as contact angle.¹ A perfectly hydrophobic surface will have a contact angle of 180°, so all surfaces will have contact angle values between 180° and 0°. This phenomenon can be attributed to a combination of physical and chemical properties of the surface. In the case of the Lotus leaf, the structure of Papillae, which are protrusions from the leaf surface, create surface roughness which produces a hydrophobic effect. This is because the material at the micrometre level is biphasic where it makes contact with the water, consisting of air which has a contact angle of 180° and the papillae. The contact angle on this surface can then be described using Cassie’s law which
describes the effective contact angle of a liquid on a composite surface. A successful use of this effect is the nanopin film. This material is covered with nanoscale cone structures perpendicular to a borosilicate glass substrate and yields a contact angle of 178°, only 2° below the maximum possible value for contact angle. Of greater interest here however, are the chemical properties of surfaces, and again, in the case of the Lotus leaf, the surface is covered in a waxy substance which is primarily long chain hydrocarbons. Such hydrocarbons are non-polar molecules and will repel water, thus making it energetically favourable for the water bead to stay in a spherical shape with the minimal surface contact.

Much work has been done in creating hydrophobic surfaces for different applications. As such, many publications have reported fabrication methods such as vapour and particle deposition, plasma treatments and sol-gel methods. A common motif in many reports is the use of hydrophobic fluorocarbons, compounds composed primarily and sometimes exclusively of carbon and fluorine. The C-F bond is so polar that it possesses a degree of ionic character and the hold of fluorine on the electrons is so strong that they have a very limited ability to form the transitory dipoles necessary for Van der Waals forces. In fact, fluorine has the lowest polarisability of any element. It is this characteristic that accounts for fluorocarbon’s hydrophobicity. A water droplet on a coating surface will adopt the most favourable energetic arrangement and it is desirable to maintain the maximum amount of hydrogen bonding and limit the free or hydroxyl groups, keeping the droplet intact. Van der Waals forces can destabilise this network and interact with the water leading to surface wetting. Fluorocarbons, both alkyl and aryl, are also very stable compounds due to the strength of the C-F bond which may be above 500 KJ mol⁻¹. This is due to the partial ionic character of the bond which shortens the bond length and provides favourable coulombic interactions. Additionally, having geminal C-F bonds adds further stability by increasing the
carbon’s partial charge and multiple C-F bonds can increase the strength of the molecules carbon backbone via the inductive effect.

### 7.3 Preparation of fluorinated sol-gel additives

#### 7.3.1 Synthesis of fluorinated triethoxysilanes

Silylation is a broad term used in organic synthesis to describe the addition of a silicon containing group to a molecule, usually a substituted silyl group. This type of reaction is most commonly utilised in protecting group chemistry however it also provides the most straightforward route to the preparation of sol-gel precursors in the form of alkoxysilanes. The aryl silylation shown in Scheme 7.1 was carried out to prepare several derivatives with varying levels of fluorination. The products were isolated in yields up to 34% via vacuum distillation and the mono and trifluoro derivatives have not been previously reported. This purification method was chosen because alkoxy silanes are not generally amenable to chromatography as they may irreversibly bind to silica.

**Scheme 7.1: The synthesis of fluorophenyl triethoxysilanes.**

In the case of the perfluoro derivative 1, it was isolated as a mixture with the by-product 2 (Scheme 7.2). Attempts to separate these two compounds were not successful.
Scheme 7.2: The synthesis of perfluorophenyl triethoxysilane and a disubstituted by-product.

The other approach to aryl silylation is the use of transition metal catalysts, mainly palladium and rhodium. This has been demonstrated in several reports via the coupling of triethoxysilane and various aryl halides.\textsuperscript{7–9} It has been shown to be an effective method with both activating and deactivating substituents including some fluorinated analogues.\textsuperscript{10,11} However, no trifluoro or pentafluoro analogues have been synthesised by this method.

7.3.2 Synthesis of fluorinated mesoporous silicates

Mesoporous silicates (MPS) are silica particles that contain pores or cavities. They have a variety of applications such as catalysis, sensors and molecular filters.\textsuperscript{12–15} They are prepared by using a template which the precursor molecules, in this case tetraethyl orthosilicate (TEOS), condense around (Figure 7.1). The template used here is the surfactant cetyltrimethylammonium bromide (CTAB), which forms micelles in solution. Once the MPS have been formed the template is removed and this may be done thermally or chemically.
In the procedure developed here the MPS are functionalised as they form by the addition of a fluorinating agent to the reaction mixture. The fluorinating agent used is \( \text{1H,1H,2H,2H-perfluorooctyl triethoxysilane} \) (PFOTS) and this is incorporated into the silicate network (Scheme 7.3). Microwave heating is utilised which rapidly forms the MPS. The solvent is evaporated and the resulting solid is dried. This solid is then heated at reflux in a mixture of methanol and HCl to yield the final fluorinated MPS. This is the chemical method of removing the template. As mentioned previously, the template can also be removed thermally, by placing the particles in a furnace and heating to approximately 500 °C for several hours. This option is unsuitable here because it would also remove the fluorocarbon chains.

**Figure 7.1: General preparation process for mesoporous silicates.**
Fluorinated MPS were prepared in quantities up to 50 g. The particles themselves are relatively uniform in size usually ranging from 400-500 nm as shown in scanning electron microscope (SEM) images (Figure 7.2).

Using energy-dispersive X-ray spectroscopy (EDX), an elemental map of the surface can be acquired. This has been used qualitatively in this case to confirm the presence of fluorine. The maps also show silicon and oxygen which are the component atoms of the silicate (Figure 7.3).
Dye doped hybrid sol-gels

Hybrid sol-gels are prepared from a mixture of silicon and transition metal alkoxide precursors. Here, hybrid sol-gel materials were prepared from MAPTMS and zirconium (IV) propoxide (ZPO) along with the incorporation of an organic dye. The dye selected was trypan blue (TB) and this is commonly used as a biological stain. It is a heavily conjugated azo dye, and as the name suggests, it has a strong blue colour (Figure 7.4). The prepared hybrid sol-gels and coatings prepared from them were examined by transmission electron microscopy (TEM), IR and UV-Vis spectroscopy.

Figure 7.4: The structure of trypan blue dye.
7.4.1 Coating preparation and formulation

The formulations described in Table 7.1 were used to prepare stable, homogenous hybrid sol-gels. These formulations differ only in the concentration of methacrylic acid (MAAH). This material behaves as a bi-dentate ligand and complexes the zirconium centre. This chelation affects the subsequent hydrolysis and condensation reactions that occur in the sol-gel and results in significant morphological changes in the final materials. This effect will be discussed in detail in the following sections.

Table 7.1: Hybrid sol-gel formulations\(^{[a]}\).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>MAPTMS</th>
<th>ZPO(^{[b]})</th>
<th>Dye(^{[c]})</th>
<th>H(_2)O</th>
<th>0.1M HNO(_3)</th>
<th>MAAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>15.00/60</td>
<td>7.07/15</td>
<td>0.15/0.15</td>
<td>1.26/70</td>
<td>0.80/0.08</td>
<td>1.31/15</td>
</tr>
<tr>
<td>B</td>
<td>15.00/60</td>
<td>7.07/15</td>
<td>0.15/0.15</td>
<td>1.26/70</td>
<td>0.80/0.08</td>
<td>0.33/4</td>
</tr>
<tr>
<td>C</td>
<td>15.00/60</td>
<td>7.07/15</td>
<td>0.15/0.15</td>
<td>1.26/70</td>
<td>0.80/0.08</td>
<td>----</td>
</tr>
</tbody>
</table>

\(^{[a]}\) All values are given in the format grams/millimoles (g/mmol). \(^{[b]}\) Provided as a 70% wt. in propanol. \(^{[c]}\) 1 mol% with respect to zirconium.

The procedure for preparing these hybrid sol-gels is illustrated in Figure 7.5. In one vessel the ZPO, dye and the MAAH are mixed for 45 minutes. This allows chelation of the zirconium centre to occur. Concurrently the MAPTMS and HNO\(_3\) are mixed in a separate vessel. This is referred to as pre-hydrolysis and converts the MAPTMS ethoxy groups to hydroxyl groups. The pre-hydrolysed solution is then slowly added to the chelated solution. After 3 minutes water is added and an exothermic reaction is observed. After 24 hours stirring the hybrid sol-gels are ready to be coated onto an appropriate substrate. In this case they were applied to glass and aluminium substrates by a spin coating process at a rate of 1000 rpm for 40 seconds. The samples were then cured at varying temperatures.
Figure 7.5: Procedure for the preparation of dye doped hybrid sol-gels.

7.4.2 Structural characterisation of hybrid sol-gels

7.4.2.1 Transmission electron microscopy

Figure 7.6 shows TEM images of the three formulations. A progressive increase in the particle size is observed as the degree of chelation of the zirconium atom is decreased. For A, most of the particles are in the nanometre scale (<10 nm). The TEM image of B indicates that it is relatively homogeneous and dense with a particle size varying from 10 to 200 nm. However, the particle size of C is in the micron range with an apparent gradual decrease in the density from the centre to the surface, as observed by the change in the contrast of the image of the particle. These observations suggest that the formulation of these 3 materials has a direct impact on the reactivity of the hybrid systems to hydrolysis and condensation reactions, as well as on the subsequent structure and morphology of the formed particles. This has been identified in previous studies in catalysing the formation of siloxane bonds and participating to the formation of the inorganic backbone of the material.¹⁶–¹⁸
Figure 7.6: TEM images of hybrid sol-gel formulations A, B and C respectively (Provided by M. Oubaha).

The only variable here is the concentration of MAAH and hence, the degree of chelation of the zirconium centre. In A the ligand is added in a stoichiometric amount with respect to zirconium so only 50% of propoxide groups can undergo hydrolysis and condensation. In B it is 75% of propoxide groups and in C all propoxide groups are available. So it can be definitively stated that the availability of the zirconium centre to participate in condensation reactions significantly impacts the structure of the hybrid sol-gels.

7.4.2.2 Infrared spectroscopy

IR spectroscopy may provide information about the nature of the chemical bonding in the surface coatings prepared from the formulations. Figure 7.7 shows the spectra of the formulations applied to aluminium substrates. The absorption bands have been identified based on the results presented in other studies.\textsuperscript{19–21} The broad band located at 800–1100 cm\textsuperscript{-1} is characteristic of the silicate network resulting here mainly from the superimposition of the Si-OH vibration (950 cm\textsuperscript{-1}), Si-O-Si and Si-O-Zr vibrations (1000–1100 cm\textsuperscript{-1}). The Zr-OH and Zr-O-C bonds composing the zirconium complex are located in the region 1300–1650 cm\textsuperscript{-1}. The bands located at 1730, 2800–3000 and 3200–3600 cm\textsuperscript{-1} are due to the C=O (stretching), C-H (stretching) and residual Si-OH and Zr-OH groups (stretching), respectively. The intensities of the chemical vibrations due to the zirconium complex located
at 1300–1650 cm\(^{-1}\) are clearly seen to decrease along with the MAAH concentration. There is a corresponding increase in intensity at approximately 1100 cm\(^{-1}\), again corresponding to Si-O-Zr vibrations.

