Synthesis of Unsymmetrical Cyclopentadienones for use in Polyphenylene Dendrimer Synthesis

Volume 1 of 1

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SCHOOL OF CHEMISTRY
1 Chapter 1: Introduction

1.1 An introduction to dendrimers

1.2 Dendrimer synthesis

1.2.1 Divergent growth method

1.2.2 Convergent growth method

1.2.2.1 Advantages and disadvantages of both methods

1.2.3 ‘Click’ chemistry

1.2.4 Other methods

1.2.4.1 ‘Lego’ chemistry

1.2.4.2 Double exponential growth method

1.2.4.3 Double-stage convergent method

1.3 Characteristics of dendrimers

1.4 Polyphenylene dendrimers

1.4.1 Polyphenylene dendrimer synthesis

1.4.1.1 Suzuki coupling reaction

1.4.1.2 Diels-Alder cycloaddition reaction

1.4.2 Characteristics of a polyphenylene dendrimer

1.4.3 Incorporating functionality into polyphenylene dendrimers

1.4.3.1 A review

1.4.3.1.1 Incorporating chromophores

1.4.3.1.2 Functionalisation at the core

1.4.3.1.3 Heterocyclic functionality

1.4.3.1.4 Incorporating naphthalene

1.4.3.1.5 Other uses of cyclopentadienons

1.5 Aims and objectives

2 Chapter 2: Results and discussion

2.1 Synthesis of cyclopentadienones

2.1.1 Sonogashira coupling reaction
2.1.1.2 Synthesis of cores..................................................41
2.1.1.3 Synthesis of a core containing nitrobenzene..........44
2.1.2 [3+2] Cycloaddition reaction.................................48
2.1.3 Synthesis of diketones..............................................52
2.1.4 Base catalysed condensation reaction..................55
2.2 Synthesis of dendrimers.............................................59
2.2.1 Diels-Alder reaction..............................................59
2.3 Conclusions and future work.................................66

3 Chapter 3: Experimental..................................................68
3.1 General experimental..................................................69
3.2 Synthesis of 3,4-bis(4-bromophenyl)-2,5-diphenyl-2,4- cyclopentadien-1-one60..................................................70
3.3 Synthesis of 3,4-bis(4-methoxyphenyl)-2,5-diphenyl-2,4-cyclopentadien-1-one61..................................................71
3.4 Synthesis of 2-(phenylethynyl)pyridine55........................72
3.5 Synthesis of 1-phenyl-2-(2-pyridinyl)-1,2-ethanediene62.....73
3.6 Synthesis of 1-methoxy-6-(phenylethynyl)naphthylene55....74
3.7 Synthesis of 1-(6-methoxynapthyl)-2-phenyl-1,2-ethanediene62........75
3.8 Synthesis of 3-(6-methoxynapthyl)-2,4,5-triphenyl-2,4-cyclopentadien-1-one60..................................................76
3.9 Synthesis of dendrimer 45..............................................77
3.10 Synthesis of dendrimer 42..............................................79
3.11 Synthesis of 1-\{3-(2-pyridinylethynyl)phenyl\}ethynyl\}2- pyridine55..................................................81
3.12 Synthesis of compound 43..............................................82
3.13 Synthesis of dendrimer 44..............................................83
3.14 Synthesis of 1-(2-nitrophenyl)piperidine55..................84
3.15 Synthesis of (\{3,5-bis[\{trimethylsilyl\}ethynyl\}phenyl\}ethynyl) (trimethyl)silane ......................................................85
3.16 Synthesis of 1,3,5-triethynylbenzene11......................86
3.17 Synthesis of 1-(\{3,5-bis[\{6-methoxy-2- naphthyl\}ethynyl\}phenyl\}ethynyl)-6-methoxynapthalene55..........87
3.18 Synthesis of 1-ethynyl-3-[(4-nitrophenyl)ethynyl]benzene......88

4 References........................................................................89
Tables

Table 1: The Sonogashira reactions carried out during this project

Figures

Figure 1: A generalised structure for a third-generation dendrimer
Figure 2: A universal scheme showing the divergent growth method
Figure 3: A generalised scheme for the convergent growth method
Figure 4: The first successful application of a ‘click’ reaction to dendrimer synthesis
Figure 5: A representation of ‘Lego’ chemistry
Figure 6: A generalised diagram of the double exponential growth method
Figure 7: A scheme showing the first ever synthesis of a polyphenylene dendrimer
Figure 8: The synthesis of a polyphenylene dendrimer by the divergent growth method
Figure 9: A polyphenylene dendrimer containing porphyrin at the core and benzoquinone end groups
Figure 10: A polyphenylene dendrimer containing pyridine rings
Figure 11: Crystal structure of 1-(2-nitrophenyl)piperidine

Schemes

Scheme 1: A route to synthesise cyclopentadienones
Scheme 2: A reaction between the terminal alkyne, the base and the copper iodide
Scheme 3: The formation of the palladium(II) complex
Scheme 4: Final steps of the Sonogashira coupling reaction
Scheme 5: The synthesis of 2-(phenylethynyl)pyridine
Scheme 6: The synthesis of 1-methoxy-6-(phenylethynyl)napthylene
Scheme 7: The synthesis of 1,3,5-triethynylbenzene
Scheme 8: The synthesis of 2-={[3-(2-pyridinylethynyl)phenyl]ethynyl}pyridine
Scheme 9: The synthesis of 1-{3,5-bis[6-methoxy-2-naphthyl]ethynyl}phenyl}-6-methoxynaphthalene
Scheme 10: An attempted coupling reaction using 1-chloro-2-nitrobenzene
Scheme 11: An attempted synthesis of a highly reactive dienophile…………………..45
Scheme 12: The mechanism of a nucleophilic aromatic substitution reaction between
1-bromo-4-nitrobenzene and piperidine……………………………………..46
Scheme 13: Synthesis of compound 27………………………………………48
Scheme 14: A [3+2] cycloadditon between 2-(phenylethynyl)pyridine 14 and
1,3-diphenylcyclopropenone 28……………………………………..48
Scheme 15: The reaction carried out by Wender et al..................................50
Scheme 16: The ring opening of pyridine………………………………………52
Scheme 17: An alternative route for the synthesis of cyclopentadienones………52
Scheme 18: The mechanism for the oxidation on 2-(phenylethynyl)pyridine 14 using
potassium permanganate..............................................................53
Scheme 19: The synthesis fo 1-(6-methoxynapthyl)-2-phenyl-1,2-ethanedione……55
Scheme 20: A reaction between potassium hydroxide and
1,3-diphenylcyclopropenone 33........................................................56
Scheme 21: A reaction between the enolate ion 36 and diketone…………………56
Scheme 22: Formation of the cyclopentadienone...........................................56
Scheme 23: A scheme for the formation of a cyclopentadienone proposed by
Newkome et al..............................................................................58
Scheme 24: The mechanism for the Diels-Alder reaction between a cyclopentadienone
and an alkyne...............................................................59
Scheme 25: Synthesis of dendrimer 42........................................................60
Scheme 26: Synthesis of dendrimer 44........................................................61
Scheme 27: The synthesis of dendrimer 45....................................................63
Scheme 28: A predicted outcome for a reaction between core 21 and a
cyclopentadienone...............................................................64

**Spectra**

Spectrum 1: A mass spectrum of 1-methoxy-6-(phenylethynyl)napthylene.........40
Spectrum 2: The isotope pattern from ES-MS for dendrimer 42.......................66
Appendices

Appendix 1: A $^1$H NMR spectrum of a mixture containing compound 25 and 1-(4-nitrophenyl)piperidine.................................................................97

Appendix 2: A $^1$H NMR spectrum of the product formed from a rhodium-catalysed reaction between 2-(phenylethynyl)pyridine 14 and 1,3-dipheynylcyclopropenone 28.................................................................98

Appendix 3: A COSY NMR spectrum of the product formed from a rhodium-catalysed reaction between 2-(phenylethynyl)pyridine 14 and 1,3-dipheynylcyclopropenone 28.................................................................99

Appendix 4: A $^{13}$C NMR spectrum of the product formed from a rhodium-catalysed reaction between 2-(phenylethynyl)pyridine 14 and 1,3-dipheynylcyclopropenone 28.................................................................100

Appendix 5: The $^1$H NMR spectrum published by Wender et al. for compound 31...101

Appendix 6: The $^1$H NMR spectrum of 3,4-bis(4-methoxyphenyl)-2,5-diphenyl-2,4-cyclopentadien-1-one 41.................................................................102

Appendix 7: Crystal data for 1-(2-nitrophenyl)piperdine.................................................103
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Declaration

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Abstract

Dendrimers are macromolecules that consist of a well-defined architecture. The ability to construct a dendrimer containing certain functional groups that can be placed in certain positions has resulted in dendrimers receiving a considerable amount of interest. Due to the increase of efficient, commercially viable methods to synthesise dendrimers over the past two decades, they are starting to emerge in commercial applications. Due to their rigidity and high thermal stability, polyphenylene dendrimers, a family of dendrimers largely consisting of benzene rings, are becoming increasingly popular. An array of functionality has been incorporated into their structure at various positions, leading to their application as light harvesting systems. However, there is a lack of publications concerning the synthesis of polyphenylene dendrimers containing naphthalene or heterocyclic groups, which have interesting properties. This dissertation reports the synthesis of various novel components and demonstrates the way that they could be used for the synthesis of polyphenylene dendrimers by model reactions.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>PAMAM</td>
<td>Polyamidoamine</td>
</tr>
<tr>
<td>MAP</td>
<td>Multiple Antigen Peptides</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>PEG</td>
<td>Polyethylene Glycol</td>
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<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
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<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
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<tr>
<td>APCI-MS</td>
<td>Atmospheric Pressure Chemical Ionisation-Mass Spectroscopy</td>
</tr>
<tr>
<td>ES-MS</td>
<td>Electrospray-Mass Spectroscopy</td>
</tr>
<tr>
<td>EI-MS</td>
<td>Electron Impact-Mass Spectroscopy</td>
</tr>
<tr>
<td>MALDI</td>
<td>Matrix Assisted Laser Desorption Ionisation</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation Spectroscopy</td>
</tr>
<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectroscopy</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier Transform Infrared</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest Unoccupied Molecular Orbital</td>
</tr>
<tr>
<td>$R_f$</td>
<td>Retardation Factor</td>
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<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>K</td>
<td>Kelvin</td>
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<tr>
<td>Hz</td>
<td>Hertz</td>
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<tr>
<td>m.p.</td>
<td>Melting point</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per Million</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
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<tr>
<td>d</td>
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<td>m</td>
<td>Multiplet</td>
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1 Chapter 1: Introduction
1.1 An introduction to dendrimers

‘Dendrimers are molecular (nano) architectures of a well-defined size and number of terminal groups’. Every dendrimer has three generic components that make them distinguishable: a core, an interior layer of repeating units that is attached to the core, and surface groups that are attached to the outermost interior units as shown in Figure 1.

![Diagram of a generalised structure for a third-generation dendrimer.](Taken from 3.)

C = Core, B = Branching Points, O = Outer Surface Groups.
The numbers represent the layers or generations.

**Figure 1: A generalised structure for a third-generation dendrimer.**
*Taken from 3.*

The name ‘Dendrimer’ originated from the Greek words *dendron* and *meros* meaning tree and part respectively. The first ever description of a dendrimer structure was in February 1978, in an article in which Vogtle and co-workers reported the use of a ‘repeating step principal’ to synthesise branched and acyclic structures that had repeated units throughout the body of the structure. However, the word dendrimer was
not mentioned once.\textsuperscript{4} It was not until 1984 when Tomalia published the synthesis and full characterisation of a novel class of polyamidoamine-PAMAM macromolecules and referred to these as dendrimers.\textsuperscript{5} Vogtle described his strategy as ‘cascade-like’ and ‘nonskid-chain-like’\textsuperscript{4}, a strategy that we now know as the divergent growth method.

1.2 Dendrimer synthesis
1.2.1 Divergent growth method

The divergent growth method is one of two well-established methods for the synthesis of dendrimers; the other strategy is the convergent growth method. In the former method, the dendrimer is assembled from the core outwards\textsuperscript{3}, building the dendrimer layer by layer, with each layer being called a generation.\textsuperscript{6} Here, a core containing several sites of attack or addition is reacted with two or more moles of reagent that contain at least two protected sites of attack. This is followed by the deprotection of these sites, prior to the molecule being subjected to a reaction with two or more moles of reagent once again (Figure 2). This stepwise strategy is repeated until the desired structure is achieved. Examples of dendrimers that have been synthesised via this method are PAMAM dendrimers\textsuperscript{2} that consist of an alkyl diamine core and tertiary amine branches.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Figure2.png}
\caption{A universal scheme showing the divergent growth method.}
\end{figure}

\textit{Taken from}\textsuperscript{2}.
1.2.2 Convergent growth method

On the other hand, the convergent growth method, which was first reported by Hawker and a co-worker in 1989, works in the opposite way. Rather than starting at the core, it starts from what will be the surface groups of the dendrimer and works its way inwards. This method allows the branches or dendrons of the structure to be made independently from the core (Figure 3). Once the dendrons have been made to the desired size, they can be reacted with the core to convert molecules of relatively small molecular weight into a high mass structure in a single step reaction.

![Figure 3: A generalised scheme for the convergent growth method. Taken from 2.](image)

1.2.2.1 Advantages and disadvantages of both methods

In the divergent growth method, a large number of reactive sites are functionalised in each step. Therefore, this method requires a) excessive monomer loading to drive the reaction to completion and b) lengthy chromatographic separation to purify. In comparison, during the convergent growth approach, only a small number of reactive sites are functionalised in each step, making the possibility of a large number of side reactions being produced unlikely, hence making purification a lot easier. Also, the type of reaction used when utilising the divergent growth method must be chosen very carefully; only those that are very efficient should be used i.e. those that produce over 99% yields; using inefficient reactions increases the amount of side products dramatically. Another advantage of the convergent growth method is that it allows one to precisely control the molecular weight and assemble structures that have functionality in precise positions and numbers. The most attractive feature of the convergent method is the ability to prepare well-defined, bi-functional dendrimers, where two dendrons exhibit multiple groups of different functionality.
However, the convergent growth method limits one to the construction of low mass dendrimers compared with those that can be produced by the divergent growth method.\textsuperscript{2} For example, in a paper published which details the synthesis of dendrimers functionalised with carbohydrates by the convergent growth method, the authors state that reactions used to produce high mass dendrimers did not work due to steric issues that were encountered when attaching the dendrons to the core, therefore spacer units had to be added. They also commented on how isolation of pure compounds from crude reaction mixtures proved to be a challenging task.\textsuperscript{9} The reason for this is that as a dendron structure increases in generation, the similarity between the starting materials used and product formed also increase\textsuperscript{2} making the task of separating them very challenging.

Therefore, although the traditional methods to synthesise dendrimers have unique advantages, both also have major flaws.\textsuperscript{5} Excessive monomer loading using the divergent growth method results in either the waste of valuable starting materials if they are not recovered, or the use of valuable time if they are recovered. This, coupled with the necessity to dispose of these in a safe manner would mean high production costs when carried out at an industrial scale. Via these methods, the typical synthesis of a fourth-generation dendrimer requires a minimum of eight steps\textsuperscript{7}, without including the synthesis of the monomers required. This coupled with the need to use purification techniques, results in a very long and time-consuming synthesis with extortionate costs of labour and equipment. It is these flaws that have prevented dendrimer structures from moving forward at a faster rate than they are currently, and from being produced and exploited commercially.\textsuperscript{10} This is why there are only a small number of dendrimer-based products that have reached the industrial development stage, the first of these being PAMAM dendrimers.\textsuperscript{2} There is only one commercially available dendrimer-based product that is about to come on the market. This is a gel-based formulation to protect women from sexually transmitting infections to partners, called VivaGel\textsuperscript{®} made by StarPharma.\textsuperscript{10}

Interest in dendrimers continues to increase; currently there are over fifteen thousand papers, over ten thousand scientific reports and one thousand patents dealing with dendrimer structures.\textsuperscript{7} Due to the ever-increasing interest in dendrimers and their application, the requirement for new methods or strategies for their commercial
syntheses has grown and as a result there are now several modern methods to assemble these molecules. One of these is the concept of ‘click’ chemistry.

1.2.3 ‘Click’ chemistry

Sharpless and co-workers introduced the ‘click’ concept in 2001. However, it was not the reactions which had been given this label that were novel, in fact these were already known to chemists at the time that their paper was published. It was the idea that was unique: the idea that rather than trying to synthesise very complex molecules with difficulty, one should use reactions that have a high thermodynamic driving force and therefore favour the production of only one type of molecule. As a result of this, compounds would be easier to synthesise but would still have the same functionality incorporated into their structure and thus could be successfully used in the same applications. This would allow chemists to discover new molecules more rapidly. Although Sharpless emphasised and focused on the merits of application of his concept within the pharmaceutical industry, it has also been used to generate molecules that are being used in different fields of interest and for different purposes: one of these fields is dendrimer synthesis.

The first successful application of click chemistry to dendrimer synthesis was in 2004, when a convergent synthesis using a ‘click’ reaction was used to synthesise a dendrimer with triazole rings in each generation in a high yield and excellent purity (Figure 4). Here the author reported that the reaction was highly selective, that there was no evidence of the formation of by products and that the reaction proceeded rapidly at room temperature in less than 30 hours. The reaction used in the synthesis of this dendrimer was the copper-catalysed alkyne-azide click reaction that is currently the most popular click reaction within dendrimer synthesis, so much so, that the reaction itself has been called click chemistry. Once the reaction was complete, the copper salts were removed by simply washing the product with ammonium hydroxide/citrate aqueous buffer and the product could either be isolated by filtration or extraction. Dendrimers have also been synthesised via the divergent growth method using the same ‘click’ concept. Therefore, the advantages of using the divergent growth method over the convergent method can also be utilised using click
reactions. This reaction has also been applied to the synthesis of linear polymers, polymer networks, polymeric nanoparticles and other polymeric architectures.\textsuperscript{11}

\[
\begin{align*}
\text{R}^1 & \equiv \equiv + \text{N}_3 \rightarrow \text{R}^2 \quad \text{a)} \\
\text{N} & \equiv \equiv \text{N} \equiv \equiv \quad \text{R}^1 \quad \text{R}^2 \\
a) & : \text{Cu(I)}
\end{align*}
\]

**The copper-catalysed azide-alkyne ‘click’ reaction**

\[
\begin{align*}
\equiv & \equiv \equiv + \text{N}_3 \rightarrow \text{R}^2 \\
\text{R}^2 & \equiv \equiv \text{N} \equiv \equiv \quad \text{R}^2 \\
a) & : \text{Cu(I)} \\
b) & : \text{Deprotection step}
\end{align*}
\]

**Figure 4: The first successful application of a ‘click’ reaction to dendrimer synthesis.\textsuperscript{10}**

‘Click’ chemistry is the term given to any coupling reactions that a) are highly selective; b) yield the desired product in over 99%; c) are able to proceed in the presence of a variety of solvents irrespective of their chemical properties; d) have a high tolerance to other functional groups and e) proceed at various types of interfaces.\textsuperscript{7} Reactions that fulfil these requirements give chemists the unique tool of being able to use a wide range of building blocks and it allows them to synthesise molecules that are not approachable by any other means. However, it is the extraordinarily high yield, which these coupling reactions produce, that makes this concept a very interesting and attractive tool in the synthesis of dendrimers. The ability of these reactions to produce almost 100% conversion and that to with the use of stoichiometric amounts of starting material eliminates any possibility of the production of side products.\textsuperscript{7} Furthermore, once the reaction is complete, the presence
of starting material is extremely small, which from a commercial aspect is not only economically efficient, due to minimal waste and therefore minimal loss of money, but it also makes purification of the product quick and easy: the most that is required to afford the desired product is its extraction or precipitation. There is no requirement to carry out flash column chromatography\textsuperscript{10}: which reduces time and labour costs. Compared to the eight steps that it takes to produce fourth-generation dendrimers \textit{via} the divergent growth method or the convergent growth method, it only takes four steps using click chemistry.\textsuperscript{11} Currently, the only waste that the copper-catalysed alkyne-azide reaction produces is the copper catalyst.\textsuperscript{13} However, there has been a recent report of the use of a reusable copper catalyst\textsuperscript{10}, which would increase the commercial viability of such reactions further. Therefore, the concept of ‘click’ chemistry addresses all the issues and concerns that chemists have been faced with for many years whilst trying to synthesise dendrimers for commercial applications. Armed with this relatively new technology, we hope to see many more dendrimer-based products on the market in the near future.

1.2.4 Other methods

1.2.4.1 ‘Lego’ chemistry

Although ‘click’ chemistry is by far the most popular and best-documented method used for the synthesis of dendrimers, there was a surge in the publication of other strategies after the realisation that a more economical method was required than the traditional two. One of these methods is known as ‘Lego’ chemistry\textsuperscript{2}, which was first proposed in 1994. This method, like the others that will be discussed in this section, offers unique advantages such as a) the production of only environmentally friendly by-products such as nitrogen gas and water\textsuperscript{14}; b) phosphorus atoms can be incorporated both into the structure\textsuperscript{15} and at the surface of the dendrimer, as can aldehyde groups which led to dendrimers that had numerous properties and which can be used in many applications\textsuperscript{14}; c) there is no requirement for the protection or deprotection step that all dendrimer syntheses require therefore reducing production time by almost half. The starting materials used in this method are a core and two heavily branched monomers. One of these branched monomers is reacted with the core. The functional groups at the extremities of each of these molecules are designed in such a way that they can selectively react with one another forming the first
generation dendrimer without the need to protect and de-protect them.\textsuperscript{15} This
dendrimer is then subjected to a reaction with the second monomer which allows
chemists to produce a dendrimer with alternating generations or layers and one with
many surface groups, going from 48 to 250 end groups in just one step (Figure 5).\textsuperscript{2}
Similar to a ‘click’ reaction, only stoichiometric amounts of the starting materials are
required to drive the reaction forward and purification of the desired product is
achieved by extraction or repetitive precipitation. However, although fourth
generation dendrimers can also be synthesised within four steps, the reaction times are
much longer than a typical ‘click’ reaction, with anything from hours to days.\textsuperscript{14}

![Figure 5: A representation of ‘Lego’ chemistry.](image)

A, B, C, D and E: Functional groups

### 1.2.4.2 Double exponential growth method

 Another strategy is the double exponential growth method, which requires only one
starting material. Deprotection of the reagent takes place at both ends, in separate
reactions, and as a result produces two products that can be reacted together to form
the first generation structure. The steps are once again repeated to produce the third-
generation dendrimer (Figure 6). This method enables rapid construction of
dendrimers\textsuperscript{3}, however high generation dendrimers are problematic to synthesise \textit{via}
this method due to steric hindrance.
1.2.4.3 Double-stage convergent method

This method brings together the advantages of both the divergent growth method and the convergent growth method by using both. The divergent growth method is used to synthesise a low molecular weight core with several functional groups attached to it, and the convergent growth method is used for the synthesis of the dendrons. The branched core is then subjected to a reaction with the dendrons. This allows one to synthesise high molecular weight dendrimers without the need to use time-consuming purification techniques.

1.3 Characteristics of dendrimers

The systematic fashion in which dendrimers are synthesised results in structures that have a uniform size, shape and mass distribution: in another words they have a low polydispersity. The extent of the branching on the monomer and the core that are used for the synthesis of a dendrimer has an effect on the internal and external density of the structure. Therefore, dendrimers are becoming more and more popular as delivery vehicles as one is able to modify the density within the dendrimer and reduce
it in order to accommodate for guest molecules by carefully selecting the core and branched units. Molecules that are being transported in such a way are drug molecules\textsuperscript{3, 16, 2} and genes\textsuperscript{2, 17}. Genes have a limited permeability across cell membranes and are therefore rapidly cleared from the body.\textsuperscript{17} Dendrimers are particularly useful in the transportation of molecules through a biologically active environment as their size allows them to cross biological barriers easily. Dendrimers are useful in the transportation of drugs, as they have been shown to improve their solubility allowing them to be more bio-available. Just under half of newly developed drugs are rejected by the pharmaceutical industry because of poor bio-availability due to low water solubility.\textsuperscript{18} More importantly, the ability to construct dendrimers with specific functionality on the periphery and therefore construct carriers containing specific properties makes them very attractive. However, the use of dendrimers for drug delivery has also been shown to increase cytotoxicity as their positively charged surface groups are prone to destabilise cell membranes causing cell lysis.\textsuperscript{18} Effective transport of genes through the body is of strong interest as one could interfere with disease-causing proteins at an early stage of gene expression and prevent them from occurring.\textsuperscript{17}

Arrays of new and better methods are available to use, and many different dendrimer structures have been synthesised that can be arranged into two groups, these are chiral dendrimers and achiral dendrimers. It is not surprising that the list of achiral dendrimers that have been synthesised is a lot longer than the list of chiral dendrimers as they are less challenging to synthesise. PAMAM dendrimers are by far the most popular type of chiral dendrimers. Their synthesis has been perfected and they are now produced commercially on a multi-kilogram scale.\textsuperscript{1} PAMAM dendrimers are the most extensively reported moiety for almost all existing applications of dendrimer but most invested for their use in drug delivery as they offer many advantages such as immunogenicity and water solubility. As well as this, their internal cavities allow guest molecules to be encapsulated within the dendrimer and the dendrimer terminal amine groups act as binding sights for guest molecules.\textsuperscript{2}
1.4 Polyphenylene dendrimers

1.4.1 Polyphenylene dendrimer synthesis

1.4.1.1 Suzuki coupling reaction

Another family of dendrimers are polyphenylene dendrimers. Polyphenylene dendrimers are dendrimer structures that largely consist of benzene rings. The first ever synthesis of a polyphenylene dendrimer structure was reported by Miller and Neenan in 1990, in which they used the convergent growth method, using one of two methods that are now available to chemists to produce this type of dendrimer. The convergent growth method utilises the widely used Suzuki coupling reaction and involves the coupling of an aryl boronic acid such as compound 1 to an aryl bromide containing a trimethylsilane protecting group such as compound 2. This is then followed by the conversion of the trimethylsilane group to a reactive boronic acid group enabling it to be once again coupled with an aryl bromide. This sequence of reactions is repeated until a dendron of the desired size is achieved, which is when they are coupled to an aryl bromide core such as compound 3 forming a polyphenylene dendrimer such as compound 4 (Figure 7). However, the reactions used in this synthesis can not be classified as ‘click’ reactions which is why they did not go to completion and were not very selective, thus producing a variety of side products, which not only made purification of the target compound difficult but also resulted in very low yields. These are only a few of the reasons why this method has not been widely executed for the synthesis of polyphenylene dendrimers.
a): BBr₃, KOH

b): Pd(PPh₃)₄, Na₂CO₃

Figure 7: A scheme showing the first ever synthesis of a polyphenylene dendrimer.¹⁹