![IR spectra](image)

**Figure 7.7**: IR spectra of the formulations coated on an aluminium substrate and cured at 100 °C.

### 7.4.3 Photophysical changes of trypan blue

The UV–Vis absorption spectrum of TB dispersed in isopropanol is shown in Figure 7.8. The dye exhibits one large band composed of two superimposed bands located in the 400–600 nm region and a large absorption extending from around 300-350 nm. TB is a symmetrical molecule that contains unsaturated and conjugated C=C and N=N bonds, in addition to amino, hydroxyl and sulfonyl groups. The absorption domain above 400 nm can be attributed to the n→\(\pi^*\) electronic transitions of the amino, hydroxyl and sulfonyl groups. The absorption domain below 400 nm can be attributed to the \(\pi→\pi^*\) electronic transitions of the unsaturated C=C and N=N bonds.
When incorporated into the 3 formulations, the $\lambda_{\text{max}}$ of the dye absorption is red shifted in all cases. The initial $\lambda_{\text{max}}$ of 610 nm is found to be 624, 620 and 617 in formulations A, B and C respectively (Figure 7.9). The smaller particles in the most heavily condensed networks (A) provide the greatest red shift and this decreased along with the chelation in B and C.
What is also observed is a progressive decrease in the absorption intensity with the decrease in particle size (or the increase in chelation) so that absorption for A is lower than B which is lower than C. This trend follows the particle size (or the increase in chelation) so suggests that the more heavily condensed networks do not interact with the dye molecules to as great an extent. A possible coordination of the dye is shown in Figure 7.10. This would explain the decrease in the $n\rightarrow\pi^*$ electronic transitions. It is suggested that this process is happening almost completely in formulation A hence the weak absorption in that spectral region.

Figure 7.10: The proposed binding of dye molecules and the zirconium network.
When formulation C is applied to the substrate and cured at different temperatures it affects both the $\lambda_{\text{max}}$ and absorption intensity of the dye (Figure 7.11). When the curing temperature is increased from 100 °C to 120 °C the $\lambda_{\text{max}}$ is blue shifted from 617 to 613 nm. On increasing the curing temperature to 150 °C the $\lambda_{\text{max}}$ is further blue shifted to 588 nm. This curing temperature also shows a significant increase in absorption in $\pi\rightarrow\pi^*$ region of 300-400 nm. Each successive increase in curing temperature gives reduced absorption in the $n\rightarrow\pi^*$ region indicating more coordination of the dye and the zirconium centre. Presently no explanation is offered for the blue shifting of the $\lambda_{\text{max}}$ between samples.

![Figure 7.11: UV-vis absorption spectra of formulation C coated on glass substrates at three different curing temperatures.](image)

**Figure 7.11: UV-vis absorption spectra of formulation C coated on glass substrates at three different curing temperatures.**

### 7.5 Conclusion

A range of fluorinated aryl triethoxysilanes were prepared in yields up to 34% for application in hydrophobic surface coatings. Fluorinated MPS were also prepared for the same application and these were evaluated to show that they had been successfully fluorinated.
Finally, the addition of a dye in hybrid silicon-zirconium sol-gels was investigated. Manipulation of the coating morphology was demonstrated by using varying concentrations of chelating ligand. This morphology subsequently altered the physicochemical properties of the dye, both the UV-vis absorption intensity and $\lambda_{\text{max}}$ values.
7.6 References


8.0 Conclusions and Future Work

This chapter summarises the outcomes of this thesis and details suggestions for future work and further development of certain aspects of the work.

8.1 Preparation of asymmetric ligands based on [2.2]paracyclophane

The aim of the work with regard to [2.2]paracyclophane (Pc) was to prepare novel asymmetric ligands based on the Pc framework. To begin, the Pc framework was functionalised and 5 monosubstituted analogues were successfully prepared. Subsequent functionalisation garnered 4 disubstituted derivatives, two of which have not been previously reported. Attempts were made at the resolution of two selected monosubstituted derivatives, namely the amino and bromo analogues. The amino derivative was resolved but the yields were not satisfactory at 5%. The bromo derivative was successfully resolved using a novel procedure and proceeded in a moderate yield of 35%. A range of 7 phenyl-oxazoline compounds were prepared via the Witte-Seeliger reaction, two of which have not been previously reported. A selection of these analogues were coupled to the Pc framework via the palladium catalysed Buchwald-Hartwig amination. Column chromatography and recrystallisation allowed a one-pot synthesis and resolution procedure which garnered two novel enantiopure ligands. These compounds were characterised and X-Ray crystallography allowed determination of the absolute configuration of one of the ligands. The yields however were not satisfactory at <10% so alternative synthetic routes were investigated. This did not prove successful in the preparation of the desired ligands but did afford another previously unreported Pc analogue.

Further work should first be aimed at increasing the yields of the final Buchwald-Hartwig coupling. It is suggested that microwave heating, as shown in Scheme 8.1, may provide improved yields along with shorter reaction times. Toluene is not an ideal solvent for
microwave assisted reactions because of its low susceptibility to microwave heating. The structurally similar trifluoromethylbenzene (or benzotrifluoride, BTF) is more efficiently heated by this method and has been shown to provide increased yields, as well as significantly shorter reaction times, in comparison to thermal heating using toluene.\textsuperscript{1,2} Increased yields when using microwave heating has been demonstrated previously in the Buchwald-Hartwig coupling of phenyl-oxazolines.\textsuperscript{3} If successful this may then be extended to other analogues.

Scheme 8.1: Proposed microwave assisted route for the optimisation of ligand synthesis.

Another approach would be the use of thiophene-oxazoline compounds for coupling. Such derivatives have been prepared previously and may be more amenable for coupling to the Pc framework to prepare asymmetric Pc ligands.\textsuperscript{4} The routes presented in Scheme 8.2 may afford these ligands.
Once a suitable procedure for the preparation of these ligands is established the next course of action is to model their ability to bind metals. The best way to model this would be to isolate the ligand-metal complexes and obtain their crystal structures for study. The suggested metals for this are palladium and zinc. These metals are used in reactions of interest such as the asymmetric addition of diethyl zinc to aldehydes and asymmetric allylic alkylations.

## 8.2 Preparation of asymmetric ligands based on octafluoro[2.2]paracyclophane

Two synthetic routes were investigated towards the preparation of octafluoro[2.2]paracyclophane (OPc). The first route was a two-step synthesis beginning with a silylation followed by a fluoride catalysed 1,6 elimination. This final step allowed isolation of OPc in 18%. The other synthetic route consisted of three steps beginning with the...
preparation of germinal difluoride from an aldehyde and a subsequent radical chlorination. The final step was a zinc catalysed \textit{homo}-coupling which was reported to garner OPc in yields up to 60%. However, this procedure could not be reproduced here. Different batches of zinc and several washing procedures for the catalyst were utilised with no success. A recent patent reports this reaction but with an additional additive included. A large range of additives were tested and KI proved the most efficacious garnering OPc in 46\%.\textsuperscript{5} This method may be useful for a higher yielding synthesis of OPc.

The OPc prepared was subsequently nitrated and reduced to the corresponding amine. This material was utilised in the Buchwald-Hartwig amination along with an iodo phenyl-oxazoline, however none of the desired product was detected. It is proposed that if a system for the preparation of the hydrocarbon Pc analogues is optimised that this be extended to the OPc framework.

### 8.3 Parylene coating pre-treatment and adhesion promotion

A series of sol-gel formulations were prepared and used as pre-treatments for aluminium substrates. The sol-gel formulations were characterised by \textsuperscript{29}Si NMR to show the difference in the extent of hydrolysis and condensation which had occurred. IR spectroscopy was carried out on the pre-treated aluminium substrates and a progressive increase in coating thickness was shown. These substrates were subsequently coated in parylene N and the adhesion of the parylene was assessed using the cross hatch measurement. In all formulations, with the exception of one, the parylene coatings showed better adhesion than the industrial benchmark. Generally it was found that thinner sol-gel coatings were better pre-treatments than their thicker counterparts. This pre-treatment method should also allow better reproducibility over a large number of samples. Future investigations in this area should be aimed at optimising adhesion on other substrates. Parylene coatings have a wide variety of
applications so effective pre-treatments for different substrates would be industrially valuable.

8.4 Sol-gel coating additives

Two classes of fluorinated additives were prepared, intended to be used in the preparation of hydrophobic sol-gel coatings. These were three fluorinated aryl triethoxysilanes, two of which have not been previously reported, and fluorinated mesoporous silicate particles. The fluorinated silanes were prepared via a modified Grignard reaction and isolated by vacuum distillation. The fluorinated particles were prepared using a modified microwave assisted Stöber process. The particles were characterised with SEM imaging and EDX spectroscopy.

The incorporation of the dye trypan blue into hybrid sol-gel formulations, prepared from silicon and zirconium precursors, was also briefly investigated. It was shown that the addition of varying amounts of a chelate could alter the size of particles formed in the sol-gel. These varied from 10 nm to 1 micron in size as shown in TEM imaging. The organic dye demonstrated molecular interactions with the zirconium centre and these interactions were shown to be affected by the particle size. Changes in the UV-Vis absorption spectra in both the absorption intensity and $\lambda_{\text{max}}$ values were found across the formulations. It is proposed that smaller particle sizes result in more efficient interaction of the dye species with the zirconium centre. It was found curing temperatures also impacted the UV-Vis absorption of the dye, and that higher curing temperatures led to a decrease in absorption. Again, this implies more efficient interaction of the dye and the zirconium centre. Future work could examine the use of different metals such as titanium and tantalum and also different organic dyes. Coloured sol-gel coatings are industrially desirable for simple aesthetics however coatings with tuneable optical properties may have applications.
8.5 References


9.0 Experimental

9.1 General experimental

$^1$H NMR (400 MHz), $^{19}$F NMR (376 MHz), $^{13}$C NMR (100 MHz) and $^{29}$Si NMR (79 MHz) spectra were recorded on a Bruker Avance 400 MHz spectrometer at room temperature in deuterated solvents using tetramethylsilane as an internal standard. Chemical shifts (δ) are given in parts per million and coupling constants are given as absolute values in Hertz. Infrared spectra were recorded on a Perkin Elmer Spotlight 400N FT-IR. UV-vis spectra were recorded on a Perkin Elmer Lambda 900 UV/VIS/NIR spectrometer. UV-vis spectra were collected both in the solution phase using plastic cuvettes and in solid phase as coatings on glass slides (coating procedure described in section 7.4.1). Mass spectra were collected using a Maldi-Q-TOF premier mass spectrometer. SEM images were obtained on a Hitachi SU-70 field emission scanning electron microscope. X-ray crystal structures were taken using a Rigaku Saturn-724 instrument. Melting points were determined in open capillary tubes in a Stuart melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was carried out on aluminium sheets pre-coated with silica gel 60 F254 (Sigma). Column chromatography separations were performed using Davisil LC60A (0.035-0.070 mm). All reagents and solvents were purchased from Sigma-Aldrich and Apollo Scientific and used as received unless otherwise stated. Oxygen free argon was obtained from BOC gases and was used as received.
9.2 Monosubstituted [2.2]paracyclophanes

9.2.1 \((\text{rac})-4\)-Bromo[2.2]paracyclophane

A solution of [2.2]paracyclophane (5.00 g, 24 mmol) and iron powder (0.34 g, 6 mmol) in DCM (250 ml) was stirred for one hour at room temperature. To this was added bromine (3.84 g, 24 mmol) and the mixture was heated at reflux for 20 hours. The organic phase was washed with 10% Na$_2$S$_2$O$_3$ (2 x 100 ml), water (100 ml), dried over MgSO$_4$ and the solvent removed in vacuo to yield the title compound as a white solid (6.61 g, 96%); mp = 134-136 °C; R$_f$ = 0.55 (8:2 Cy/DCM); $^1$H NMR (400 MHz, CDCl$_3$): δ = 7.16 (dd, $J = 8$, 1.6, 1H), 6.44-6.57 (m, 6H), 3.45 (ddd, $J = 15.6$, 10, 2, 1H), 2.78-3.23 (m, 7H); $^{13}$C NMR (100 MHz): δ = 141.6, 139.6, 139.3, 139.1, 137.3, 135.1, 133.3, 132.9, 132.3, 131.5, 128.7, 127.0, 35.7, 35.5, 34.8, 33.5; IR: 2923, 1586, 1493, 1391, 1035 cm$^{-1}$ (See Section 3.2.1 and Appendix 1-3).