1.4.1.2 Diels-Alder cycloaddition reaction

The other method, which is now used to synthesise most of the polyphenylene dendrimers, is one that uses a ‘click’ reaction: the Nobel prize winning Diels-Alder cycloaddition reaction. This was the first ‘click’ reaction out of three to be discovered¹³, which in the synthesis of polyphenylene dendrimers, involves the reaction between a cyclopentadienone (the diene) and a carbon-carbon triple bond (the dieneophile) that produces a stable benzene ring. Otto Diels and Kurt Alder invented the Diels-Alder reaction in 1982, but it was not until the 1990s that this was successfully incorporated into the synthesis of polyphenylene dendrimers. Mullen and coworkers achieved this¹³ after there was a requirement for a higher yielding, commercially viable route to synthesis polyphenylene dendrimers.
This reaction is carried out at a relatively high temperature\(^{19}\) and due to the elimination of carbon monoxide during the reaction, shifts the equilibrium irreversibly towards the formation of the new ring. However, very recently this reaction has been shown to be reversible when a Diels-Alder reaction between two bicyclic adducts takes place, forming two possible isomers, the \textit{endo} and \textit{exo} isomer that are exclusively favoured by kinetic or thermodynamic consideration. When this has been applied to the synthesis of dendrimers, thermal decomposition has taken place that has armed scientists with the technology of a thermosensitive triggering system, which could allow one to control the release of species encapsulated within the cavities of the dendrimer such as drug molecules or genes.\(^{13}\)

In the typical style of a ‘click’ reaction, this reaction is also very selective; producing extremely high yields and is able to perform very well in a variety of solvents such as toluene\(^{20}\), \textit{o}-xylene\(^{19}\) and water. This, coupled with the fact that unlike the copper-catalysed alkyne-azide reaction does not require the use of metals, makes this a more environmentally friendly reaction and ideal for dendrimer synthesis.\(^{13}\)

With the use of the Diels-Alder reaction, polyphenylene dendrimers can be synthesised \textit{via} both the convergent and the divergent growth method, whereas they can only be synthesised \textit{via} the convergent growth method when using the Suzuki coupling reaction.\(^{19}\) Therefore, this method allows scientists to synthesise high mass polyphenylene dendrimers and benefit from the other advantages that the divergent growth method has to offer in comparison with the convergent growth method. Via the divergent method, a core such as \textit{5}, which has ethynyl groups attached to it, is used. A reaction between the core and stoichiometric amounts of cyclopentadienone containing protected ethynyl groups such as \textit{6} is carried out, producing the first-generation dendrimer \textit{7}. The ethynyl groups on the resulting dendrimer are de-protected to which cyclopentadienones are once again reacted. In the final step cyclopentadienones that do not contain protected ethynyl groups are used (\textbf{Figure 8}). Using this method, purification of the product can be carried out by precipitation.\(^{13}\) Muller \textit{et al} carried out the first divergent synthesis of polyphenylene dendrimers in 1997 using this method.
1.4.2 Characteristics of a polyphenylene dendrimer

Figure 8: The synthesis of a polyphenylene dendrimer by the divergent growth method.

In comparison to the other types of dendrimers that can also be synthesised by very efficient methods, the large number of benzene rings that polyphenylene dendrimers
encompass within their structure arm them with physical and chemical properties that are unique to this class of dendrimer.

Due to the close proximities of the large benzene rings within the structure, and the ability for the structure to rotate around the inter-ring carbon-carbon bonds only\textsuperscript{19}, the rings twist in a way that they interlock, which reduces their mobility, producing a very rigid and what is known as a ‘shape persistent’ structure. This information has been obtained from a variety of studies of polyphenylene dendrimers using techniques such as solid-state NMR experiments that together with neutron diffraction experiments have shown that the benzene rings in polyphenylene dendrimers, especially those within the core and the scaffold of the structure, display very limited and heavily restricted movements, with the density of these structures increasing towards the periphery of the molecules.\textsuperscript{21} They have also shown that internal voids or areas of low density within polyphenylene dendrimers have a far more defined structure in comparison to other dendrimers.

Another characteristic of polyphenylene dendrimers is that they only start to decompose at temperatures above 450 ºC with degradation in some polyphenylene dendrimer structures starting at temperatures as high as 575 ºC under a nitrogen atmosphere. In particular, it is the rigid characteristic that these structures hold, which has not been available from the use of the majority of dendrimers around today. This is because they are all relatively flexible and have therefore hindered the use of dendrimers in a number of applications in which polyphenylene dendrimers could show success. One example of this is the use of polyphenylene dendrimers in the construction of multiple antigen peptides (MAPs). MAPs are nano particles on which several recognisable polypeptides are attached, that when introduced into an organism are able to trigger an immune response. These structures have proven to exhibit amplified immogenicity however, the branched polylysine dendritic matrix on which these polypeptides have been attached till present, do not possess a defined spatial structure, allowing interactions to occur that are believed to have an unfavourable affect to their function. Therefore, the attachment of these polypeptides to rigid polyphenylene dendrimer structures could prevent these unfavourable effects from occurring and pave a way towards fully synthetic vaccines.\textsuperscript{22}
However, the enclosure of just benzene rings within polyphenylene dendrimers have impeded the use of these dendrimers for applications such as catalysis as they do not contain functional groups capable of binding to metal ions. Therefore, continued efforts are being made to incorporate functionality into the synthesis of polyphenylene dendrimers that has enabled these structures to be the subject of interest as possible delivery agents for drugs or DNA. This is because fragments that are capable of binding to biological material can be attached to the dendrimer, which coupled with the inert and non-toxic properties that polyphenylene dendrimers hold, make them strong candidates for this application.

1.4.3 Incorporating functionality into polyphenylene dendrimers

The way that functionality has been incorporated into the structure of a polyphenylene dendrimer is by incorporating functionality into the building blocks that are used in their synthesis i.e. the cyclopentadienone and the core. This is another reason why the method that uses the Diels-Alder cycloaddition reaction to synthesise these dendrimers has been so popular, as this reaction is not influenced by the substituents present on the cyclopentadienone. Therefore, a wide range of functional groups can be incorporated into a polyphenylene dendrimer via this method provided that they can survive the relatively high reaction temperatures that are required for this reaction to go to completion.

Incorporating functionality into the cyclopentadienone allows chemists with great control, where one is able to place a defined number of groups both within the scaffold of the structure and at the periphery of the dendrimer structure. Also, by using several cyclopentadienones that each possess different functionality, one can incorporate several different types of functionality into the dendrimer, allowing the potential for a structure to be used for numerous applications. Functionalisation exclusively at the periphery of the polyphenylene dendrimer can be achieved by restricting the use of functionalised cyclopentadienones to the final step of the synthesis of the dendrimer. Compared with flexible dendrimers, where functional groups that are attached to the outer generation distribute evenly throughout the structure of the dendrimer, functional groups that are attached to the periphery of polyphenylene dendrimers stay at the periphery, as the rigid structure of the
dendrimer does not allow the back folding of branches to take place. This produces a layer that shields the aromatic structure and changes properties such as the polarity, solubility and adsorption of the dendrimer, whilst maintaining the advantage of rigidity and stability. Therefore chemists have the ability to ‘tune’ these dendrimers to accommodate their needs.\textsuperscript{19}

Functionalisation of a polyphenylene dendrimer within the scaffold also has many advantages. It allows one to introduce functionality to the internal cavities of the dendrimer and affects their chemical properties, allowing the dendrimer to be used to bind with metal clusters that fit into these cavities. Not only this, but the overall functionalisation of the dendrimer can be increased, which would increase the overall intensity of the absorption or emission of the dendrimer, if the molecules incorporated into the dendrimer were chromophores.

Another way that functionality can be introduced into polyphenylene dendrimers is by functionalisation of the core. By using this method, the functionality at the core is shielded by the dendrons of the dendrimer and therefore prevents any interaction between the functionality on the core and other species from taking place. This method of functionalisation has proved useful where such interactions have prevented the use of dendrimers for applications that they were primarily intended for. Just one example of this is when dyes have been incorporated into dendrimer structures. In these cases, the chromophores have formed aggregates due to the interactions that have taken place between each other.\textsuperscript{21}

1.4.3.1 A review

Various functionalities have been successfully introduced into polyphenylene dendrimers using these strategies, with the majority of them being dendrimers that have been functionalised at the periphery as this is the easiest. Polyphenylene dendrimers have been synthesised with polar groups such as carboxylic acids, nitriles and amines on their surface. This has allowed chemists to a) bind an array of other molecules to the surface of polyphenylene dendrimers\textsuperscript{21} and to b) understand how different groups on the surface of this family of dendrimer changes the characteristics of them. Polyphenylene dendrimers have also been functionalised at the periphery to
study the self-assembly of polyphenylene dendrimers, for which functionality at the periphery plays a vital role.24

Polyphenylene dendrimers generally assemble into micrometer long non-fibres but have been shown to self assemble into ordered layers when they have been functionalised with dodecyl or octyl groups. They have also been functionalised with pentafluorophenyl units and the number of these units have shown to play a part in the type of structure the dendrimer assembles into, due to the change in intermolecular interaction and surface affinity.24 Other groups that have been attached to the periphery of polyphenylene dendrimers are peptides, to be used as MAPs as mentioned earlier22, and ester groups, such as 2-bromo-2-methylpropionic ester that has allowed a polyphenylene dendrimer to be soluble in aliphatic non-polar solvents and has enabled it to adjust its surface polarity depending on the environment it is in. This type of structure could therefore be used to carry molecules through media of varying polarity.25 Acid groups such as lipoic acid, which has the ability to bind with noble metals, have also been attached to the periphery of polyphenylene dendrimers, and has allowed them to serve as linkers between two metal surfaces.26

In our group, the periphery of first-generation polyphenylene dendrimers has been functionalised with either polyethylene glycol (PEG) or sugar molecules. The attachment of either PEG or sugar molecules onto the surface of hydrophobic dendrimers allows them to be water-soluble. The attachment of PEG has also shown to reduce the cytotoxic nature of polyphenylene dendrimers. The dendrimers’ ability to enable a water insoluble drug to become water-soluble was evaluated which showed that the drug became increasingly water-soluble as the concentration of the dendrimer increased.

1.4.3.1.1 Incorporating chromophores

However, it is the attachment of one particular group of compounds to polyphenylene dendrimers that is receiving a considerable amount of interest; these molecules are chromophores. Chromophores have been introduced to polyphenylene dendrimers at all three positions of the structure: the core27, the scaffold and the periphery. Polyphenylene dendrimers exhibit strong fluorescence, which increases with the
increase in generation. By incorporating a chromophore such as perylenediimide into the core of the dendrimer, that has the ability to collect the energy produced by the dendrons and exhibit a strong emission when the dendritic arms are indirectly excited\textsuperscript{27}, allows them to be evaluated as light harvesting systems and potential alternative energy sources. In some cases, these chromophores have been embedded within the core of a dendrimer and attached to the periphery of the same structure. This has proved useful to study and gain a better understanding of the energy transfer that occurs between the chromophores, which mimics natural processes such as photosynthesis (Figure 9). An attempt to study this mechanism using more flexible dendrimers has proven to be difficult as it has resulted in the chromophores being in close proximity and thus the mechanism occurs at too fast a speed to study.\textsuperscript{28} One particular chromophore, perylene monoimide, has been incorporated into the scaffold of a polyphenylene dendrimer.\textsuperscript{29} Incorporation of chromophores into the scaffold not only allows the emission or absorption properties of the dendrimer to be increased but it has also allowed the space between adjacent layers to be extended that has resulted in the density at the periphery of the dendrimer to be decreased.\textsuperscript{29} The high density at the periphery of polyphenylene dendrimers has meant that these dendrimers have not been synthesised above four generations. Therefore reducing the peripheral density can allow the synthesis of larger polyphenylene dendrimers. This has been demonstrated by the synthesis of a six-generation polyphenylene dendrimer, the largest reported till date, from the incorporation of oligo($p$-phenylene) spacers into a polyphenylene dendrimer.\textsuperscript{30}
Figure 9: A polyphenylene dendrimer containing porphyrin at the core and benzoquinone end groups.\textsuperscript{28}

1.4.3.1.2 Functionalisation at the core

Functionality has been incorporated into cores that can be used in the construction of polyphenylene dendrimers. Examples of this are the incorporation of photo responsive molecules such as azobenzene\textsuperscript{31} and metals such as ruthenium\textsuperscript{21} and iridium.\textsuperscript{32} Azobenzene is a photo-responsive molecule that exhibits a small conformation change upon excitation from exposure to either ultra violet light or visible irradiation.\textsuperscript{31} Another molecule with the same property is stilbene that can undergoes cis-trans isomerisation on photo-irradiation in a benzene solution.\textsuperscript{33} When used as a dendrimer core, it can allow one to change the structure of the dendrimer considerably, simply by exposure to the light stimulus. It may therefore be possible for these polyphenylene dendrimers to be used not only as light harvesting systems, but also ‘as model systems mediating the conversion of light into other forms of energy’. They could also be used
to study the photochemical isomerisation mechanism that both azobenzene and stibene undertake.\textsuperscript{34}

### 1.4.3.1.3 Heterocyclic functionality

However, although several cyclopentadienones that contain heterocyclic functionality e.g. carbazole\textsuperscript{35}, furan\textsuperscript{20}, pyridine\textsuperscript{20, 23, 36} have been synthesised, there have not been as many reported syntheses of polyphenylene dendrimers containing heterocyclic functionality.