9.2.2 \((\text{rac})-4\)-Formyl[2.2]paracyclophane

A solution of [2.2]paracyclophane (4.52 g, 22 mmol) in DCM (200 ml) was cooled to 0 °C. To the solution was added TiCl$_4$ (8.30 g, 44 mmol) followed by dichloromethoxymethane (2.54 g, 22 mmol). The mixture was warmed to room temperature and stirred for 20 hours. Water (100 ml) was added to the mixture and stirring was continued for 3 hours. The phases were
then separated and the aqueous phase was washed with DCM (100 ml). The combined organic phases were dried over MgSO$_4$ and the solvent removed in vacuo. The title compound was isolated by flash column chromatography as a white solid (3.28 g, 63\%); decomp. = 142-144 °C (151-152 °C)$^1$; $R_f = 0.57$ (9:1 Cy/EtOAc); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 9.94$ (s, 1H), 7.01 (d, $J = 2$, 1H), 6.73 (dd, $J = 8$, 2, 1H), 6.59 (d, $J = 8$, 1H), 6.56 (dd, $J = 8$, 2, 1H), 6.50 (dd, $J = 8$, 2, 1H) 6.43 (dd, $J = 8$, 2, 1H), 6.37 (dd, $J = 8$, 2, 1H), 4.07-4.13 (m, 1H), 2.91-3.30 (m, 7H); $^{13}$C NMR (100 MHz): $\delta = 192.0$, 143.3, 140.7, 139.5, 139.4, 138.1, 136.6, 136.4, 136.1, 133.3, 132.9, 132.4, 132.2, 35.3, 35.2, 35.0, 33.7; IR: 2925, 2855, 1676, 1589, 1226, 1143 cm$^{-1}$ (See Section 3.2.2 and Appendix 4-6).

**9.2.3 (rac)-4-Hydroxy[2.2]paracyclophane**

![Diagram of (rac)-4-Hydroxy[2.2]paracyclophane](image)

To a solution of 4-formyl[2.2]paracyclophane (1.00 g, 4.2 mmol) in MeOH/DCM (40 ml) was added conc. H$_2$SO$_4$ (0.10 g, 1 mmol) and 30\% H$_2$O$_2$ (0.67 g, 6 mmol). This mixture was stirred at room temperature for 20 hours. The solvent was evaporated and the residue dissolved in DCM (50 ml) and washed with water (50 ml). The aqueous phase was washed again with DCM (50 ml) and the combined organic phases were dried over MgSO$_4$. The solvent was removed in vacuo and the title compound was isolated by flash column chromatography as an orange solid (0.52 g, 55\%); decomp. = 224-227 °C (lit. 229-232 °C)$^2$; $R_f = 0.37$ (9:1 Cy/EtOAc); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.00$ (dd, $J = 8$, 2, 1H), 6.55 (dd, $J = 8$, 2, 1H), 6.44 (dd, $J = 8$, 2, 1H), 6.37-6.40 (m, 2H), 6.25 (dd, $J = 8$, 2, 1H), 5.54 (d, $J = 2$, 1H), 4.42 (s, 1H), 3.29-3.36 (m, 1H), 2.86-3.11 (m, 6H), 2.61-2.69 (m, 1H); $^{13}$C NMR (100 MHz): $\delta = 153.7$, 142.0, 139.6, 138.8, 135.5, 133.6, 132.8, 131.9, 127.9, 125.4, 125.0, 122.6,
35.3, 34.8, 33.8, 31.1; IR: 3416, 2921, 2849, 1566, 1493, 1416, 1087 cm\(^{-1}\) (See Section 3.2.3 and Appendix 7-9).

9.2.4 (\textit{rac})-4-Nitro[2.2]paracyclophane

\[
\begin{array}{c}
\text{C}_5\text{H}_9\text{NO}_2
\end{array}
\]

A mixture of [2.2]paracyclophane (20.00 g, 96 mmol) in AcOH (300 ml) was heated to 90 °C. The solution was allowed to cool to 70 °C and fuming HNO\(_3\) (30 ml, 720 mmol) was carefully added in one portion. The mixture was stirred for approximately 45 seconds and immediately poured onto ice. The aqueous phase was extracted with DCM (3 x 150 ml). The combined organic phases were washed with 1M NaOH (3 x 250 ml), dried over MgSO\(_4\) and the solvent was removed \textit{in vacuo} and the title compound was isolated by flash column chromatography as a pale yellow solid (6.56 g, 27 %); mp = 154-155 °C (156-157 °C); \(R_f = 0.30\) (7:3 Cy/DCM); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.22\) (s, 1H), 6.79 (d, \(J = 8\), 1H), 6.54-6.63 (m, 4H), 6.48 (d, \(J = 8\), 1H), 4.00-4.06 (m, 1H), 3.03-3.25 (m, 6H), 2.85-2.94 (m, 1H); \(^{13}\)C NMR (100 MHz): \(\delta = 142.1, 139.8, 139.3, 137.8, 137.4, 136.5, 133.2, 133.1, 132.4, 130.0, 129.6, 36.0, 35.0, 34.8, 34.5\); IR: 2923, 1735, 1513, 1331 cm\(^{-1}\) (See Section 3.2.4 and Appendix 10-12).

9.2.5 (\textit{rac})-4-Amino[2.2]paracyclophane

\[
\begin{array}{c}
\text{C}_5\text{H}_9\text{NH}_2
\end{array}
\]
A solution of 4-nitro[2.2]paracylophane (3.00 g, 11.8 mmol) in H₂O/EtOH (150 ml) was stirred for 30 minutes followed by the addition of iron powder (1.80 g, 32 mmol). The mixture was heated to reflux and conc. HCl (20 ml) was added over 5 minutes. The temperature was maintained for 1 hour after which time the mixture was poured onto ice and 1M NaOH (300 ml). The mixture was extracted with DCM (3 x 40 ml), dried over MgSO₄ and the solvent removed in vacuo to yield the title compound as a yellow solid (2.19 g, 83%); decomp. = 227-230 °C (lit. 239-242 °C); Rₓ = 0.43 (8:2 Cy/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 7.16 (dd, J = 8, 2, 1H), 6.58 (dd, J = 8, 2, 1H), 6.38 (dd, J = 8, 2, 2H), 6.26 (d, J = 8, 1H), 6.12 (dd, J = 8, 2, 1H), 5.39 (d, J = 2, 1H), 3.57 (s, 2H), 2.91-3.16 (m, 6H), 2.78-2.86 (m, 1H), 2.60-2.71 (m, 1H); ¹³C NMR (100 MHz): δ = 144.8, 141.1, 139.0, 138.9, 135.3, 133.5, 132.4, 131.5, 126.8, 124.6, 123.0, 122.3, 35.4, 35.0, 33.0, 32.3; IR: 3463, 3382, 2920, 2849, 1735, 1611, 1498, 1425 cm⁻¹ (See Section 3.2.5 and Appendix 13-15).

9.2.6 (Rₓ)-4-Amino[2.2]paracyclophane

To a stirred solution of 4-amino[2.2]paracyclophane (2.50 g, 11.2 mmol) in EtOAc (80 ml) was added (1S)-(+)10-camphorsulfonic acid (2.50 g, 11 mmol), and the mixture was kept at 0 °C for 4 days. After filtration, the resulting solid was poured into fresh ethyl acetate (35 ml) and stirred for 3 days at room temperature. The last treatment was then repeated. The salt was filtered and treated with 0.1 M NaOH to give (Rₓ)-4-amino[2.2]paracyclophane (0.12 g, 5%). NMR data was in agreement with that collected for the racemate (See Section 3.4.1 and Appendix 22).
**9.2.7 4-(4-Tolylsulfinyl)-[2.2]paracyclophane**

\( n\text{-BuLi (2.5 M in hexanes, 13.3 ml, 33.25 mmol) was added dropwise to a solution of 4-bromo[2.2]paracyclophane (9.08 g, 31.6 mmol) in dry THF (175 ml) at -78 °C under argon. The resulting solution was stirred for 2 hours and then a solution of (1R,2S,5R)-(-)-menthyl(S)-\( p \)-toluenesulfinate (9.80 g) in dry THF (175 ml) was added, maintaining a temperature of -78 °C. The solution was slowly warmed to room temperature over 24 hours. Saturated NH\(_4\)Cl (150 ml) was added to the solution and the organic phase was extracted. The aqueous phase was further extracted with Et\(_2\)O (3 x 150 ml) and the combined organic phases dried over Mg\(_2\)SO\(_4\). The solvent was removed in vacuo and the resulting residue purified by flash column chromatography (19:1 petrol/EtOAc) to give the title compounds (See Section 3.4.2).**

\( (S\_P S)-4-(4-Tolylsulfinyl)-[2.2]paracyclophane: \) white solid (3.00 g, 26%); mp = 153-158 °C (lit. 148-150 °C\(^1\)); \( R_f \) 0.20 (9:1 petrol/EtOAc); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.36 (d, J = 8, 2H), 7.15 (d, J = 8, 2H), 7.11 (d, J = 2, 1H), 6.96 (d, J = 7.6, 1H), 6.59-6.62 (m, 2H), 6.51-6.52 (m, 2H), 6.43 (d, \( J = 8, 1H \)), 3.47-3.53 (m, 1H), 3.33 (ddd, \( J = 5.2, 10, 13.2, 1H \)), 3.03-3.20 (m, 5H), 2.86 (ddd, \( J = 5.2, 10.4, 13.6, 1H \)), 2.29 (s, 3H); \(^1\)C NMR (100 MHz): \( \delta = 144.4, 142.2, 141.9, 141.3, 139.6, 139.0, 136.6, 135.8, 135.4, 133.1, 133.0, 131.5, 129.9, 127.8, 125.7, 35.3, 35.2, 34.7, 32.9, 21.4; \) IR: 2924, 2848, 1594, 1081, 1059, 1028, 909, 808, 719 cm\(^{-1}\) (See Appendix 16-18).
(R_P S)-4-(4-Tolylsulfinyl)-[2.2]paracyclophane: white solid (2.88 g, 25%); mp = 149-145 °C (lit. 175-177 °C); R_f 0.30 (9:1 petrol/EtOAc); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.39\) (d, \(J = 8.4, 2H\)), 7.25 (d, \(J = 8, 2H\)), 6.79 (d, \(J = 8, 1H\)), 6.52-6.59 (m, 4H), 6.46 (d, \(J = 8.4, 1H\)), 6.38 (d, \(J = 8.4, 1H\)), 3.81-3.88 (m, 1H), 3.36 (ddd, \(J = 4.8, 10.4, 12.8, 1H\)), 2.92-3.20 (m, 5H), 2.79 (ddd, \(J = 5.2, 10.8, 13.2, 1H\)), 2.38 (s, 3H); \(^{13}\)C NMR (100 MHz): \(\delta = 142.0, 141.3, 141.1, 140.8, 140.7, 140.0, 139.1, 137.6, 136.6, 133.2, 132.7, 132.6, 132.5, 132.4, 129.6, 125.2, 35.5, 35.2, 34.9, 32.9, 21.4\); IR: 2924, 2853, 1585, 1079, 1036, 817, 718 cm\(^{-1}\) (See Appendix 19-21).

**9.2.8 (S_P)-4-Bromo[2.2]paracyclophane**

\(t\)-BuLi (1.7 M in pentane, 9 ml, 15.3 mmol) was added dropwise to a solution of (S_P)-4-(4-Tolylsulfinyl)-[2.2]paracyclophane (1.05 g, 3.0 mmol) in dry THF (30 ml) at -78 °C. The solution was stirred for 10 minutes followed by the addition of bromobenzene (4.49 g, 28.6 mmol). The solution was slowly returned to room temperature and stirred for 2 days. Saturated NH\(_4\)Cl (50 ml) was added to the solution and the organic phase was extracted. The aqueous phase was further extracted with Et\(_2\)O (3 x 50 ml) and the combined organic phases dried over Mg\(_2\)SO\(_4\). The solvent was removed \textit{in vacuo} and the resulting residue purified by flash column chromatography (Cy) to give the title compound as a white solid (0.30 g, 35%). NMR data was in agreement with that collected for the racemate (See Section 3.4.2 and Appendix 23).
9.3 Disubstituted [2.2]paracyclophanes

9.3.1 (rac)-4-Bromo-13-nitro[2.2]paracyclophane

A solution of 4-nitro[2.2]paracyclophane (1.00 g, 3.9 mmol), iron powder (0.02 g, 0.4 mmol) and bromine (0.63 g, 4.0 mmol) in DCM (50 ml) was heated at reflux for 20 hours. The mixture was cooled to room temperature and washed with 10% Na$_2$S$_2$O$_3$ (2 x 50 ml). The organic phase was dried over MgSO$_4$ and the solvent removed in vacuo. The title compound was isolated by flash column chromatography as a pale yellow solid (0.36 g, 28%); $R_f = 0.27$ (8:2 Cy:DCM); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.58$ (d, $J = 2$, 1H), 6.77 (dd, $J = 7.6$, 2, 1H), 6.71 (d, $J = 1.2$, 1H), 6.65-6.58 (m, 3H), 4.35-4.42 (m, 1H), 3.63-3.70 (m, 1H), 2.99-3.21 (m, 6H); $^{13}$C NMR (100 MHz): $\delta = 141.1$, 138.8, 138.0, 137.7, 136.5, 136.2, 134.8, 131.5, 128.0, 127.4, 35.4, 34.7, 34.4, 32.7 (See Section 3.3.1 and Appendix 24-25).

9.3.2 (rac)-4-Bromo-13-amino[2.2]paracyclophane

A solution of 4-bromo-13-nitro[2.2]paracyclophane (1.00 g, 3.0 mmol) in water/EtOH (50 ml) was stirred for 30 minutes followed by the addition of iron powder (1.80 g, 32 mmol). The mixture was heated to reflux and conc. HCl (7 ml) was added dropwise over 10 minutes. The temperature was maintained for 4 hours at which time the mixture was poured onto ice and sat. NaHCO$_3$ (50 ml). The mixture was extracted with DCM (3 x 40 ml), dried over MgSO$_4$
and the solvent removed in vacuo. The title compound was isolated by flash column chromatography as an off white solid (0.62 g, 68%); R_f = 0.46 (8:2 Cy/EtOAc); ^1H NMR (400 MHz, CDCl_3): \( \delta = 6.83 \) (d, \( J = 1.6 \), 1H), 6.42-6.49 (m, 2H), 6.38 (d, \( J = 8 \), 1H), 6.11 (dd, \( J = 7.6 \), 1.6, 1H), 5.69 (d, \( J = 1.6 \), 1H), 3.66-3.73 (m, 3H), 3.33 (ddd, \( J = 14.4 \), 10, 2.4, 1H), 2.83-3.15 (m, 6H); ^13C NMR (100 MHz): \( \delta = 147.0 \), 141.0, 140.6, 138.1, 135.4, 135.3, 135.2, 132..7, 123..4, 123.1, 122.4, 121.0, 34.9, 34.7, 33.1, 31.5; IR: 3480, 3394, 2921, 2850, 1738, 1611, 1422 cm\(^{-1}\) (See Section 3.3.2 and Appendix 26-28).

### 9.3.3 (rac)-4-Nitro-13-formyl[2.2]paracyclophane

A solution of 4-nitro[2.2]paracyclophane (2.73 g, 10.8 mmol) in DCM (100 ml) was cooled to 0 °C. To this solution was added TiCl_4 (4.17 g, 22 mmol) and dichloromethoxymethane (1.38 g, 11.2 mmol) and the mixture was warmed to room temperature. After 20 hours stirring, water (100 ml) was added and stirring was continued for an additional 2 hours. The organic layer was extracted, dried over MgSO_4 and the solvent removed in vacuo. The title compound was isolated by flash column chromatography as a pale yellow solid (0.55 g, 18%); R_f = 0.38 (9:1 DCM:Cy); ^1H NMR (400 MHz, CDCl_3): \( \delta = 9.94 \) (s, 1H, CHO), 7.15 (d, \( J = 2 \), 1H, Ar-CH), 7.10 (d, \( J = 2 \), 1H, Ar-CH), 6.83 (dd, \( J = 7.6 \), 1.6, 1H, Ar-CH), 6.78 (dd, \( J = 7.6 \), 2, 1H, Ar-CH), 6.74 (d, \( J = 7.6 \), 1H, Ar-CH), 6.67 (d, \( J = 8 \), 1H, Ar-CH), 4.15-4.23 (m, 1H, CH_2), 3.98-4.06 (m, 1H, CH_2), 3.05-3.24 (m, 6H, CH_2); ^13C NMR (100 MHz): \( \delta = 190.4 \) (CHO), 149.5 (Ar-C), 142.6 (Ar-C), 141.9 (Ar-C), 140.1 (Ar-C), 137.9 (Ar-C), 137.5 (Ar-C), 137.4 (Ar-C), 136.2 (Ar-C), 136.1 (Ar-C), 135.6 (Ar-C), 134.7 (Ar-C), 128.2 (Ar-C), 34.5 (CH_2), 34.2 (CH_2), 31.7 (CH_2) (See Section 3.3.3 and Appendix 29-30).
9.3.4 (rac)-4-Amino-7-formyl[2.2]paracyclophane

A solution of 4-amino[2.2]paracyclophane (0.50 g, 2.2 mmol) in DCM (25 ml) was cooled to 0°C. To this solution was added TiCl₄ (0.83 g, 4.4 mmol) and dichloromethoxymethane (0.25 g, 2.2 mmol) and the mixture was warmed to room temperature. After 20 hours stirring, water (25 ml) was added and stirring was continued for an additional 2 hours. The organic layer was extracted, dried over MgSO₄ and the solvent removed in vacuo. The title compound was isolated by flash column chromatography as a yellow solid (0.15 g, 26%); Rᵣ = 0.74 (7:3 EtOAc:Cy); ¹H NMR (400 MHz, CDCl₃): δ = 9.76 (s, 1H, CHO), 7.11 (dd, J = 8, 2, 1H, Ar-CH), 6.83 (s, 1H, Ar-C), 6.51 (dd, J = 8, 2, 1H, Ar-CH), 6.47 (dd, J = 8, 2, 1H, Ar-CH), 6.40 (dd, J = 8, 2, 1H, Ar-CH), 5.40 (s, 1H, Ar-CH), 4.11 (s, 2H, NH₂), 3.97-4.03 (m, 1H, CH₂), 2.97-3.23 (m, 5H, CH₂), 2.61-2.77 (m, 2H, CH₂); ¹³C NMR (100 MHz): δ = 189.9 (CHO), 150.6 (Ar-C), 146.3 (Ar-C), 140.3 (Ar-C), 138.9 (Ar-C), 138.7 (Ar-C), 132.5 (Ar-C), 132.2 (Ar-C), 131.3 (Ar-C), 128.3 (Ar-C), 127.3 (Ar-C), 123.3 (Ar-C), 35.3 (CH₂), 33.2 (CH₂), 32.6 (CH₂), 31.8 (CH₂) (See Section 3.3.4 and Appendix 31-32).

9.4 General procedure for the preparation of substituted aryl-oxazolines

The appropriate aryl nitrile (13 mmol) and the appropriate amino alcohol (11 mmol) were dissolved in dry chlorobenzene (20 ml) under an atmosphere of argon. The solution was
stirred for 20 minutes at 60 °C followed by the addition of ZnCl₂ (1 M solution in Et₂O, 4 ml). The solution was heated to 145 °C for 4 days, cooled and the solvent evaporated, with the title compounds being isolated by flash column chromatography (See section 3.5).

**9.4.1 2-(4,5-Dihydrooxazol-2-yl)aniline**

![Chemical structure of 2-(4,5-Dihydrooxazol-2-yl)aniline](image)

Flash column solvent system (19:1 petrol/EtOAc); yellow solid (0.43 g, 24%); mp = 53-55 °C; Rᵣ = 0.39 (9:1 petrol/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 7.69 (dd, J = 8, 1.6, 1H), 7.19 (ddd, J = 8, 7.2, 1.6, 1H), 6.69 (dd, J = 8, 7.2, 1.2, 1H), 6.05 (s, 2H), 4.29-4.34 (m, 2H), 4.07-4.12 (m, 2H); ¹³C NMR (100 MHz): δ = 164.9, 148.5, 132.0, 129.6, 116.1, 115.7, 109.2, 65.8, 55.0; IR: 3416, 3298, 2926, 2880, 1627, 1251, 1049, 943 cm⁻¹ (See Appendix 33-35).

**9.4.2 (S)-2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)aniline**

![Chemical structure of (S)-2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)aniline](image)

Flash column solvent system (19:1 petrol/EtOAc); yellow solid (1.84 g, 82%); mp = 66-68 °C (lit. 67-69 °C); Rᵣ = 0.50 (9:1 petrol/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 7.68 (dd, J = 8, 1.6, 1H), 7.19 (ddd, J = 8.4, 7.2, 1.6, 1H), 6.68 (dd, J = 8, 0.8, 1H), 6.64 (ddd, 8, 7.2, 0.8, 1H), 6.13 (s, 2H), 4.31 (dd, J = 9.6, 8, 1H) 4.07-4.13 (m, 1H), 3.99 (app. t, J = 8, 1H), 1.72-1.83 (m, 1H), 1.02 (d, J = 6.8, 3H), 0.93 (d, J = 6.8, 3H); ¹³C NMR (100 MHz): δ = 163.52, 148.6, 131.9, 129.6, 116.0, 115.6, 109.2, 72.9, 68.8, 33.2, 19.0, 18.6; IR: 3387, 3252, 2957, 2951, 2879, 1631, 1491, 1254 cm⁻¹ (See Appendix 36-38).
Experimental

Chapter 9

9.4.3  (S)-2-(2-Bromophenyl)-4-isopropyl-4,5-dihydrooxazole

Flash column solvent system (8:2 DCM/Cy); clear oil (1.24 g, 42%); R_f = 0.22 (8:2 DCM/Cy); ¹H NMR (400 MHz, CDCl₃): δ = 7.67 (dd, J = 8, 1.6, 1H), 7.63 (d, J = 8, 1H), 7.33 (t, J = 7.6, 1H), 7.26 (dt, J = 7.6, 1.6, 1H), 4.40-4.46 (m, 1H), 4.13-4.19 (m, 2H), 1.85-1.97 (m, 1H), 1.05 (d, J = 6.8, 3H), 0.98 (d, J = 6.8, 3H); ¹³C NMR (100 MHz): δ = 162.9, 133.7, 131.5, 131.3, 130.2, 127.1, 121.8, 73.0, 70.4, 32.7, 18.8, 18.3; IR: 2960, 1655, 1024, 952 cm⁻¹ (See Appendix 39-41).