Incorporation of heterocyclic groups, those that contain nitrogen in particular, into any dendrimer structure has many advantages. This has been proven by the incorporation of triazole rings into many dendrimers. One particular example is a bifunctional dendrimer that had 16 mannose groups on the periphery each made with triazole linkages. This dendrimer has shown to be 240 times more potent than monomeric mannose when in a hemagglutination assay.\textsuperscript{11} Dendrimers containing nitrogen heterocycles are useful in biological applications as they are relatively stable to metabolic degradation and do not diminish in activity when employed for such applications.\textsuperscript{10} Other advantages of incorporating heterocyclic functionality into polyphenylene dendrimers have been demonstrated by Shifrina \textit{et al} from the synthesis of polyphenylene dendrimers containing pyridine rings both within the scaffold and at the periphery, the only reported synthesis of this type of polyphenylene dendrimer to our knowledge (Figure 10).\textsuperscript{23} Not only does the rigidity and shape-persistent structure of polyphenylene dendrimers hinder the aggregation of metal nanoparticles encapsulated within the well determined cavities of the dendrimer onto metallic sites\textsuperscript{37}, the nitrogen centre of the heterocycle has the ability of bind to a variety of transition metals.\textsuperscript{10} In addition to this, the thermal stability of polyphenylene dendrimers could allow the catalysis of reactions that would be impossible by other means. Shifrina \textit{et al} showed that the presence of pyridine within the dendrimer allowed the encapsulation of palladium(II) acetate, which on reduction, led to the formation of fixed palladium(0) nano particles. However, only dendrimers with pyridine rings on the interior of the structure allowed for this to occur whereas dendrimers with pyridine rings on the periphery precipitated out from the reaction solution due to intermolecular co-ordination with palladium salts.\textsuperscript{37}
1.4.3.1.4 Incorporating naphthalene

Naphthalene has also been a very useful molecule in relation to dendrimer synthesis; the active compound of Vivage®, the only dendrimer-based product about to be commercialised, is a dendrimer decorated with 32 naphthalene disulfonate units. A number of other dendrimers that have been synthesised for the study of energy transfer and as potential light harvesting components in systems useful for the conversion of solar energy contain naphthalene in either the scaffold or at the periphery of the structure, as it is a chromophore, exhibiting significant absorption at an excitation wavelength of 266 nm acting as an energy donor group. At the same time, the presence of naphthalene in a dendrimer can also act as a shield, protecting the core from degradation in solvents.
Due to such an array of advantages available from introducing functionality into polyphenylene dendrimers, the synthesis of functionalised monomers used in the synthesis of this type of dendrimer, i.e. the cyclopentadienone and the core are of great interest not only in this field, but also in fields where such molecules are of the same value.

1.4.3.1.5 Other uses of cyclopentadienones

Cyclopentadienones have also been used as ligands in metal complexes that act as catalysts for reactions such as the dehydrogenation of secondary alcohols to ketones and the hydrogenation of ketones and as ligands that can be reduced, leading to the thermodynamic stability of metal complexes. Some, due to the functionality they contain, can also act as bridging ligands giving rise to chiral co-ordination polymers. However, cyclopentadienones have been mainly used as intermediates and building blocks to form larger molecules, such as dendrimers, and a variety of polymers.

1.5 Aims and objectives

Therefore, the aim of this project was to synthesise building blocks containing heterocyclic functionality and naphthalene molecules that could be used for the syntheses of polyphenylene dendrimers. The aim was to do this by synthesising cyclopentadienones and cores containing this functionality that could be converted into polyphenylene dendrimers via the Diels-Alder reaction. It was also planned to evaluate the efficiency of the Diels-Alder reaction in the synthesis of polyphenylene dendrimers.
2 Chapter 2: Results and discussion
2.1 Synthesis of cyclopentadienones

An elegant two step method for the synthesis of cyclopentadienones was found during a literature review and is shown in Scheme 1:

\[
\text{R}^1\text{Br} \quad \underset{\text{Sonogashira Coupling}}{\longrightarrow} \quad \text{R}^1\text{C} \quad \text{O}
\]

\[
\text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{OMe}
\]

a): 1 mol\% \([\text{RhCl(CO)}_2]_2\), toluene (0.3 M), 80°C, 2 hours.

Scheme 1: A route to synthesise cyclopentadienones.\(^{20}\)

It had been demonstrated that the second step of this method could tolerate a variety of alkynes, including those that contain heterocyclic rings, and several arylalkylcyclopropenones.\(^{20}\) Therefore, the syntheses of 2-(phenylethynyl)pyridine and 1-methoxy-6-(ethynylphenyl)napthylene were attempted using Sonogashira coupling reactions.

2.1.1 Sonogashira coupling reaction

The Sonogashira coupling reaction is part of a group of reactions that use a palladium catalyst to couple two relatively simple unsaturated reactants together. This reaction is the coupling of terminal alkynes with aryl or vinyl halides. The catalytic process for this reaction requires the use of a palladium(0) complex. The reaction is performed in the presence of a base and traditionally uses copper iodide as a co-catalyst.\(^4^5\) The copper iodide, the base and the terminal alkyne react together resulting in the formation of an organocopper intermediate (Scheme 2).
Scheme 2: A reaction between the terminal alkyne, the base and the copper iodide.\textsuperscript{45}

The palladium(0) complex 9 is formed via an initial ligand dissociation of an 18-electron non-reactive or stable species 8. This produces a complex that is a coordinatively unsaturated 14-electron species and that is electron rich which therefore undergoes oxidative addition with the aryl or vinyl halide forming a palladium(II) complex 10 (Scheme 3):

Scheme 3: The formation of the palladium(II) complex.

This complex then undergoes transmetalation with the organocopper intermediate followed by reductive elimination to regenerate the palladium(0) complex and yield the coupled alkyne 11 (Scheme 4):
Scheme 4: Final steps of the Sonogashira coupling reaction.\textsuperscript{45}

A number of literature precedents have appeared that have evaluated this coupling reaction by carrying out many reactions that use the same reactants but differ in the conditions under which each reaction is carried out (i.e. the base, the palladium catalyst, the solvent system and the temperature) in order to discover the conditions that produce the optimum result for those reactants.\textsuperscript{46, 47, 48} The results produced from these studies show that the yield of the Sonogashira coupling reaction is dependant on the conditions employed. They also show that the conditions that produce the optimum results are dependant on the reactants used, in particular the choice of halide employed. Thus, the conditions that produce the highest yield for the coupling of aryl iodides will not produce the best results when using aryl bromides. Therefore, the conditions must be altered if switching the organohalide component. Aryl chlorides are by far the most difficult to couple, with the highest yields being produced only by the use of expensive catalysts\textsuperscript{49} that are not as readily available as those that are used for bromides and iodides. ‘Therefore the search for practical catalysts that exhibit high activity and broad generality is a field of continuing interest’.\textsuperscript{50} For this reason, aryl bromides were used throughout this project for this coupling reaction.

### 2.1.1.1 Synthesis of alkynes

The synthesis of 2-(phenylethynyl)pyridine 14 was pursued via the coupling of ethynylbenzene 12 and 2-bromopyridine 13 using the conditions traditionally employed for a Sonogashira coupling reaction i.e. bis(triphenylphosphine)palladium(II) chloride as the catalyst, copper iodide as the co-catalyst and triethylamine as the base. These conditions had been well documented for these reactants producing yields greater than 90\% and were also employed successfully in reactions using other aryl bromides.\textsuperscript{51,52,53,54} However, this procedure was not successful and NMR analysis of the crude product indicated that 2-bromopyridine 13 was still present in a large quantity leading to the conclusion that
little reaction had occurred. Therefore, different conditions were employed that involved the introduction of an aqueous solvent system (water/acetone 1g:1g) and the removal of the copper iodide co-catalyst, conditions that are becoming increasingly popular and attractive as the requirement for environmentally friendly reactions grow (Scheme 5). This reaction produced the desired product in a good yield (69%) but had to be purified by flash column chromatography due to the production of several side products that was shown by TLC. The reaction was primarily carried out at 120 °C and then again at 60 °C at a larger scale that produced identical results. This proved that temperature does not have an affect on the yield or any other part of this reaction. This conclusion complemented the results from a study carried out by Shi and Zhang.

\[ \begin{align*} 
  \text{12} + \text{Br} & \rightarrow \text{14} \\
\text{a): Piperidine, palladium(II) chloride, triphenylphosphine, (distilled water/acetone 1g:1g), 60°C, 24 hours.} 
\end{align*} \]

Scheme 5: The synthesis of 2-(phenylethynyl)pyridine.

As these conditions produced good results for this reaction, they were also used for the synthesis of 1-methoxy-6-(phenylethynyl)naphthylene 16 that was carried out at the lower temperature (Scheme 6). Once again the product was purified by flash column chromatography followed by recrystallisation in hexane to remove a yellow coloured impurity that was preventing the detection of the molecular ion (M+H)+ by mass spectroscopy. Before the product had been recrystallised, a molecular ion (M+H)+ with a mass of 536 had being detected using APCI-MS. However, after the product was recrystallized, a molecular ion (M+H)+ with a mass of 291 was detected by the same method, and when the same product was analysed using electrospray-mass spectroscopy (ES-MS), a molecular ion (M+H)+ with a mass of 173 was detected. It was only when the alkyne was analysed using electron impact-mass spectroscopy (EI-MS) that a molecular ion (M+H)+ with a mass of 258 was detected (Spectrum 1).
Once recrystallised, the product was a white crystalline solid. However, the isolated yield from this reaction was considerably less than the previous one.

\[ 
\begin{align*}
\text{12} & + \text{Br1215} \quad \text{a)} \\
\text{15} & \rightarrow \text{16}
\end{align*}
\]

a): Piperidine, palladium(II) chloride, triphenylphosphine, (distilled water/acetone 1g:1g), 60°C, 24 hours.

**Scheme 6: The synthesis of 1-methoxy-6-(phenylethynyl)napthylene**\(^{55}\).

**Spectrum 1: A mass spectrum of 1-methoxy-6-(phenylethynyl)napthylene.**
2.1.1.2 Synthesis of cores

Since the core that is used in the synthesis of a polyphenylene dendrimer governs its topology\textsuperscript{19}, two different substructures for the core were used in an attempt to produce polyphenylene dendrimers of different structures. These were 1,3-diethynylbenzene, that was readily available commercially, and 1,3,5-triethynylbenzene \textsuperscript{18}, that was synthesised from literature methods as shown in Scheme 7:

\begin{itemize}
  \item a): Diethylamine, copper iodide, \([Pd(PPh\textsubscript{3}Cl)]\textsubscript{2}\), 50 °C, 7 hours.\textsuperscript{56}
  \item b): Anhydrous \(K_2CO_3\), anhydrous methanol, room temperature, 3 hours.\textsuperscript{57}
\end{itemize}

\textbf{Scheme 7: The synthesis of 1,3,5-triethynylbenzene.}

Once again, traditional conditions were employed for the Sonogashira coupling reaction used that produced target product \textsuperscript{17} in a shorter time period than the 48 hours reported by Shi and Zhang to produce a similar product.\textsuperscript{55} Compound \textsuperscript{17} was purified by column chromatography as a white solid from which the trimethylsilane groups were removed in the next step. This deprotection was very efficient with almost 100% conversion. A dark brown flaky product was isolated by the removal of the anhydrous methanol followed by extraction of product \textsuperscript{18} into dichloromethane.

The reaction used for the deprotection of compound \textsuperscript{17} demonstrates why this reaction has been used for the deprotection of a large number of ethynyl groups during the synthesis of polyphenylene dendrimers: it is very efficient and does not produce side products. As a result of this, a complex purification method is not required. The substructures 1,3-diethynylbenzene \textsuperscript{19} and 1,3,5-triethynylbenzene \textsuperscript{18} were then functionalised using 2-bromopyridine \textsuperscript{13} and 1-bromo-6-methoxynaphthalene \textsuperscript{15} respectively by Sonogashira coupling reactions to produce
cores 20 and 21 (Scheme 8 and 9). Table 1 shows all the coupling reactions that were carried out during this project and the yields that each reaction produced.

Scheme 8: The synthesis of 2-\{3-(2-pyridinylethynyl)phenyl|ethynyl|pyridine.\}

Scheme 9: The synthesis of 1-\{3,5-bis\{(6-methoxy-2-naphthyl)ethynyl|phenyl|ethynyl\}-6-methoxynapthalene.
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<th>Isolated Yield (%)</th>
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<th>Duration of reaction (hours)</th>
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Conditions used: Palladium(II) chloride, triphenylphosphine, piperidine, (distilled water/acetone 1g:1g), 60 ºC.55

Table 1: The Sonogashira coupling reactions carried out during this project.
The results shown in Table 1 back up the findings from the literature as either change of the terminal alkyne or the bromo halide whilst using the same conditions produced a negative effect on the yield of the reaction in all cases. Therefore, the conditions should be changed according to the reactants used. Another possible reason for the low yields could have been due to the fact in all the reactions undertaken; a black precipitate was produced once the reaction vessel was at 60 °C. This was insoluble in any organic medium and was therefore separated by filtration during work up of the reaction. This could have been the consequence of the palladium catalyst slowly decomposing once at 60 °C resulting in the production of elemental palladium also known as ‘palladium black’ as it forms a black precipitate. Once the catalyst decomposes it can no longer catalyse the reaction that as a result stops. This may also be the reason why Sonogashira coupling reactions are typically carried out at room temperature. Therefore, one way to increase the yield of the reactions could be to carry them out below 60 °C.