9.4.4  (S)-2-(2-Iodophenyl)-4-isopropyl-4,5-dihydrooxazole

Flash column solvent system (8:2 DCM/Cy); yellow oil (1.66 g, 48%); R_f = 0.22 (8:2 DCM/Cy); ¹H NMR (400 MHz, CDCl₃): δ = 7.92 (dd, J = 8, 1.2, 1H, Ar-CH), 7.61 (dd, J = 8, 1.6, 1H, Ar-CH), 7.36 (dd, J = 7.2, 1.2, 1H, Ar-CH), 7.09 (dd, J = 7.6, 1.6, 1H, Ar-CH), 4.41-4.47 (m, 1H, N-CH), 4.11-4.18 (m, 2H, O-CH₂), 1.85-1.97 (m, 1H, CH(CH₃)₂), 1.07 (d, J = 6.8, 3H, CH₃), 0.99 (d, J = 6.8, 3H, CH₃); ¹³C NMR (100 MHz): δ = 163.8 (Ar-C), 140.4 (Ar-C), 133.9 (Ar-C), 131.5 (Ar-C), 130.7 (Ar-C), 127.8 (Ar-C), 94.7 (O-C=N), 73.1 (O-CH₂), 70.5 (N-CH), 32.8 (CH(CH₃)₂), 19.0 (CH₃), 18.5 (CH₃); IR: 2960 (C-H), 1654 (C=N), 1468 (C=C), 1351, 1242, 1013 (C-O) cm⁻¹ (See Appendix 42-44).

9.4.5  (S)-2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)-4,5-dimethoxyaniline

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Flash column solvent system (8:2 Cy/EtOAc); off white solid (1.31 g, 45%); mp = 122-123 °C; R<sub>f</sub> = 0.40 (7:3 Cy/EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.15 (s, 1H, Ar-CH), 6.23 (s, 1H, Ar-CH), 5.95 (s, 2H, Ar-NH<sub>2</sub>), 4.30 (dd, J = 9.2, 8, 1H, N-CH), 4.05-4.11 (m, 1H, O-CH<sub>2</sub>), 3.98 (app. t, J = 8, 1H, O-CH<sub>2</sub>), 3.85 (s, 3H, OC<sub>H</sub><sub>3</sub>), 3.82 (s, 3H, OC<sub>H</sub><sub>3</sub>), 1.70-1.82 (m, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.01 (d, J = 6.8, 3H, CH<sub>3</sub>), 0.92 (d, J = 6.8, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz): δ = 163.3 (Ar-CH), 152.7 (Ar-CH), 144.5 (Ar-CH), 140.4 (Ar-CH), 111.7 (Ar-CH), 100.6 (Ar-CH), 99.2 (O-C≡N), 72.9 (O-CH<sub>2</sub>), 68.7 (N-CH), 56.4 (OCH<sub>3</sub>), 55.7 (OCH<sub>3</sub>), 33.3 (CH(CH<sub>3</sub>)<sub>2</sub>), 19.0 (CH<sub>3</sub>), 18.6 (CH<sub>3</sub>); IR: 3391 (N-H), 2968 (C-H), 1637 (C≡N), 1514 (C=C), 1209 (C-N), 1003 (C-O) cm<sup>-1</sup> (See Appendix 45-47).

9.4.6 (S)-2-(4-Benzyl-4,5-dihydrooxazol-2-yl)aniline

Flash column solvent system (19:1 petrol/EtOAc); yellow solid (1.61 g, 58%); mp = 55-57 °C (lit. 54-56 °C)<sup>4</sup>; R<sub>f</sub> = 0.59 (9:1 petrol/EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.67 (dd, J = 8, 1.6, 1H), 7.17-7.32 (m, 6H), 6.62-6.70 (m, 2H), 6.09 (s, 2H), 4.56-4.64 (m, 1H), 4.27 (app. t, J = 9.2, 1H), 4.02 (dd, J = 8.4, 7.2, 1H), 3.12 (dd, J = 13.6, 6, 1H), 2.76 (dd, J = 13.6, 8, 1H); <sup>13</sup>C NMR (100 MHz): δ = 164.1, 148.7, 138.4, 132.1, 129.6, 129.3, 128.5, 126.5, 116.0, 115.7, 109.0, 70.3, 68.1, 42.3; IR: 3389, 3266, 2906, 1625, 1488, 1453, 1362, 1263 cm<sup>-1</sup> (See Appendix 48-50).

9.4.7 (S)-2-(4-(Tert-butyl)-4,5-dihydrooxazol-2-yl)aniline

Flash column solvent system (19:1 petrol/EtOAc); yellow solid (0.95 g, 40%); mp = 63-65 °C (lit. 65-66 °C)<sup>4</sup>; R<sub>f</sub> = 0.59 (9:1 petrol/EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.67 (dd,
Experimental

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\[ J = 8, 1.6, 1H, 7.19 (\text{ddd}, J = 8, 7.2, 1.6, 1H), 6.70 (\text{dd}, J = 8, 1.2, 1H), 6.64 (\text{ddd}, 8, 7.2, 1.2, 1H), 6.15 (s, 2H), 4.21-4.27 (m, 1H), 4.07-4.13 (m, 2H), 0.94 (s, 9H); ^{13}\text{C} \text{NMR (100 MHz):} \delta = 163.5, 148.7, 131.9, 129.6, 115.9, 115.6, 109.2, 76.4, 66.9, 33.9, 25.9; \text{IR:} 3426, 3272, 2960, 2863, 1635, 1360, 1256 \text{ cm}^{-1} (\text{See Appendix 51-53}). \]

9.5 General procedure for preparation of substituted phenyl–oxazoline-

[2.2]paracyclophanes

A Schlenk tube was charged with the appropriate oxazoline (1 mmol), 4-
bromo[2.2]paracyclopane (0.345 g, 1.2 mmol), BINAP (0.126 g, 0.2 mmol), Pd(dba)$_2$ (0.092 g, 0.1 mmol) and KOtBu (0.224 g, 2 mmol) under an atmosphere of argon. Freshly distilled toluene (15 ml) was then added and the mixture was heated at 120 °C for 5 days. The solvent was removed \textit{in vacuo} and the product was isolated by flash column chromatography. The product was further purified by recrystallisation from EtOAc (See Section 3.6).
9.5.1  (S,S)-N-(2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-
[2.2]paracyclophane-4-amine

Flash column solvent system (8:2 Cy/DCM); Appears as a white crystalline solid (0.025 g, 6%); Rf = 0.57 (6:4 Cy/DCM); ¹H NMR (400 MHz, CDCl₃): δ = 10.34 (s, 1H, Ar-NH), 7.81 (dd, J = 8, 1.6, 1H, Ar-CH), 7.20 (dd, J = 8, 2, 1H, Ar-CH), 7.14-7.18 (m, 1H, Ar-CH), 6.87 (dd, J = 8.4, 0.8, 1H, Ar-CH), 6.67-6.71 (m, 1H, Ar-CH), 6.56 (dd, J = 8, 2, 1H, Ar-CH), 6.44-6.52 (m, 4H, Ar-CH), 6.01 (d, J = 1.2, 1H, Ar-CH), 4.46 (dd, J = 9.6, 8, 1H, N-CH), 4.29-4.35 (m, 1H, O-CH₂), 4.11 (app. t, J = 8, 1H, O-CH₂), 2.86-3.11 (m, 7H, CH₂), 2.66 (ddd, J = 13.2, 10, 6.8, 1H, CH₂), 1.88-2.00 (m, 1H, CH(CH₃)₂), 1.22 (d, J = 6.8, 3H, CH₃), 1.08 (d, J = 6.8, 3H, CH₃); ¹³C NMR (100 MHz): δ = 163.9 (Ar-C), 145.8 (Ar-C), 141.2 (Ar-C), 139.9 (Ar-C), 139.2 (Ar-C), 139.0 (Ar-C), 135.7 (Ar-C), 135.0 (Ar-C), 133.5 (Ar-C), 132.9 (Ar-C), 132.0 (Ar-C), 131.4 (Ar-C), 130.7 (Ar-C), 129.8 (Ar-C), 128.6 (Ar-C), 128.4 (Ar-C), 116.1 (Ar-C), 112.3 (Ar-C), 108.9 (O-C=N), 73.3 (O-CH₂), 69.0 (N-CH), 35.3 (CH₂), 34.9 (CH₂), 34.3 (CH₂), 33.9 (CH₂), 33.4 (CH(CH₃)₂), 19.3 (CH₃), 18.9 (CH₃); IR: 3232 (N-H), 2957 (C-H), 2926 (C-H), 2853 (C-H), 1630 (C=N), 1583 (C=C), 1520, 1450 (C-H), 1276 (C-N), 1050 (C-O), 906, 729 cm⁻¹; HRMS (ES⁺) calculated for C₂₈H₃₁N₂O [M+H]⁺: 411.2436, found: 411.2433 (See Appendix 54-56 and 106).
9.5.2 \((S,S)\)-N-(2-(4-Benzyl-4,5-dihydrooxazol-2-yl)phenyl)-
[2.2]paracyclophane-4-amine

Flash column solvent system (8:2 Cy/DCM); Appears as a white solid (0.032 g, 7%); \(R_f = 0.47\) (6:4 Cy/DCM); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ = 10.29 (s, 1H, Ar-NH), 7.83 (dd, \(J = 8, 2, 1\)H, Ar-CH), 7.34-7.46 (m, 5H, Ar-CH), 7.17-7.21 (m, 1H, Ar-CH), 6.96 (dd, \(J = 8, 2, 1\)H, Ar-CH), 6.91 (dd, \(J = 8.4, 0.8, 1\)H, Ar-CH), 6.69-6.73 (m, 1H, Ar-CH), 6.51 (dd, 8, 2, 1H, Ar-CH), 6.38-6.48 (m, 3H, Ar-CH), 5.93 (dd, \(J = 8, 2, 1\)H, Ar-CH), 5.91 (d, \(J = 1.6, 1\)H, Ar-CH), 4.80-4.88 (m, 1H, N-CH), 4.49 (app. t, \(J = 8.8, 1\)H, O-CH\(_2\)), 4.16 (dd, \(J = 8, 7.2, 1\)H, O-CH\(_2\)), 2.92-3.14 (m, 8H, CH\(_2\)), 2.79-2.86 (m, 1H, CH\(_2\)), 2.61-2.68 (m, 1H, CH\(_2\)); \(^{13}\)C NMR (100 MHz): δ = 164.3, 145.5, 141.1, 139.6, 139.1, 138.8, 138.7, 135.7, 134.0, 133.3, 132.6, 132.1, 131.4, 129.9, 129.8, 129.4, 128.7, 128.2, 126.6, 116.2, 112.5, 108.8, 70.7, 68.4, 43.0, 35.1, 34.8, 34.2, 33.7, 29.7; IR: 3190 (N-H), 3030 (C-H), 2923 (C-H), 2890 (C-H), 2855 (C-H), 1636 (C=N), 1593 (C=C), 1527, 1492, 1453 (C-H), 1284 (C-N), 1055 (C-O), 960, 744 cm\(^{-1}\); HRMS (ES\(^+\)) calculated for C\(_{32}\)H\(_{31}\)N\(_2\)O [M+H]\(^+\): 459.2436, found: 459.2428 (See Appendix 57-59).
9.6 \((\text{rac})\)-2-(4-Amino[2.2]paracyclophane)-4,5-dimethoxybenzonitrile