2.1.1.3 Synthesis of a core containing nitrobenzene

Although the conditions that were used for the Sonogashira coupling reactions carried out in this project work relatively well for a variety of functional groups as shown by Shi and Zhang\textsuperscript{55}, they do not work well for electron withdrawing groups that was evident by the failure of the reaction between 1-chloro-2-nitrobenzene \textsuperscript{23} and 1,3-diethynylbenzene \textsuperscript{19} (Table 1,entry 6). This reaction was carried out in order to produce core \textsuperscript{24} in which the ethynyl groups (the dienophiles during a Diels-Alder reaction with cyclopentadienones) are connected to strong electron-withdrawing groups (Scheme 10).

\[ \text{19} + \text{ClNO}_2 \rightarrow \text{23} \xrightarrow{a)} \text{24} \]

\text{a): Palladium(II) chloride, triphenylphosphine, piperidine, (distilled water/acetone 1g:1g), 60 °C, 48hrs.}\textsuperscript{55}

\textbf{Scheme 10: An attempted coupling reaction using 1-chloro-2-nitrobenzene.}
Diels-Alder reactions occur at a faster rate when electron-withdrawing groups are attached to the dienophile, as it becomes more reactive. This is because the electron-withdrawing groups pull electrons away from the carbon atom that it is connected to and thus lowers the energy of the LUMO of the dienophile. This reduces the energy difference between the frontier molecular orbitals of the diene and dienophile giving them a better overlap in the transition state. This was shown to be true for the Diels-Alder reaction between a carbon-carbon triple bond and a cyclopentadienone by Pearson and Zhou where an alkyne containing a nitrobenzene group produced a higher yield than both an alkyne containing a pyridine ring and an alkyne containing a naphthalene group. The alkyne containing naphthalene produced a higher yield than the alkyne containing the pyridine.  

It was initially thought that compound 24 was not produced as a result of the decision to use a chloro halide, as the same or similar reaction conditions have been successfully used on nitro substituted aryl bromide with yields of up to 94% but had not been used on nitro substituted aryl chlorides. Therefore, the reaction was repeated using 1-bromo-4-nitrobenzene 22 (Scheme 11).

![Scheme 11: An attempted synthesis of a highly reactive dienophile.](image)

a): Palladium(II) chloride, triphenylphosphine, piperidine, (distilled water/acetone 1g:1g), 60 °C, 48hrs.  

Although this reaction produced target compound 25 that was evident by ¹H NMR, it once again produced a bright orange side product that was clear from several additional strong peaks in the same ¹H NMR spectrum (Appendix 1). These products could not be separated by flash column chromatography. This result implied that the formation of the side product was as a result of the nitro group and not the type of
halide used. An X-ray crystallography study was then carried out on the bright orange needles that were produced on purification by column chromatography of the only product formed in the attempted synthesis of compound 24, which showed that 1-(2-nitrophenyl)piperidine 26 had been formed (Figure 11). The side products had been formed as the result of a nucleophilic aromatic substitution reaction by way of an addition-elimination mechanism between piperidine, acting as a nucleophile, and 1-chloro-2-nitrobenzene 23 or 1-bromo-4-nitrobenzene 22. The strong electron-withdrawing groups on these aryl substrates makes the carbons attached to the chlorine or bromine more susceptible to nucleophilic attack allowing the mechanism in Scheme 12 to occur.

![Crystal structure of 1-(2-nitrophenyl)piperidine.](image)

**Figure 11:** Crystal structure of 1-(2-nitrophenyl)piperidine.

![Mechanism of nucleophilic aromatic substitution reaction.](image)

**Scheme 12:** The mechanism of a nucleophilic aromatic substitution reaction between 1-bromo-4-nitrobenzene and piperidine.  

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46
Also, the nitro group acts as an anion-stabilizing group by resonance. The reason that using 1-bromo-4-nitrobenzene 22 produced some of the target compound whereas 1-chloro-2-nitrobenzene 23 did not produce any using exactly the same conditions, was because bromo compounds react slower than chloro compounds in nucleophilic aromatic substitution reactions\(^{45}\), allowing the slower Sonogashira coupling reaction to compete. Therefore, one way of preventing this side reaction from occurring would be to use 1-iodo-3-nitrobenzene, as nucleophilic aromatic substitution reactions occur the slowest and are the least efficient when using iodo compounds. In addition to this, a nucleophilic aromatic substitution reaction occurs when the anion-stabilizing group is either ortho and/or para to the leaving group.\(^{45}\) Therefore, having the nitro group meta to the leaving group, as it would be in 1-iodo-3-nitrobenzene, would further reduce the rate of the nucleophilic aromatic substitution, allowing the Sonogashira coupling reaction to occur. The results show that nucleophilic aromatic substitution reactions occur faster than Sonogashira coupling reactions when using a bromo halide and therefore reducing the duration of the reaction from 24 hours to the published time of 12 hours for reactions involving nitrobenzene\(^{55}\) would not have stopped the side reaction from occurring.

Another way of preventing the nucleophilic aromatic substitution reaction from occurring is to reduce the nucleophilic properties of the base used. This was attempted by substituting piperidine that has a pKa of 11.0, for \(N,N\)-diisopropylethylamine, more commonly known as Hünigs Base, that has a pKa of 11.4, and so is slightly more basic than piperidine but more importantly it is not as nucleophilic. This is because one ethyl and two isopropyl groups surround the nitrogen and it is therefore sterically hindered, preventing it from attacking the alkyl halide. This theory has been backed up by a study carried out by Moore et. al. in which they alkylated a variety of secondary amines, one of these being piperidine, into tertiary amines in the presence of Hünigs Base. The fact that the secondary amine piperidine, was alkylated and Hünigs Base was not, shows that Hünigs Base has less nucleophilic properties than piperidine but is still a good base.\(^{59}\)

The reaction, that was carried out using 1-bromo-4-nitrobenzene 22 and 1,3-diethynylbenzene 19 in the presence of Hünigs Base, converted 33% of compound 19 into the monoadduct 27 within 12 hours, which if left for the full 24 hours or longer is
likely to have formed target compound 25 (Scheme 13). More importantly, no 1-(4-nitrophenyl)-piperidine had formed. Therefore, Hünigs Base is a good alternative under these conditions when using aryl halides containing electron-withdrawing groups.

Scheme 13: The successful synthesis of compound 27.

2.1.2 [3+2] cycloaddition reaction

The synthesis of a cyclopentadienone from an alkyne and a cyclopropenone occurs through a [3+2] cycloaddition. This reaction has been shown to be highly regioselective as shown in Scheme 14.20

Scheme 14: A [3+2] cycloaddition between 2-(phenylethynyl)pyridine 14 and 1,3-diphenylcyclopropenone 28.

The reaction shown above was carried out in accord with the literature method, at 80 °C for 24 hours.20 Analysis of the crude product by TLC showed that the reaction had not gone to completion, and some of both starting materials still remained present.
Flash column chromatography was performed on the product using a mixture of hexane and ethyl acetate as the eluent after the removal of the toluene had been carried out, and the product was successfully separated from the starting materials. A small amount of hexane was added to the product that produced a dark brown solid in a yellow solution. The solid was collected via filtration and was analysed by TLC to show that this was a product that had formed from the reaction. A \(^1\)H NMR spectrum of this solid was obtained that produced baffling results.

In light of the fact that cyclopentadienone 29, that was expected to be formed from this reaction, contains a pyridine group, one would expect to see a doublet of doublet of doublets between \(\delta 8.5\) and \(\delta 8.6\) corresponding to the hydrogen that is attached to the carbon adjacent to the nitrogen in the pyridine ring (due to the nitrogen being more electronegative than carbon) making the carbon next to it positively charged and the hydrogen attached to that carbon more deshielded, therefore making the peak corresponding to this hydrogen atom move downfield. The rest of the hydrogens in the pyridine ring are characteristically seen between \(\delta 7.4\) and \(\delta 7.8\). However, in the \(^1\)H NMR of the product formed from this \([3+2]\) cycloadditon reaction, these peaks did not appear. Instead a multiplet with integration of 1 appeared at \(\delta 5.4\) (peak 1), a doublet with an integration of 2 appeared at \(\delta 6.05\) (peak 2), and a doublet with an integration of 1 appeared at \(\delta 6.35\) (peak 3) as shown in Appendix 2, which by COSY are shown to be coupled to one another (Appendix 3). However, the peaks between \(\delta 7.0\) and \(\delta 7.5\) (peaks 4), totalling to integration of 15, appeared (as expected for the three phenyl groups attached to cyclopentadienone 29) but a peak in the \(^{13}\)C NMR at 195 ppm, characteristic of a carbonyl group, could be clearly seen. Two peaks around 85 ppm could also be seen that are characteristic of quaternary carbons in an alkyne (Appendix 4). This data matched data that has been published for a proposed \([\text{RhCl(CO)}_2]_2\) catalysed \([3+2]\) cycloaddition reaction between 1,3-diphenylcyclopropenone 28 and 1-(2-pyridiny1)-3-methoxypropy1-1-nyl 30 as shown in Scheme 15. The proposed \(^1\)H NMR spectrum of compound 31 can be seen in Appendix 5.
Initially it was thought that this change in shift could have been the result of an interaction between the pyridine ring and the cyclopentadienone structure, as an accurate mass measurement of the brown solid showed that the it had the mass of 386.1527 g/mol and had the mass and therefore composition of the expected compound (386.1539 g/mol, C$_{28}$H$_{20}$O$_1$N$_1$). Also, this change in shift had not been seen in any of the structures containing pyridine that had been synthesised in the lab before. Therefore, a comprehensive literature review was carried out to find NMR data for any cyclopentadienones containing one or more pyridine rings in its structure.

In a study conducted by Newkome et al., several cyclopentadienones were synthesised ranging from ones containing all phenyl groups to those containing all pyridine rings. This was accomplished via base catalysed condensation reactions between various diketones and propan-2-ones. Their data showed that an interaction between the pyridine ring(s) and the 5-membered rings or the carbonyl group attached to this does not take place in this type of molecule and that the $^1$H NMR resonance of the hydrogen attached to the carbon adjacent to the nitrogen in the pyridine ring appears between δ 8.42 and δ 8.53 as expected. The rest of the hydrogen atoms on the ring appear between the region of δ 6.8 and δ 7.8, the same region in which the hydrogens on the phenyl groups should appear. This data was complemented by more recent studies carried out by Shifrina et al. in which 2,3,4,5-tetra(2-pyridyl)-2,4-cyclopentadien-1-one was synthesised via the same method. They
showed that all the peaks in the \(^1\)H NMR of this structure should appear between \(\delta\) 6.93 and \(\delta\) 8.69.\(^{23,37}\)

Another piece of evidence which suggested that target compound 29 was not synthesised by the reaction that was carried out, was that these studies show that cyclopentadienones containing pyridine rings are no different from any other cyclopentadienones in that they too appear as the dark red crystalline solid that is characteristic for many cyclopentadienones. All the cyclopentadienones that were synthesised in the lab during this project were either a red or purple crystalline solids. However, the product that was synthesised by the [3+2] cycloaddition reaction was a dark brown coloured solid substance, and a yellow coloured oil had been reported by Wender et. al. from their published reaction. However, all the other products synthesised in Wenders study using the same conditions were of a red or purple solid.\(^{20}\)

The appearance of the two peaks on the \(^{13}\)C NMR of the dark brown solid at 85 ppm suggests that a cycloaddition reaction at the alkynes triple bond did not take place and that actually a reaction took place between 1,3-diphenylpropen-2-one 28 and the pyridine ring of 2-(phenylethynyl)pyridine 14 causing the observed dramatic change in shifts in the \(^1\)H NMR. This is backed up by the fact that when this reaction has been carried out without the involvement of a pyridine substituted alkyne, the two peaks on the \(^{13}\)C NMR spectrum at 85 ppm have not appeared which suggests that it is in fact the pyridine ring that causes a different reaction to take place.\(^{20}\)

It is unlikely that the rhodium catalyst used in this reaction was the cause of this change, as a study was carried out by Lautens and Yoshida, which also reacted alkynes containing pyridine rings using a rhodium catalyst but did not show the same shift of peaks in the \(^1\)H NMR.\(^{51}\) It could therefore be a combination of the 1,3-diphenylpropen-2-one 28 and the rhodium catalyst that caused the change, or 1,3-diphenylpropen-2-one 28 on its own.

The position of the three peaks in the \(^1\)H NMR spectrum between \(\delta\) 5.0 and \(\delta\) 6.5 suggests that these could be due to hydrogens that are part of a series of vinyl or
ethenyl groups that could have been formed due to the opening of the pyridine ring as shown in Scheme 16:

Scheme 16: The ring opening of pyridine.