To a Schlenk tube was added 2-amino-4,5-dimethoxybenzonitrile (0.178 g, 1 mmol), 4-bromo[2.2]paracyclophane (0.345 g, 1.2 mmol), BINAP (0.063 g, 0.1 mmol), Pd(dba)$_2$ (0.046, 0.05 mmol) and KOtBu (0.224 g, 2 mmol) under an atmosphere of argon. Freshly distilled toluene (15 ml) was added and the mixture was heated at 120 °C for 2 days. The resulting mixture was diluted with DCM (50ml) and filtered, followed by aqueous extraction. The aqueous layer was then extracted with DCM (3 x 25 ml) and the combined organic layers were dried over MgSO$_4$. The title compound was isolated by flash column chromatography (8:2 Cy/EtOAc) as a waxy solid (0.12 g, 32%); $R_f = 0.66$ (6:4 Cy/EtOAc); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.15$ (dd, $J = 2, 8$, 1H, Ar-CH), 6.23 (s, 1H, Ar-CH), 6.57 (dd, $J = 2, 8$, 1H, Ar-CH), 6.43-6.53 (m, 5H, Ar-CH), 6.01 (s, 1H, Ar-NH), 5.92 (d, $J = 1.2$, 1H, Ar-CH), 3.84 (s, 3H, OCH$_3$), 3.66 (s, 3H, OCH$_3$), 2.90-3.12 (m, 7H, CH$_2$), 2.64-2.74 (m, 1H, CH$_2$); $^{13}$C NMR (100 MHz): $\delta = 154.3$ (Ar-C), 143.7 (Ar-C), 142.6 (Ar-C), 142.0 (Ar-C), 139.3 (Ar-C), 138.9 (Ar-C), 138.3 (Ar-C), 136.2 (Ar-C), 133.6 (Ar-C), 132.9 (Ar-C), 132.8 (Ar-C), 131.3 (Ar-C), 128.8 (Ar-C), 128.0 (Ar-C), 127.4 (Ar-C), 118.5 (Ar-C), 113.6 (C≡N), 98.3 (Ar-C), 88.1 (Ar-C), 56.5 (OCH$_3$), 55.9 (OCH$_3$), 35.2 (CH$_2$), 34.8 (CH$_2$), 33.8 (CH$_2$); IR: 3319 (N-H), 2926 (C-H), 2853 (C-H), 2203 (C≡N), 1584 (C≡C), 1499, 1449, 1410, 1256, 1210 (C-O) cm$^{-1}$; HRMS (ES$^+$) calculated for C$_{25}$H$_{23}$N$_2$O$_2$ [M-H]: 383.1760, found: 383.1771 (See Section 3.7 and Appendix 60-63).
9.7 Octafluoro[2.2]paracyclophane and precursors

9.7.1 1,4-bis-Dichloromethylbenzene

\[
\begin{array}{c}
\text{CHCl}_2 \\
\text{CHCl}_2
\end{array}
\]

Procedure A: A mixture of terephthaldehyde (14.4 g, 107 mmol), DMF (1.9 g, 26 mmol) and SOCl₂ (24.5 g, 206 mmol) was heated at 90 °C for 1 hour under an atmosphere of argon. The same quantities of DMF and SOCl₂ were again added to the mixture and the temperature maintained for an additional 2 hours. The mixture was then poured onto cold water (600 ml) forming a precipitate. The precipitate was filtered, dissolved in DCM (200 ml) and washed with water (2 x 100 ml). The organic layer was dried over MgSO₄ and the solvent was removed \textit{in vacuo} to yield the title compound as a white solid (18.29 g, 70%); mp 91-93 °C (lit. 92-93 °C)⁵; \( R_f = 0.57 \) (9:1 petrol/EtOAc); \(^1\)H NMR (400 MHz, CDCl₃): \( \delta = 7.63 \) (s, 4H), 6.71 (s, 2H); \(^1\)³C NMR (100 MHz): \( \delta = 141.8, 126.7, 70.8 \); IR: 1422, 1310, 1214, 800 cm\(^{-1}\) (See Section 5.2.1 and Appendix 64-66).

Procedure B: Terephthaldehyde (1 g, 7.5 mmol) was dissolved in dry hexane (50 ml) under an atmosphere of argon and 1M BCl₃ in pentane (15 ml, 15mmol) was added. The solution was heated at reflux for 4 hours and quenched with water (25 ml). The organic layer was separated and dried over MgSO₄. The solvent was removed \textit{in vacuo}. The crude material was purified using flash column chromatography and yielded the title compound as a white solid (0.82 g, 45%).
9.7.2  1,4-bis-Difluoromethylbenzene

![1,4-bis-Difluoromethylbenzene](image)

Terephthaldehyde (0.5 g, 3.7 mmol) was dissolved in dry DCM (20 ml) under an atmosphere of argon. DAST (1.83 g, 11.4 mmol) was added dropwise followed by a catalytic amount of absolute EtOH. The reaction was heated at reflux for 20 hours, cooled to room temperature and quenched with water (20 ml). The organic layer was extracted and the aqueous layer was washed with DCM (20 ml). The combined organic layers were dried over MgSO₄ and the solvent removed in vacuo to give an orange oil which was purified by flash column chromatography to yield the title compound as a colourless clear oil (0.44 g, 67%); R₇ = 0.5 (9:1 petrol/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 7.59 (s, 4H), 6.67 (t, J = 56, 2H); ¹³F NMR (376 MHz): δ = -111.7 (d, J = 56, 4F); ¹³C NMR (100 MHz): δ = 136.7 (t, J = 23), 126.0 (t, J = 6), 114.0 (t, J = 238); IR: 1430, 1370, 1220, 1018, 809 cm⁻¹ (See Section 5.2.2 and Appendix 67-70).

9.7.3  1,4-bis-Chlorodifluoromethylbenzene

![1,4-bis-Chlorodifluoromethylbenzene](image)

1,4-bis-Difluoromethylbenzene (3 g, 16.8 mmol) was added to a solution of AIBN (0.2 g, 1.2 mmol) and SO₂Cl₂ (30 ml) under an atmosphere of argon. This solution was heated at reflux for 5 days, cooled to room temperature, then added to water (150 ml) and allowed to stir for 1 hour. The mixture was extracted with DCM (3 x 40 ml) and the organic phase dried over MgSO₄ and the solvent removed in vacuo. The crude oil was purified using flash column
chromatography to yield the title compound as a colourless clear oil (0.83 g, 20%); \( R_f = 0.65 \) (petrol); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.75 \) (s, 4H); \(^{19}\)F NMR (376 MHz): \( \delta = -50.0 \) (s, 4F); \(^{13}\)C NMR (100 MHz): \( \delta = 139.0 \) (t, \( J = 27 \)), 125.6 (t, \( J = 289 \)), 125.2 (t, \( J = 5 \)); IR: 1413, 1272, 1053, 912, 822, 730 cm\(^{-1}\) (See Section 5.2.3 and Appendix 71-74).

9.7.4 1-(Trimethylsilyl)difluoromethyl-4-trifluoromethylbenzene

Magnesium turnings (1.73 g, 72 mmol) were added to dry DMF (80 ml) under an atmosphere of argon. Chlorotrimethylsilane (15.6 g, 144 mmol) was added to the mixture followed by the dropwise addition of 1,4-bis-trifluoromethylbenzene (7.7 g, 36 mmol) over 1 hour. The mixture was then allowed stir for an additional 30 minutes. The reaction was quenched with water (80 ml) and extracted with hexane (3 x 60 ml). The organic phase was dried over MgSO\(_4\) and the solvent removed \textit{in vacuo} to give a brown oil which was purified by flash column chromatography to yield the product as a colourless clear oil (3.09 g, 32%); \( R_f = 0.44 \) (petrol); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.55 \) (d, \( J = 8 \), 2H), 7.33 (d, \( J = 8 \), 2H), 0.015 (s, 9H); \(^{19}\)F NMR (376 MHz): \( \delta = -113.2 \) (s, 2F), -62.8 (s, 3F); \(^{13}\)C NMR (100 MHz): \( \delta = 142.0 \) (t, \( J = 21 \)), 131.0 (q, \( J = 32 \)), 126.3 (q, \( J = 264 \)), 125.3 (q, \( J = 4 \)), 125.2 (t, \( J = 8 \)), 123.9 (t, \( J = 402 \)), -5.0; IR: 1411, 1323, 1128, 1068, 998, 827 cm\(^{-1}\) (See Section 5.2.4 and Appendix 75-78).

9.7.5 1,1,2,2,9,9,10,10-Octafluoro[2,2]paracyclophane
A mixture of 1-(Trimethylsilyl)difluoromethyl-4-trifluoromethylbenzene (1 g, 3.7 mmol), CsF (0.060 g, 0.4 mmol) and Pd$_2$(dba)$_3$ (20 mg, 0.02 mmol) in dry anisole (80 ml) was heated at reflux for 24 hours under an atmosphere of argon. The solvent was removed in vacuo and the title compound was isolated by flash column chromatography as a white crystalline solid (0.12 g, 18%); mp 261-263 °C (lit. 261 °C)$^6$; R$_f$ = 0.62 (6:4 Cy/DCM); $^1$H NMR (400 MHz, CDCl$_3$): δ = 7.16 (s, 8H); $^{19}$F NMR (376 MHz): δ = -118.2 (s, 8F); $^{13}$C NMR (100 MHz): δ = 134.9 (t, $J$ = 27), 129.8, 118.6 (t, $J$ = 272); IR: 1401, 1257, 1130, 1086, 923, 823, 712 cm$^{-1}$ (See Section 5.2.5 and Appendix 79-82).