Since the data for the [3+2] cycloaddition was not in accordance with a successful synthesis of 2-(2-pyridinyl)-3,4,5-triphenyl-2,4-cyclopentadien-1-one 29, an alternative route was required. Another viable route that was found, which also used an alkyne as the starting material, was to oxidise alkyne 14 using potassium permanganate to produce its respective diketone 32 that could in turn be reacted with 1,3-diphenylpropan-2-one 33 to produce product 34 via the base catalysed condensation reaction used in the synthesis of many cyclopentadienones (Scheme 17).60,61

Scheme 17: An alternative route for the synthesis of cyclopentadienones.

2.1.3 Synthesis of diketones

There are a variety of ways to oxidise alkynes to produce diketones but as was found in a study by Walsh and Mandal, not only is potassium permanganate readily
available, but the use of this reagent allows quick and easy work up of the reaction, and the other oxidation methods do not produce yields as high when heterocyclic groups are attached to the alkyne.\textsuperscript{35}

When using potassium permanganate to oxidise alkynes, one must be very careful because if the solution that the reaction is carried out in is either too warm or too basic, the oxidation proceeds to generate two carboxylate anions which on acidification generates two carboxylic acids. Therefore in order to obtain a good yield of the desired diketone, one must ensure that the solution in which the reaction is carried out in is cool and at a neutral pH (pH 7.0-7.5) so that the reaction proceeds \textit{via} the correct mechanism shown in Scheme 18:

\begin{center}
\includegraphics[width=\textwidth]{Scheme18.png}
\end{center}

\textbf{Scheme 18: The mechanism for the oxidation on 2-(phenylethynyl)pyridine 14 using potassium permanganate.}

The method that was used to oxidise the alkynes was a reaction reported by Srinivasan and Lee in which sodium hydrogen carbonate and magnesium sulfate are added to the reaction mixture. These are reported to serve as a buffer and neutralise the hydroxide ions that are produced during the reduction of the permanganate.\textsuperscript{62} The importance of a neutral solution was shown when the reaction was first carried out with the addition of definite amounts of sodium hydrogen carbonate (0.09 g) and magnesium sulfate (0.14 g) to a solution of acetone and distilled water (34 mL) as recommended in the literature.\textsuperscript{62} However when the product was extracted from the acidic solution (pH 1), resulting from the addition of a solution of sodium nitrite in sulfuric acid, a creamy yellow solid was produced. The acidic solution was then basified to pH 12 with the addition of sodium hydroxide, and an attempt to extract the product was once again made. However, NMR data showed that the only thing that had been extracted was the alkyne starting material but only 7 mgs had been extracted whereas 100 mgs of starting material had been used. Analysis of the \textsuperscript{1}H NMR of the
solid extracted from the acidic solution showed the definite existence of a pyridine ring due to the appearance of a doublet at $\delta$ 8.7, a triplet at $\delta$ 8.3, a doublet at $\delta$ 7.9 and a triplet at $\delta$ 7.7, all with the same integration. However, these peaks where further downfield than the peaks that were produced by the pyridine ring in alkyne 14 implying that a reaction had taken place. This was not the desired oxidation reaction as there were no peaks that could be attributed to a phenyl group that would be expected if the desired diketone 32 had been formed. Therefore, it is likely that the pyridine carboxylic acid had been formed and a peak at 200 ppm did not appear on the $^{13}$C NMR as it was present in a very low concentration. Any carboxylic acids would have been removed by addition of dilute sodium hydroxide followed by extraction using diethyl ether that was used in the literature method however this was not involved in the work up of this reaction.

The reaction was then repeated and although the same amount of sodium hydrogen carbonate and magnesium sulphate was used with respect to the volume of solution that was used, the pH of the solution was also measured before the reagents were added which showed that the solution was at a pH of 8.4. The solution was made to the pH of 7.5 by the dropwise addition of dilute hydrochloric acid (1 M) and the reaction was carried out which afforded the desired product in a 24% yield. The peaks produced in the $^1$H NMR by the pyridine ring of this structure match those produced from the creamy yellow solid extract from the acidic solution from the previous reaction further backing the assumption that the carboxylic acid had been formed due to the reaction being carried out at a pH of 8.4.

Alongside the oxidation of 2-(phenylethynyl)pyridine 14, the oxidation of 1-methoxy-6-(phenylethynyl)naphthylene 16 was also carried out, which afforded the desired product 35 in 68% yield, a yield almost three times that which was produced from the oxidation of 2-(phenylethynyl)pyridine 14 (Scheme 19). These results back up results found by Walsh and Mandal in which ‘the pyridine derivatives gave slightly lower yields in the oxidation reaction’. This is due to the pyridine ring being electron-withdrawing which has an affect on the oxidation reaction. On the other hand, 1-methoxy-6-(phenylethynyl)naphthylene 16 produced better results as the methoxy is an electron donating substituent making the naphthalene ring electron rich and therefore facilitating the reaction. This data complements results found by Walsh and
Mandal when the attempt to oxidise an alkyne containing a pyridine ring and a very strong electron withdrawing phthalonitrile ring failed but alkynes containing electron rich carbazoles and thiophenes worked well.\textsuperscript{35}

\begin{center}
\begin{tikzpicture}
\node at (0,0) (a) [draw,shape=circle,inner sep=1mm] {16};
\node at (2,0) (b) [draw,shape=circle,inner sep=1mm] {35};
\draw [->] (a) -- node[above] {a)} (b);
\end{tikzpicture}
\end{center}

\begin{itemize}
\item a): KMnO\textsubscript{4}, distilled water, acetone, pH 7.5, room temperature, 4 hours.\textsuperscript{62}
\end{itemize}

\textbf{Scheme 19: The synthesis of 1-(6-methoxynapthyl)-2-phenyl-1,2-ethanedione.}

When these oxidations reactions were carried out on a small scale the impurities that were produced were negligible, thus, the product was purified by a quick and easy workup as was reported by Walsh and Mandal.\textsuperscript{35} However, when they were carried out on a larger scale, this method of purification was not sufficient. Therefore, flash column chromatography had to be carried out to purify the diketones. Some of the products that had been produced from side reactions that occurred during the oxidation of 1-methoxy-6-(phenylethynyl)naphthylene 16 were isolated using column chromatography. These products were at a higher \( R_f \) than the desired diketone on a TLC plate and were present in a high concentration. A total mass of 0.5 g of the impurities was isolated for this reaction, 0.1 g less than the isolated mass of the target compound.

\textbf{2.1.4 Base catalysed condensation reaction}

One of the most common ways to synthesise cyclopentadienones is \textit{via} a base catalysed aldol condensation reaction between a diketone and a propan-2-one. Here, a small amount of base is used, usually potassium hydroxide, which deprotonates the propan-2-one to form a nucleophilic enolate ion 36 (\textbf{Scheme 20}).\textsuperscript{45}
Scheme 20: A reaction between KOH and 1,3-diphenylcyclopropenone 33.\textsuperscript{45}

Each enolate ion 35 will then attack a diketone to form an alkoxide ion that will be protonated by the water formed in the first step. These steps are then repeated (Scheme 21).\textsuperscript{45}

Scheme 21: A reaction between the enolate ion 36 and a diketone.\textsuperscript{45}

An elimination reaction occurs subsequently producing the cyclopentadieneone (Scheme 22).

Scheme 22: Formation of a cyclopentadienone.
Several diketones (those synthesised in the lab, 32 and 35, as well as those that are commercially available, such as 4,4-dibromobenzil 37 and 4,4-dimethoxybenzil 38) were reacted in this way to produce their respective cyclopentadienones, 34, 39, 40 and 41, all producing almost exactly the same yield, an average of 65%. The commercially available diketones 37 and 38 were not only used to become familiar with this reaction and evaluate its efficiency, but also because cyclopentadienones 40 and 41 produced from this reaction have been used in the synthesis of polyphenylene dendrimers. Once 3,4-bis(4-bromophenyl)-2,5-diphenyl-2,4-cyclopentadien-1-one 40 has been attached to the core, it allows the addition of trimethylsilylacetylene to the cyclopentadienone via a Sonogashira coupling reaction. The ethynyl groups can then be deprotected as demonstrated in this project and reacted with another cyclopentadienone to form another dendrimer generation. Both cyclopentadienones 40 and 41 allow an additional reaction to be carried out at the periphery of the dendrimer so that it can be functionalised further.

All the cyclopentadienones were isolated by utilising their relative insolubility in the solvent that the reactions were carried out in, ethanol, causing the cyclopentadienone, once formed, to precipitate out, allowing one to simply subject the reaction mixture to vacuum filtration and collect the product. However, the cyclopentadienones were not completely insoluble in ethanol, which meant that some of the target compound was dissolved into the ethanol that resulted in a deep red filtrate being formed when the cyclopentadienone was collected via vacuum filtration. Therefore, a lower yield than that which could have been achieved was obtained which would have been increased if the cyclopentadienone in the filtrate had also been isolated by flash column chromatography.

However, 2,3,5-triphenyl-4-(2-pyridinyl)-2,4-cyclopentadien-1-one 34, whose synthesis was attempted from the reaction between 1-phenyl-2-(2-pyridinyl)-1,2-ethanedione 32 and 1,3-diphenylpropan-2-one 33, was not successfully isolated. When the starting materials were added, the reaction mixture went from the initial yellow colour to a resulting deep red colour that is characteristic for this type of reaction. However, when the reaction mixture was subjected to vacuum filtration, nothing was collected, implying that the pyridine ring of the resulting cyclopentadienone made the compound far more soluble in ethanol than those that do
not contain a pyridine ring. Therefore, the solvent was removed and the crude product was analysed by TLC, which showed a red spot characteristic for cyclopentadienones. However, there was also a large amount of impurity in the crude product. This was because diketone 32 had not been purified by flash column chromatography as it gave a clean NMR spectrum. However, it still contained a variety of impurities. This evidence once again shows that several extractions are not sufficient to produce a relatively pure diketone and other purification techniques should also be implemented to purify the target compound further.

In all the previously published reports where cyclopentadienones containing pyridine rings have been synthesised\textsuperscript{23,36,37}, it is argued that the resulting compound from the base catalysed aldol condensation reaction is not the cyclopentadienone but is the 4-hydroxy-cyclopent-2-en-1-one, which when dissolved into ethylene glycol and heated to 200 °C for 30 minutes, forms the desired cyclopentadienone as shown in Scheme 23.

\begin{align*}
\text{R}^1\text{C} = \text{O} & \quad \text{R}^2\text{C} = \text{O} \quad a) \quad \text{KOH, ethanol, reflux, 30 minutes.} \\
\text{R}^3\text{C} = \text{O} & \quad \text{R}^4\text{C} = \text{O} \quad b) \quad \text{EG, reflux, 10 minutes.}
\end{align*}

\textbf{Scheme 23: A scheme for the formation of a cyclopentadienone proposed by Newkome et al.}\textsuperscript{36}

A study carried out in 1975 shows that as well as cyclopentadienones containing pyridine rings, a reaction between 1,3-diphenylpropan-2-one and 1,2-diphenyl-1,2-ethanedione also exhibited the same result. This was proven by analysis of the product by $^1\text{H}$ NMR in which a one-hydrogen singlet was observed between δ 4.5 and δ 4.6 that was attributed to the hydroxy group.\textsuperscript{36} However, from analysis of the NMR data created from all of the products produced \textit{via} the same reaction in this project, there is
no suggestion that the 4-hydroxycyclopent-2-ene-1-one intermediate had been formed (Appendix 6) and neither is there any mention of this in other literature.\textsuperscript{60,61}

2.2 The synthesis of dendrimers
2.2.1 The Diels-Alder reaction

The Diels-Alder reaction is part of a group of reactions that falls under the category called pericyclic or cycloaddition reactions, which involves the movement of electrons out of the \(\pi\) orbitals and into the \(\sigma\) orbitals.\textsuperscript{45} The reaction occurs between a conjugated diene and a dieneophile, which is typically an alkene and is initiated by heat, which can be derived from the number of \(\pi\) electrons that are contained within the reactions aromatic transition state. The dienes that were used for the Diels-Alder reactions carried out in this project were all cyclopentadienones: as they permanently adopt the \textit{s-cis} conformation, they are exceptionally good at this type of reaction.\textsuperscript{45} The dieneophiles that were used were alkynes as shown in Scheme 24.

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{O} & \quad \text{R} \\
\text{R} & \quad \text{R} \\
\text{R} & \quad \text{R}
\end{align*}
\]

\[
\begin{align*}
\text{R'} & \quad \text{R'} \\
\text{O} & \quad \text{R'} \\
\text{R'} & \quad \text{R'} \\
\text{R'} & \quad \text{R'}
\end{align*}
\]

\[
\text{CO} \quad \text{heat}
\]

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} \\
\text{R} & \quad \text{R}
\end{align*}
\]

\[
\begin{align*}
\text{R'} & \quad \text{R'} \\
\text{O} & \quad \text{R'} \\
\text{R'} & \quad \text{R'} \\
\text{R'} & \quad \text{R'}
\end{align*}
\]

Scheme 24: The mechanism for the Diels-Alder reaction between a cyclopentadienone and an alkyne.

As the aromatic transition states of these reactions contain six \(\pi\) electrons, two from the alkyne and four from the cyclopentadiene, they satisfy the rule that for a cycloaddition to occur thermally, it must have \((4n+2)\) \(\pi\) electrons in its aromatic transition state, and can therefore be initiated by heat. The six \(\pi\) electrons in their transition states is one of the reasons that this reaction works so well, as they make it
aromatic in character and therefore has some of the special stabilisation properties of benzene. This is the driving force for these reactions.

A reaction between 1,3-diethynylbenzene 19 and 3,4-bis(4-bromophenyl)-2,5-diphenyl-2,4-cyclopentadien-1-one 40 was carried out in o-xylene at a temperature of 175 °C and at a concentration of 0.03 gmL⁻¹ to produce the first generation dendrimer 42 shown in Scheme 25.

Scheme 25: Synthesis of Dendrimer 41.

A reaction was initially carried out at a concentration of 0.03 gmL⁻¹ for the duration of 27 hours, however, a reaction failed to take place. This was considered to be because the reaction was stopped too early. Therefore, a second reaction was carried out for the duration of 84 hours. However, analysis of the crude reaction mixture by TLC showed that the only compounds that were present were the starting materials, therefore, a reaction had not taken place. The same reaction was then carried out again but this time at a concentration of 0.3 gmL⁻¹ and for a period of only 22 hours which produced the desired product that proves that this reaction is concentration dependant.
Diels-Alder reactions between the cores 1,3-diethynylbenzene 19 and 2-\{[3-(2-pyridinylethynyl)phenyl]ethynyl\}pyridine 20 that had been synthesised, and the cyclopentadienone 3,4-bis(4-methoxyphenyl)-2,5-diphenyl-2,4-cyclopentadien-1-one 41, were then also carried out at the higher concentration of 0.3gml⁻¹ (Scheme 26). Unfortunately, enough of core 21 was not obtained to carry out a Diels-Alder reaction on it.

\[
\text{Scheme 26: Synthesis of dendrimer 44.}
\]

Purification of all the products made via this method was very difficult to achieve as the cyclopentadienone starting materials were always present in the crude product. This was either because the reactions would not go to completion, or because the cyclopentadienones were present in excess from the beginning. As cyclopentadienone 40 and dendrimer 42 are very similar in structure, they have very similar properties, and would therefore appear as spots that were very close to each other on the TLC plate. This resulted in a light pink solid being isolated by column chromatography due to the product 42, a white solid, being contaminated with a small amount of cyclopentadienone 40, a red solid. The most effective purification technique was to add the crude mixture that was dissolved into \(\alpha\)-xylene, dropwise into a small volume of ethanol. Due to the insolubility of the product in ethanol, which was slightly more than that of starting material 40, would cause most of the product to form a precipitate and allow most of cyclopentadienone 40 to dissolve into the ethanol thus separating one from the other. However, a small amount of the
cyclopentadienone would also form a precipitate and contaminate the product, and a small amount of product would also dissolve into the ethanol. Therefore this procedure had to be repeated several times to achieve complete purity, which resulted in a low isolated yield for dendrimer 42. However, when the ethanol solution was left to slowly evaporate over a period of two weeks, the product ‘crashed out’ of the solution forming a crystalline solid that could be collected by filtration. This was because it was in a higher concentration in solution than starting material 40. However, the crystals that were formed from this were too small to be analysed by X-ray crystallography. Attempts were made to grow crystals of the dendrimer structures that were synthesised, however they were either insoluble or only partially soluble in most organic solvents, thus making crystallisation of these dendrimers very difficult.

The purification technique that has been described could not be used to purify product 44, that contained pyridine rings as this did not form a solid when added to ethanol, which complemented the results found during the synthesis of cyclopentadienones that the addition of a pyridine ring to a largely non-polar molecule makes it more soluble as the molecules becomes more polar. This also matches the study by Shifrina et al., which found that the dendrimers that contained pyridine but exclusively had phenyl groups at the periphery, would precipitate in ethanol or hexane that was independent of the generation. However, polyphenylene dendrimers that had pyridine rings on the periphery of the structure were found to be soluble in these solvents. However, product 44 was a lot easier to purify by column chromatography, as there was a greater difference in polarity between the non-polar cyclopentadienone 41 and the polar product 44, which resulted in a higher yield but not the 90% that has been reported for these reactions. This is because the reaction between 2-[[3-(2-pyridinylethynyl)phenyl]ethynyl]pyridine 20 and 3,4-bis(4-methoxyphenyl)-2,5-diphenyl-2,4-cyclopentadien-1-one 41 produced both the monoadduct 43 and the target compound 44 as shown in Scheme 26, which was made apparent from the appearance of two different spots on the TLC plate that were separated by column chromatography.

The lower spot was monoadduct 43 that was concluded from the appearance of two peaks in the $^1$H NMR spectrum: one at δ 8.1 and the other at δ 8.5. Both these peaks are characteristic of a hydrogen that is attached to a carbon adjacent to the nitrogen in
a pyridine ring and therefore showed that two pyridine rings in different environments were present in the structure, and since the peak at $\delta 8.5$ matched the peak in the $^1$H NMR spectrum of 2-[[3-(2-pyridinylethynyl)phenyl]ethynyl]pyridine 20 corresponding to the hydrogen that is attached to a carbon adjacent to the nitrogen in a pyridine ring, it was clear that monoadduct 43 had been formed. This was backed up by the analysis of monoadduct 43 by matrix assisted laser ionisation (MALDI) which showed the molecular ion (M+H)$^+$ of 697. The target product 44 was also analysed using the same method giving a molecule ion (M+H)$^+$ of 1113. The formation of monoadduct 43 was the result of the addition of the pyridine rings on to alkyne 20, as the reaction between 1,3-diethynylbenzene 19 and cyclopentadienone 41 produced only the expected target compound 45 (Scheme 27).

Scheme 27: The synthesis of Dendrimer 45.

This shows that when the pyridine rings were not attached to 1,3-diethynylbenzene, a Diels-Alder reaction was able to take place at both triple bonds at the same time resulting in the formation of only the target compound 45. However, when pyridine rings were attached to 1,3-diethynylbenzene 19, a Diels-Alder reaction was unable to
take place at both the triple bonds at the same time due to steric hindrance from the extra pyridine rings. Instead, a Diels-Alder reaction would occur at one triple bond first forming monoadduct 43 and then at the other triple bond forming the target compound 44 causing this reaction to be a lot slower than when the pyridine rings were absent. A yield of 43% of the target compound was produced from a reaction between 1,3-diethynylbenzene 19 and 3,4-bis(4-methoxyphenyl)-2,5-diphenyl-2,4-cyclopentadien-1-one 41 within 24 hours whereas to produce a yield of about the same, 47% of target compound 44, from reaction a between the same cyclopentadienone and 2-\{3-(2-pyridinylethynyl)phenyl\}ethynyl\}pyridine 20 took just under 6 days.

Therefore, it can be predicted that if a Diels-Alder reaction between 2-\{\(3,5\)-bis\{\(6\)-methoxy-2-naphthyl\}ethynyl\}phenyl\}ethynyl\}-6-methoxynaphthalene 21 and a cyclopentadienone was attempted, the reaction would have produced three products, the mono adduct 46, the diadduct 47 and the target compound 48 as the group attached to the triple bonds on this molecule is larger than a pyridine ring thus causing greater steric hinderance. As a result, it is very likely that this reaction would have taken longer to yield target dendrimer 48 (Scheme 28).
Scheme 28: A predicted outcome for a reaction between core 21 and a cyclopentadienone.

The two first-generation dendrimers that were synthesised, 42 and 45, were characterised by ES-MS and a comparison between the isotope patterns produced by the molecule with the expected isotope patterns showed that the desired products had been produced (Spectrum 2).
2.3 Conclusions and future work

The typical conditions used for a Sonogashira coupling reaction failed to produce the desired result and therefore copper free conditions were utilised whose performance was dependant on the starting materials used. There is overwhelming evidence to show that the base used for this reaction causes a nucleophilic aromatic substitution reaction to take place when halides containing a strong withdrawing group at either the ortho or meta position to the leaving groups are used. Exchanging piperdine for Hünigs base can prevent this.

There is insufficient evidence to conclude whether 2,3,4-triphenyl-5-(2-pyridinyl)-2,4-cyclopentadien-1-one $29$ was or was not synthesised from the rhodium catalysed cycloaddition reaction between 2-(phenylethynyl)pyridine $14$ and 2,3-diphenyl-2-cyclopropen-1-one $28$ and therefore warrants further investigation.
The synthesis of a novel unsymmetrical cyclopentadienone containing a naphthalene group was successfully carried out by the oxidation of alkyne 16 using potassium permanganate followed by a base catalysed condensation reaction of diketone 35 with 1,3-diphenylpropan-2-one 33. Oxidation of alkynes using potassium permanganate is very pH sensitive but works well when a) the initial pH of the mixture of water and acetone is 7.5 and b) electron donating groups are attached to the triple bond. This cyclopentadiene has the potential to be used to incorporate naphthalene molecules into the structure of polyphenylene dendrimers, which has been modelled in this project by the synthesis of several novel polyphenylene dendrimer structures via Diels-Alder reactions that are concentration dependant. However, it is clear that the incorporation of bulky functionality, such as pyridine and naphthalene, into polyphenylene dendrimers can not be efficiently carried out by their attachment onto the core as this would give rise to structural defective molecules that would be difficult to separate.

The efficiency of the Diels-Alder reaction could not be evaluated in this project but it would be interesting to see what effect the electronic nature of the cyclopentadienone and alkyne have on the ease of this reaction.
3 Chapter 3: Experimental
3.1 General Experimental

All air sensitive reactions were carried out under a nitrogen atmosphere. All melting points were measured on a Stuart Scientific SMP10 and all IR spectra were recorded on a Bruker Alpha IR. NMR spectra were recorded at 400 MHz for $^1$H and 100 MHz for $^{13}$C NMR on Bruker 400 spectrometers at 298 K. Chemical shifts are reported in $\delta$ (ppm) and coupling constants in Hz. All spectra were run using CDCl$_3$ as the solvent. Unless otherwise stated, chemicals were obtained commercially and used as received. The progress of all reactions was monitored using TLC. Electrospray-mass spectroscopy was carried out on a Micro Mass Platform 2 with methanol as the mobile phase. MALDI was carried out on a Shimadzu AXIMA Confident and EI was carried out on a Thermo Finnigan Mat 95 XP. High Resolution Mass Spectroscopy was carried out on a Walters Qtos.
3.2 Synthesis of 3,4-bis(4-bromophenyl)-2,5-diphenyl-2,4-cyclopentadien-1-one

To a 50 mL round-bottom flask was added 4,4-dibromobenzil (2.944 g, 8.0 mmol), 1,3-diphenyl-2-propanone (1.586 g, 8.0 mmol) and ethanol (20 mL). To this stirring solution potassium hydroxide (0.290 g, 5.2 mmol) dissolved in ethanol (5 mL) was added. The resulting solution was heated to reflux for 1 hour, which was then left to cool to room temperature and then to 0°C with the aid of an ice-water bath. The precipitate was collected by vacuum filtration, washed with ethanol (25 mL) and left to dry to give 3,4-bis(4-bromophenyl)-2,5-diphenyl-2,4-cyclopentadien-1-one as a dark purple solid (2.865 g, 66%).

TLC R_f = 0.64 (hexane/ethyl acetate 49:1); mp = 247-248 °C; m/z: [M+Na]^+ = 465 g mol⁻¹; ^1H NMR (400 MHz, CDCl₃) δ 6.70-6.90 (d, J = 8.8 Hz, 4H), 7.15-7.30 (m, 10H), 7.30-7.40 (d, J = 8.8 Hz, 4H); ^13C NMR (100 MHz, CDCl₃) δ 123.2, 125.9, 127.9, 128.3, 130.1, 130.2, 131.0, 131.5, 131.6, 152.6, 199.6 (C=O). FTIR ν = 3048, 1712, 1480, 1390, 1088, 1071, 1007, 839, 820, 789, 756, 732, 696 cm⁻¹.
3.3 Synthesis of 3,4-bis(4-methoxyphenyl)-2,5-diphenyl-2,4-cyclopentadien-1-one

To a 100 mL round-bottom flask was added 1,3-diphenyl-2-propanone (2.154 g, 10.3 mmol), 4,4-dimethoxybenzil (2.787 g, 10.3 mmol) and ethanol (50 mL). The stirred mixture was subsequently heated to 80 °C to which potassium hydroxide (0.589 g, 10.5 mmol) was added. After 4 hours an additional amount of potassium hydroxide (0.203 g, 3.6 mmol) was added to the reaction mixture to drive the reaction to completion. The reaction was left for a further hour after which the mixture was cooled to room temperature. The resulting precipitate was collected via vacuum filtration, washed with ethanol and left to dry. This produced a purple solid that was recrystallised from methanol to yield a purple crystalline solid (3.108 g, 68 %).