9.8 Monosubstituted octafluoro[2,2]paracyclophanes

9.8.1 (rac)-4-Nitro-1,1,2,2,9,9,10,10-octafluoro[2,2]paracyclophane

Octafluoro[2,2]paracyclophane (2 g, 5.7 mmol) was added to a solution of 67% HNO$_3$ (22 ml) and H$_2$SO$_4$ (3 ml) and heated at 100 °C for 24 hours. The suspension was cooled to room temperature and added to ice water (200 ml). The resulting solid was isolated by filtration and flash column chromatography yielded the title compound as an off-white solid (0.59 g, 26%); mp 117-119 °C (lit. 119-129 °C)$^7$; R$_f$ = 0.44 (6:4 Cy/DCM); $^1$H NMR (400 MHz, (CD$_3$)$_2$CO): δ = 7.70 (m, 4H), 7.54 (m, 2H), 7.33 (d, $J$ = 8.8, 1H); $^{19}$F NMR (376 MHz): δ = -111.08 (d, $J$ = 264, 1F), -113.73 (d, $J$ = 264, 1F), -116.08 (m, 4F), -117.75 (m, 2F); IR: 1537, 1402, 1349, 1241, 1126, 1092 cm$^{-1}$ (See Section 5.3.1 and Appendix 83-86).
9.8.2 (rac)-4-Amino-1,1,2,2,9,9,10,10-octafluoro[2,2]paracyclophane

A solution of 4-nitro-octafluoro[2,2]paracyclophane (1.00 g, 2.5 mmol) in H₂O/EtOH (50 ml) was stirred for 30 minutes followed by the addition of iron powder (1.40 g, 25 mmol). The mixture was heated to reflux and conc. HCl (7 ml) was added in one portion. The temperature was maintained for 8 hours at which time the mixture was poured onto ice and 1M NaOH (100 ml). The mixture was extracted with DCM (3 x 40 ml), dried over MgSO₄ and the solvent removed in vacuo to yield the title compound as a white solid (0.73 g, 80%); mp 219-221 °C (lit. 221-223 °C); Rₛ = 0.28 (6:4 Cy/DCM); ¹H NMR (400 MHz, (CD₃)₂CO): δ = 7.99 (dd, J = 8.0, 1.6, 1H), 7.40 (dd, J = 8.8, 1.6, 1H), 7.19 (d, J = 8.4, 1H), 7.11 (d, J = 8.0, 1H), 6.95 (dd, J = 8.8, 1.2, 1H), 6.54 (dd, J = 8.8, 1.2, 1H), 6.09 (d, J = 1.2, 1H), 5.60 (s, 2H); ¹⁹F NMR (376 MHz): δ = -105.40 (d, J = 252, 1F), -107.90 (d, J = 252, 1F), -111.56 (d, J = 232, 1F), -112.30 (d, J = 240, 1F), -114.34 (d, J = 252, 1F), -115.84 (d, J = 252, 1F), -116.81 (d, J = 256, 1F), -117.82 (d, J = 248, 1F); IR: 3534, 3438, 1629, 1437, 1236, 1082 cm⁻¹ (See Section 5.3.2 and Appendix 87-90).

9.9 General procedure for the preparation of fluorinated aryl triethoxysilanes

\[
\begin{align*}
\text{Br} & \quad + \quad \text{EtO-Si-OEt} \\
& \quad \xrightarrow{\text{Mg, I₂}} \quad \text{Et₂O} \\
\end{align*}
\]

A mixture of magnesium turnings (1.27 g, 52 mmol) and 2 crystals of iodine were placed under an atmosphere of argon. To this was added TEOS (10.9 g, 52 mmol) followed by the
appropriate fluorobromobenzene (48 mmol) with stirring. To this solution was added dry
Et₂O (30 ml) at 0 °C and an exothermic event is observed. After approximately 20 minutes
the solution was allowed to return to room temperature and was subsequently heated at reflux
for 20 hours. An excess of heptane was added until a precipitation of salts is observed. The
precipitate was removed by filtration and the solvent was removed in vacuo. The resulting oil
is purified by vacuum distillation to yield the title compounds (See Section 7.3.1).

9.9.1 4-Fluorophenyltriethoxysilane

![4-Fluorophenyltriethoxysilane Structure]

Clear oil (4.22 g, 34 %); ¹H NMR (400 MHz, CDCl₃): δ = 7.67 (q, J = 6.4, 2H, Ar-CH), 7.06
(t, J = 8.8, 2H, Ar-CH), 3.87 (g, J = 7.2, 6H, OCH₂CH₃), 1.24 (t, J = 7.2, 9H, OCH₂CH₃); ¹⁹F
NMR (376 MHz): δ = -109.80 (s, 1F); ¹³C NMR (100 MHz): δ = 164.5 (d, J = 248, Ar-CF),
136.8 (d, J = 8, Ar-CH), 126.7 (d, J = 4, Ar-C-Si), 114.9 (d, J = 20, Ar-CH), 58.6
(OCH₂CH₃), 18.0 (OCH₂CH₃) (See Appendix 91-93).

9.9.2 3,4,5-Trifluorophenyltriethoxysilane

![3,4,5-Trifluorophenyltriethoxysilane Structure]

Clear oil (4.24 g, 30 %); ¹H NMR (400 MHz, CDCl₃): δ = 7.16 (t, J = 7.2, 2H, Ar-CH), 3.78
(q, J = 7.2, 6H, OCH₂CH₃), 1.16 (t, J = 7.2, 9H, OCH₂CH₃); ¹⁹F NMR (376 MHz): δ = -
135.26 (d, $J = 23$, 2F, Ar- CF), -158.53 (t, $J = 23$, 1F, Ar- CF); $^{13}$C NMR (100 MHz): $\delta = 150.4$ (dd, $J = 51$, 9, (Ar- CF), 140.5 (dd, $J = 53$, 14, (Ar- CF), 127.4, (Ar- CH), 117.4 (d, $J = 14$, (Ar- CH), 58.1 (OCH$_2$CH$_3$), 17.1 (OCH$_2$CH$_3$) (See Appendix 94-96).

9.9.3 Perfluorophenyltriethoxysilane

Clear oil (4.28 g, 27%) yield calculated based on desired product; Isolated as a mixture which could not be separated. $^1$H, $^{19}$F and $^{13}$C NMR spectra of the mixture provided in appendices (See Appendix 97-99).

9.10 Fluorinated mesoporous silicate particles

To a beaker was added EtOH (1000 ml), CTAB (55 g, 0.151 mol), H$_2$O (290 g, 16.1 mol) and 28% ammonium hydroxide solution (50 ml, 14 g, 0.4 mol) with stirring. In a second vessel a mixture of TEOS (186 g, 0.89 mol) and PFOTES (4.57 g, 9 mmol) was prepared. The silane solution was added to the EtOH solution in one portion and immediately heated using microwave (10 min, 100 W). The resulting suspension was left to evaporate at 90 °C for approximately 24 hours. The resulting solid was added to a solution of MeOH (1250 ml) and conc. HCl (65 ml) and heated at reflux for approximately 24 hours. The resulting particles were isolated by filtration and washed with a mixture of methanol (500 ml) and conc. HCl (25 ml) followed by ethanol (250 ml). The particles were then dried under vacuum at room temperature (See Section 7.3.2).
9.11 Unsuccessful procedures

9.11.1 4-Amino-13-formyl[2.2]paracyclophane

A solution of 4-nitro-13-formyl[2.2]paracyclophane (0.10 g, 0.36 mmol) in H$_2$O/EtOH (5 ml) was stirred for 30 minutes followed by the addition of iron powder (0.06 g, 1.1 mmol). The mixture was heated to reflux and conc. HCl (0.6 ml) was added in one portion. The starting material was observed to degrade almost immediately (See Section 3.3.4).

9.11.2 1,4-bis-Difluoromethylbenzene by solid phase reaction

1,4-bis-dichloromethylbenzene (2.0 g, 8.2 mmol) and CsF (7.47 g, 49 mmol) were ground in a mortar and pestle and added to a sealed glass vessel. This was heated without mixing at 180 °C for 8 hours. The resulting mixture was dissolved in DCM (100 ml) and washed with water (3 x 50 ml). The organic phase was dried over MgSO$_4$ and removed in vacuo. No product was isolated from the resulting material (See Section 5.2.2).

9.11.3 1,4-bis-Difluoromethylbenzene by phase transfer catalysis

Procedure A: To a mixture of benzene/water (10 ml) was added 1,4-bis-dichloromethylbenzene (0.25 g, 1 mmol), CsF (0.8 g, 5.3 mmol) and TBAB (0.02 g, 0.06 mmol). This mixture was heated at 100 °C with vigorous stirring, for 24 hours. The organic phase was extracted, dried over MgSO$_4$ and removed in vacuo. No product was isolated from the resulting material.

Procedure B: To dry DMF (10 ml) under an atmosphere of argon was added 1,4-bis-dichloromethylbenzene (0.25 g, 1 mmol), CsF (0.8 g, 5.3 mmol) and TBAB (0.02 g, 0.06 mmol). The mixture was heated at reflux for 24 hours. The resulting solution was diluted with water (40ml) and washed with DCM (2 x 25 ml). The organic phase was dried over
MgSO₄ and the solvent removed in vacuo. No product was isolated from the resulting material (See Section 5.2.2).

9.11.4 1,1,2,2,9,9,10,10-Octafluoro[2.2]paracyclophane by zinc coupling

A mixture of zinc (2.0 g, 30.6 mmol) in dry DMA (20 ml) was prepared under an atmosphere of argon. To this was added 1,4-bis-chlorodifluoromethylbenzene (2.0 g, 8.1 mmol) with stirring. The mixture was heated to 100 °C over 40 minutes and was maintained at this temperature for 24 hours. ¹⁹F NMR indicated only starting material was present in the reaction mixture and no traces of product were detected (See Section 5.2.5).
9.12 References

(1) Parmar, R.; Coles, M. P.; Hitchcock, P. B.; Rowlands, G. J. *Synthesis (Stuttg).* 2010, 4177.


Appendix 1: $^1$H NMR of (rac)-4-bromo[2.2]paracyclophane

Appendix 2: $^{13}$C NMR of (rac)-4-bromo[2.2]paracyclophane
Appendices

Appendix 3: IR of (rac)-4-bromo[2.2]paracyclophane

Appendix 4: $^1$H NMR of (rac)-4-formyl[2.2]paracyclophane
Appendix 5: $^{13}$C NMR of (rac)-4-formyl[2.2]paracyclophane

Appendix 6: IR of (rac)-4-formyl[2.2]paracyclophane
Appendix 7: $^1$H NMR of (rac)-4-hydroxy[2.2]paracyclophane

Appendix 8: $^{13}$C NMR of (rac)-4-hydroxy[2.2]paracyclophane
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Appendix 9: IR of (rac)-4-hydroxy[2.2]paracyclophane

Appendix 10: $^1$H NMR of (rac)-4-nitro[2.2]paracyclophane
Appendices

Appendix 11: $^{13}$C NMR of \((rac)-4\)-nitro[2.2]paracyclophane

Appendix 12: IR of \((rac)-4\)-nitro[2.2]paracyclophane
Appendix 13: $^1$H NMR of \((\text{rac})-4\)-amino[2.2]paracyclophane

Appendix 14: $^{13}$C NMR of \((\text{rac})-4\)-amino[2.2]paracyclophane
Appendices

Appendix 15: IR of (rac)-4-amino[2.2]paracyclophane

![IR spectrum of (rac)-4-amino[2.2]paracyclophane]

Appendix 16: $^1$H NMR of (S$_p$S)-4-(4-Tolylsulfinyl)-[2.2]paracyclophane

![NMR spectrum of (S$_p$S)-4-(4-Tolylsulfinyl)-[2.2]paracyclophane]
Appendices

Appendix 17: $^{13}$C NMR of $(S_p S)_4$-(4-Tolylsulfinyl)-[2.2]paracyclophane

Appendix 18: IR of $(S_p S)_4$-(4-Tolylsulfinyl)-[2.2]paracyclophane
Appendices

Appendix 19: $^1$H NMR of (R,P,S)-4-(4-Tolylsulfinyl)-[2.2]paracyclophane

[Image of NMR spectrum]

Appendix 20: $^{13}$C NMR of (R,P,S)-4-(4-Tolylsulfinyl)-[2.2]paracyclophane

[Image of NMR spectrum]
Appendix 21: IR of (R,S)-4-(4-Tolylsulfinyl)-[2.2]paracyclophane

Appendix 22: $^1$H NMR of (R)-4-amino[2.2]paracyclophane
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Appendix 23: $^1$H NMR of $(S_p)$-4-bromo[2.2]paracyclophane