TLC Rf = 0.44 (hexane/ethyl acetate 5:1); mp = 227-228 °C; HRMS calculated for C31H24O3 + H m/z = 444.1802 g/mol, found m/z = 445.1799 g/mol; 1H NMR (400 MHz, CDCl3) δ 3.60- 3.80 (s, 6H, 2 x O-Me), 6.60-6.70 (d, J = 8.0 Hz, 4H), 6.70-6.80 (d, J = 8.0 Hz, 4H), 7.10-7.25 (m, 10H); 13C NMR (100 MHz, CDCl3) δ 55.2 (Me), 113.4, 124.7, 125.3, 127.2, 128.0, 130.2, 131.2, 154.1, 159.8, 200.3 (C=O). FTIR ν = 3044, 3006, 2957, 2930, 2831, 1698, 1601, 1489, 1441, 1357, 1290, 1242, 1172, 1108, 1021, 841, 794, 779, 753, 736, 700 cm⁻¹.
3.4 Synthesis of 2-(phenylethynyl)pyridine:

To a 250 mL round-bottom flask was added palladium(II) chloride (0.057 g, 5 %), triphenylphosphine (0.135 g, 10 %), piperidine (1 mL), acetone (19 mL) and distilled water (15 mL) that was left to stir for 5 mins under nitrogen. This was followed by the addition of 2-bromopyridine (0.475 mL, 5.0 mmol) and phenylacetylene (0.66 mL, 6.0 mmol) and refluxed for 25 hours. The reaction was cooled to room temperature and extracted into ethyl acetate. The combined layers were dried with magnesium sulphate and the solvent was removed. Purification was carried out by flash column chromatography (hexane/ethyl acetate 20:1) to give a dark brown oil (0.613 g, 68 %).

TLC $R_f = 0.27$ (hexane/ethyl acetate 10:1); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.15-7.20 (ddd, 1H, J = 7.6 Hz, 4.8 Hz, 1.2 Hz, pyridine), 7.20-7.35 (m, 3H, phenyl), 7.45-7.50 (dt, 1H, J = 7.6 Hz, 1.2 Hz, 0.8 Hz, pyridine), 7.50-7.55 (m, 2H, phenyl), 7.55-7.65 (td, 1H, J = 7.6 Hz, 1.6 Hz, pyridine), 8.50-8.60 (ddd, 1H, J = 4.8 Hz, 1.6 Hz, 0.8 Hz, pyridine); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 88.6 (alkynyl), 89.2 (alkynyl), 122.2, 122.8, 127.2, 128.4, 129.0, 132.1, 136.3, 143.5, 150.0.$^{52}$
3.5 Synthesis of 1-phenyl-2-(2-pyridinyl)-1,2-ethanedione:

![Chemical structure](image)

**SK24:**

Sodium hydrogen carbonate (0.006 g, 0.071 mmol) was weighed out into a 10 mL round bottom flask to which magnesium sulphate (0.056 g, 0.47 mmol), acetone (2.2 mL) and distilled water (2.4 mL) was added. The mixture was stirred until the solid had dissolved. The pH of the solution was then measured and 1 M hydrochloric acid was added dropwise till the pH of the solution was 7.5. **2-(Phenylethynyl)pyridine (0.034 g, 0.194 mmol)** was weighed out, dissolved into acetone (2.2 mL) and added to the solution along with potassium permanganate (0.057 g, 0.359 mmol). The reaction mixture was left to stir at room temperature for 4 hours prior to sodium nitrite (1.00 g) in 10 % sulphuric acid (10 mL) being added dropwise to the mixture till the solution became transparent. The mixture was then extracted with hexane: diethyl ether (1:1, 20 mL) and the solvent was exchanged for diethyl ether which was washed with 5 % sodium hydroxide and saturated sodium chloride solution to remove any carboxylic acids formed. The organic layer was dried, filtered and the solvent was removed to produce a yellow brown solid. (0.010 g, 24 %).

TLC $R_f = 0.58$ (hexane/ethyl acetate, 1:1); m/z: [M+H]$^+ = 212$ g/mol, [M+Na]$^+ = 234$ g/mol; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.4 – 7.5 (m, 2H, phenyl), 7.45-7.5 (ddd, 1H, J = 7.6 Hz, 4.8 Hz, 1.2 Hz, H$^2$), 7.5-7.6 (m, 1H, phenyl), 7.85-7.9 (m, 3H, H$^3$ and phenyl), 8.1-8.2 (dt, 1H, 7.6 Hz, 1.2 Hz, 0.8 Hz, H$^4$), 8.55-8.65 (ddd, 1H, 4.8 Hz, 1.6 Hz, 0.8, H$^1$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 122.1, 126.1, 126.8, 127.5, 131.1, 132.6, 135.2, 147.8, 149.6, 193.0 (C=O), 194.1 (C=O).
3.6 Synthesis of 1-methoxy-6-(phenylethynyl)naphthylene:

![Chemical Structure Image]

**SK23**: To a 250 mL round bottom flask were added palladium(II) chloride (0.1603 g, 0.93 mmol), triphenylphosphine (0.40 g, 1.55 mmol), piperidine (3 mL, 31 mmol), distilled water (46.5 mL) and acetone (59 mL). The system was sealed and purged with nitrogen prior to being left to stir for 5 minutes. Subsequently, 1-bromo-6-methoxynaphthalene (3.67 g, 15.5 mmol) and phenylacetylene (2 mL, 18.6 mmol) were added to the reaction and left to stir at 60°C for 24 hours. The product was then extracted from the resulting mixture using diethyl ether that was dried with magnesium sulphate, filtered and the solvent was removed to produce a crude brown solid. This was purified by flash column chromatography (hexane/ethyl acetate 20:1) followed by recrystallisation from hexane to produce a powder (0.85 g, 21%).

TLC R<sub>f</sub> = 0.32 (hexane/ethyl acetate, 10:1); mp = 139-140°C; HRMS calculated for C<sub>19</sub>H<sub>14</sub>O + H m/z = 258.1039 g/mol, found m/z = 258.1032 g/mol; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.85-3.9 (s, 3H, O-Me), 7.03-7.08 (d, 1H, J = 2.4 Hz, napthalene), 7.08-7.13 (dd, 1H, J = 8.8Hz, 2.4 Hz, napthalene), 7.25-7.35 (m, 3H, phenyl), 7.45-7.49 (m, 1H, napthalene), 7.49-7.55 (m, 2H, phenyl), 7.6-7.65 (d, 1H, J = 8.4 Hz, napthalene), 7.65-6.68 (d, 1H, J = 8.8 Hz, napthalene), 7.9-7.95 (s, 1H, napthalene).<sup>1</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 55.4 (O-Me), 89.1 (alkynyl), 90.0 (alkynyl), 105.8, 118.2, 119.5, 123.5, 126.9, 128.2, 128.4, 128.5, 129.1, 129.4, 131.3, 131.6, 134.2, 158.3. FTIR ν = 3056, 3014, 2969, 2939, 1599, 1476, 1383, 1256, 1210, 1166, 1030, 897, 856, 819, 755, 688 cm<sup>-1</sup>. 
3.7 Synthesis of 1-(6-methoxynapthyl)-2-phenyl-1,2-ethanedione:

\[ \text{MeO} \quad \text{O} \quad \text{O} \]

\[ \text{MeO} \quad \text{O} \quad \text{O} \]

SK22 \(^\text{62}\):

Sodium hydrogen carbonate (0.007 g, 0.083 mmol) was weighed out in a 10 mL round bottom flask to which magnesium sulphate (0.066 g, 0.055 mmol), acetone (4.9 mL) and distilled water (2.8 mL) were added. The pH of the solution was monitored and hydrochloric acid (1 M) was added dropwise until the pH of the solution was at 7.5. 1-methoxy-6-(phenylethynyl)naphthylene (0.05 g, 0.194 mmol) and potassium permanganate (0.057 g, 0.359 mmol) were added to the solution and left to stir at room temperature for 4 hours. Next, sodium nitrite (1.00 g) in 10 % sulphuric acid (10 mL) was added to the stirring mixture dropwise till it became transparent. The product was then extracted from the solution using hexane: diethyl ether (1:1, 20 mL) that was in turn dried and filtered. The solvent was exchanged for diethyl ether that was then washed with sodium hydroxide solution (5 %, 20 mL) and saturated sodium chloride to remove any carboxylic acids formed. The organic layer was dried and filtered, and the solvent was remove to produce a light yellow solid (0.023 g, 41 %).

TLC \( R_f = 0.2 \) (hexane/ethyl Acetate, 10:1); mp = 83-88 °C; HRMS calculated for \( \text{C}_{19}\text{H}_{14}\text{O}_3 + \text{H} \) m/z = 290.0937 g/mol, found m/z = 290.0939 g/mol; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.05-7.1 (d, 1H, J = 2.4 Hz, naphthalene), 7.1-7.15 (dd, 1H, J = 8.8 Hz, 2.4 Hz, naphthalene), 7.4-7.5 (m, 2H, phenyl), 7.55-7.6 (m, 1H, phenyl), 7.7-7.75 (d, 1H, J = 8.8 Hz, naphthalene), 7.75-7.8 (d, 1H, J = 8.8 Hz, naphthalene), 7.9-9.5 (m, 2H, phenyl), 7.95-8.0 (dd, 1H, J = 8.8 Hz, 1.6 Hz, naphthalene), 8.2-8.3 (d, 1H, J = 1.6 Hz). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 55.5 (O-Me), 106.0, 120.2, 124.6, 127.7, 127.9, 128.4, 129.1, 130.0, 131.6, 133.2, 133.4, 134.9, 138.4, 160.7, 194.4 (C=O), 194.9 (C=O). FTIR \( \nu \) = 3061, 2999, 2963, 2939, 2893, 2841, 1648, 1616, 1477, 1262, 1198, 1187, 1160, 1027, 859, 792, 709, 685, 668, 634 cm\(^{-1}\).
3.8 Synthesis of 3-(6-methoxynaphthyl)-2,4,5-triphenyl-2,4-cyclopentadien-1-one:

![Chemical Structure](image)

SK29:

To a 10 mL round bottom flask was added 1,3-diphenyl-2-propanone (0.44 g, 2.1 mmol), 1-(6-methoxynapthyl)-2-phenyl-1,2-ethanedione (0.609 g, 2.1 mmol), and ethanol (6 mL). The mixture was then stirrer and heated to 80 °C prior to potassium hydroxide (0.12 g, 2.1 mmol) being added at once. The reaction was heated for 1 hour then left to cool to room temperature to yield a brown precipitate that was collected by vacuum filtration (0.597 g, 62 %).

TLC \( R_f = 0.3 \) (hexane/ethyl acetate, 15:1); mp = 219-220 °C; HRMS calculated for C_{33}H_{24}O_2 + H m/z = 464.1771 g/mol, found m/z = 464.1774 g/mol; \(^1\)H NMR (400 MHz, CDCl_3) \( \delta 3.35-4.0 \) (s, 3H, OMe), 6.95-6.97 (m, 1H), 6.97-7.0 (s, 1H), 7.05-7.08 (dd, 1H, J = 8.4 Hz, 1.6 Hz), 7.08-7.15 (m, 2H), 7.15-7.22 (m, 2H), 7.22-7.35 (m, 12H), 7.4-7.5 (d, 1H, J = 9.6 Hz), 7.5-7.6 (d, 1H, J = 8.8 Hz) \(^13\)C NMR (100 MHz, CDCl_3) \( \delta 55.4 \) (OMe), 105.7, 119.1, 125.1, 125.6, 126.3, 127.5, 127.6, 128.0, 128.1, 128.8, 128.9, 129.4, 130.0, 130.2, 130.8, 131.0, 133.2, 134.4, 154.4, 158.5, 200.4 (C=O). FTIR ν = 3377, 3074, 3059, 3029, 2956, 2931, 2899, 2835, 1699, 1620, 1480, 1261, 1214, 1027, 853, 745, 716, 696 cm\(^{-1}\).

3.9 Synthesis of Dendrimer 45:

[Diagram of Dendrimer 45]

SK13:

To a 50 mL round-bottom flask was added 1,3-diethynylbenzene (0.089 g, 0.7 mmol) and 3,4-bis(4-methoxyphenyl)-2,5-diphenyl-2,4-cyclopentadien-1-one (0.639 g, 1.4 mmol). The system was sealed and purged with nitrogen followed by the addition of anhydrous o-xylene (2 mL) to the mixture. The reaction mixture was heated to 170 °C for 48 hours. Once the mixture had cooled to room temperature distilled water (50 mL) was added and the product was extracted with diethyl ether (2 x 50 mL). The organic phases were combined, dried using magnesium sulphate and the solvent was exchanged for anhydrous o-xylene (3 mL). The solution was added dropwise into ethanol (75 mL) and the precipitate was collected via vacuum filtration. This step was repeated until the product was pure to yield a white solid (0.071 g). After two weeks a precipitate had formed in the filtrate that was collected by vacuum filtration and produced a light orange crystalline solid (0.214 g, 43 %).

TLC R_f = 0.38 (hexane/ethyl acetate, 2.5:1); mp = 298-300 °C; m/z: [M+Na]^+ = 981 g/mol, [M+K]^+ = 997 g/mol; ^1H NMR (400 MHz, CDCl_3) δ 3.5-3.55 (s, 6H, 2 x OMe), 3.55-3.6 (s, 6H, 2 x OMe), 6.3-6.35 (d, J = 8.8 Hz, 4H), 6.35-6.45 (d, J = 9.2 Hz, 4H), 6.5-6.55 (d, J = 8.8 Hz, 4H), 6.6-6.65 (d, J = 9.6 Hz, 4H), 6.64-6.7 (m, 4H), 6.7-6.85 (m, 10H), 6.97-7.0 (s, 1H), 7.0-7.15 (m, 11H), 7.15-7.17 (s, 2H). ^13C NMR
(100 MHz, CDCl$_3$) $\delta$ 54.9 (OMe), 55.0 (OMe), 112.2, 112.5, 125.6, 126.1, 126.