Appendix 24: $^1$H NMR of $(rac)$-4-bromo-13-nitro[2.2]paracyclophane
Appendices

Appendix 25: $^{13}$C NMR of (rac)-4-bromo-13-nitro[2.2]paracyclophane

Appendix 26: $^1$H NMR of (rac)-4-bromo-13-amino[2.2]paracyclophane
Appendix 27: $^{13}$C NMR of (rac)-4-bromo-13-amino[2.2]paracyclophane

Appendix 28: IR of (rac)-4-bromo-13-amino[2.2]paracyclophane
Appendix 29: $^1$H NMR of (rac)-4-nitro-13-formyl[2.2]paracyclophane

Appendix 30: $^{13}$C NMR of (rac)-4-nitro-13-formyl[2.2]paracyclophane
Appendix 31: $^1$H NMR of (rac)-4-amino-7-formyl[2.2]paracyclophane

Appendix 32: $^{13}$C NMR of (rac)-4-amino-7-formyl[2.2]paracyclophane
Appendix 33: $^1$H NMR of 2-(4,5-dihydrooxazol-2-yl)aniline

Appendix 34: $^{13}$C NMR of 2-(4,5-dihydrooxazol-2-yl)aniline
Appendix 35: IR 2-(4,5-dihydrooxazol-2-yl)aniline

Appendix 36: $^1$H NMR of (S)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)aniline
Appendix 37: $^{13}$C NMR of (S)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)aniline

Appendix 38: IR of (S)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)aniline
Appendix 39: $^1$H NMR of (S)-2-(2-bromophenyl)-4-isopropyl-4,5-dihydrooxazole

Appendix 40: $^{13}$C NMR of (S)-2-(2-bromophenyl)-4-isopropyl-4,5-dihydrooxazole
Appendix 41: IR of (S)-2-(2-bromophenyl)-4-isopropyl-4,5-dihydrooxazole

Appendix 42: $^1$H NMR of (S)-2-(2-iodophenyl)-4-isopropyl-4,5-dihydrooxazole
Appendix 43: $^{13}$C NMR of (S)-2-(2-iodophenyl)-4-isopropyl-4,5-dihydrooxazole

Appendix 44: IR of (S)-2-(2-iodophenyl)-4-isopropyl-4,5-dihydrooxazole
Appendix 45: $^1$H NMR of (S)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)-4,5-dimethoxyaniline

Appendix 46: $^{13}$C NMR of (S)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)-4,5-dimethoxyaniline
Appendix 47: IR of (S)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)-4,5-dimethoxyaniline

Appendix 48: $^1$H NMR of (S)-2-(4-benzyl-4,5-dihydrooxazol-2-yl)aniline
Appendix 49: $^{13}$C NMR of (S)-2-(4-benzyl-4,5-dihydrooxazol-2-yl)aniline

Appendix 50: IR of (S)-2-(4-benzyl-4,5-dihydrooxazol-2-yl)aniline
Appendix 51: $^1$H NMR of (S)-2-(4-(tert-butyl)-4,5-dihydrooxazol-2-yl)aniline

Appendix 52: $^{13}$C NMR of (S)-2-(4-(tert-butyl)-4,5-dihydrooxazol-2-yl)aniline
Appendix 53: IR of (S)-2-(4-(tert-butyl)-4,5-dihydrooxazol-2-yl)aniline

Appendix 54: $^1$H NMR of (S$_p$S)-N-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-[2.2]paracyclophane-4-amine
Appendix 55: $^{13}$C NMR of (S$_p$S)-N-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-[2.2]paracyclophane-4-amine

Appendix 56: HRMS of (S$_p$S)-N-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-[2.2]paracyclophane-4-amine
Appendix 57: $^1$H NMR of (S$_p$S)-N-(2-(4-benzyl-4,5-dihydrooxazol-2-yl)phenyl)-[2.2]paracyclophane-4-amine

Appendix 58: $^{13}$C NMR of (S$_p$S)-N-(2-(4-benzyl-4,5-dihydrooxazol-2-yl)phenyl)-[2.2]paracyclophane-4-amine
Appendix 59: HRMS NMR of \( \text{(S,S)}-\text{N-}(2-(4\text{-benzyl-4,5\text{-dihydrooxazol-2-yl})phenyl})-2.2\text{]paracyclophane-4-amine} \)

Appendix 60: \(^1\text{H NMR of (rac)-2-(4\text{-amino[2.2]paracyclophan}e)-4,5\text{-dimethoxybenzonitrile} \)
Appendices

Appendix 61: $^{13}$C NMR of (rac)-2-(4-amino[2.2]paracyclophane)-4,5-dimethoxybenzonitrile

Appendix 62: IR of (rac)-2-(4-amino[2.2]paracyclophane)-4,5-dimethoxybenzonitrile
Appendix 63: HRMS of (rac)-2-(4-amino[2.2]paracyclophane)-4,5-dimethoxybenzonitrile

Appendix 64: $^1$H NMR of 1,4-bis-dichloromethylbenzene
Appendices

Appendix 65: $^{13}$C NMR of 1,4-bis-dichloromethylbenzene

Appendix 66: IR of 1,4-bis-dichloromethylbenzene
Appendices

Appendix 67: $^1$H NMR of 1,4-bis-difluoromethylbenzene

Appendix 68: $^{13}$C NMR of 1,4-bis-difluoromethylbenzene
Appendix 69: $^{19}$F NMR of 1,4-bis-difluoromethylbenzene

Appendix 70: IR of 1,4-bis-difluoromethylbenzene
Appendices

Appendix 71: $^1$H NMR of 1,4-bis-chlorodifluoromethylbenzene

Appendix 72: $^{13}$C NMR of 1,4-bis-chlorodifluoromethylbenzene
Appendix 73: $^{19}$F NMR of 1,4-bis-chlorodifluoromethylbenzene

Appendix 74: IR of 1,4-bis-chlorodifluoromethylbenzene
Appendices

Appendix 75: $^1$H NMR of 1-(trimethylsilyl)difluoromethyl-4-trifluoromethylbenzene

Appendix 76: $^{13}$C NMR of 1-(trimethylsilyl)difluoromethyl-4-trifluoromethylbenzene
Appendix 77: $^{19}$F NMR of 1-(trimethylsilyl)difluoromethyl-4-trifluoromethylbenzene

Appendix 78: IR of 1-(trimethylsilyl)difluoromethyl-4-trifluoromethylbenzene
Appendices

Appendix 79: $^1$H NMR of octafluoro[2.2]paracyclophane

Appendix 80: $^{13}$C NMR of octafluoro[2.2]paracyclophane
Appendices

Appendix 81: $^{19}$F NMR of octafluoro[2.2]paracyclophane

Appendix 82: IR of octafluoro[2.2]paracyclophane
Appendix 83: $^1$H NMR of (rac)-4-nitro-octafluoro[2.2]paracyclophane

Appendix 84: $^{13}$C NMR of (rac)-4-nitro-octafluoro[2.2]paracyclophane
Appendix 85: $^{19}$F NMR of \((\text{rac})-4\)-nitro-octafluoro[2.2]paracyclophane

Appendix 86: IR of \((\text{rac})-4\)-nitro-octafluoro[2.2]paracyclophane
Appendix 87: $^1$H NMR of (rac)-4-amino-octafluoro[2.2]paracyclophane

Appendix 88: $^{13}$C NMR of (rac)-4-amino-octafluoro[2.2]paracyclophane
Appendix 89: $^{19}$F NMR of (rac)-4-amino-octafluoro[2.2]paracyclophane

Appendix 90: IR of (rac)-4-amino-octafluoro[2.2]paracyclophane
Appendix 91: $^1\text{H}$ NMR of 4-fluorophenyltriethoxysilane

Appendix 92: $^{13}\text{C}$ NMR of 4-fluorophenyltriethoxysilane
Appendices

Appendix 93: $^{19}$F NMR of 4-fluorophenyltriethoxysilane

Appendix 94: $^1$H NMR of 3,4,5-trifluorophenyltriethoxysilane
Appendices

Appendix 95: $^{13}$C NMR of 3,4,5-trifluorophenyltriethoxysilane

Appendix 96: $^{19}$F NMR of 3,4,5-trifluorophenyltriethoxysilane
Appendix 97: $^1$H NMR of perfluorophenyltriethoxysilane

Appendix 98: $^{13}$C NMR of perfluorophenyltriethoxysilane
Appendix 99: $^{19}$F NMR of perfluorophenyltriethoxysilane

Appendix 100: $^1$H NMR of unidentified dibromo-nitro[2.2]paracyclophane regioisomer (a)
Appendix 101: $^{13}$C NMR of unidentified dibromo-nitro[2.2]paracyclophane regioisomer (a)

Appendix 102: $^1$H NMR of unidentified dibromo-nitro[2.2]paracyclophane regioisomer (b)
Appendix 103: $^{13}$C NMR of unidentified dibromo-nitro[2.2]paracyclophane regioisomer (b)

Appendix 104: $^1$H NMR of a mixture of diamino-octafluoro[2.2]paracyclophane isomers
Appendix 105: $^{19}$F NMR of a mixture of diamino-octafluoro[2.2]paracyclophane isomers
Appendix 106: Crystal data and structure refinement for (S<sub>R</sub>S)-N-(2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-[2.2]paracyclophane-4-amine

Identification code          tcd334  
Empirical formula          C<sub>28</sub>H<sub>30</sub>N<sub>2</sub>O  
Formula weight              410.54  
Temperature                 100(2) K  
Wavelength                  1.54178 Å  
Crystal system              Monoclinic  
Space group                 P2<sub>1</sub>  
Unit cell dimensions        
a = 9.0508(4) Å   \( \square = 90^\circ \).
b = 20.3629(8) Å   \( \square = 92.8190(10)^\circ \).
c = 12.1504(5) Å   \( \square = 90^\circ \).
Volume                      2236.62(16) Å³  
Z                           4  
Density (calculated)        1.219 Mg/m³  
Absorption coefficient      0.570 mm\(^{-1}\)  
F(000)                      880  
Crystal size                0.280 x 0.140 x 0.080 mm³  
Theta range for data collection  3.642 to 70.008°.  
Index ranges               -10≤h≤11, -24≤k≤24, -14≤l≤14  
Reflections collected       31314  
Independent reflections     8372 [R(int) = 0.0346]  
Completeness to theta = 67.679°  100.0 %  
Absorption correction       Semi-empirical from equivalents  
Max. and min. transmission  0.7533 and 0.6249  
Refinement method           Full-matrix least-squares on F²  
Data / restraints / parameters 8372 / 1 / 571  
Goodness-of-fit on F²       1.036  
Final R indices [I>2σ(I)]   R1 = 0.0370, wR2 = 0.0967  
R indices (all data)        R1 = 0.0376, wR2 = 0.0978  
Absolute structure parameter 0.15(7)  
Largest diff. peak and hole  0.241 and -0.195 e.Å\(^{-3}\)
Table 1: Atomic coordinates \((x \times 10^4)\) and equivalent isotropic displacement parameters \((\text{Å}^2 \times 10^3)\) for TCD334. \(U(\text{eq})\) is defined as one third of the trace of the orthogonalized \(U_{ij}\) tensor.

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Table 4: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for TCD334.
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### Appendices

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**Table 5:** Torsion angles [°] for TCD334.

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Appendices

Table 6: Hydrogen bonds for TCD334 [Å and °].

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Appendices

List of Publications:

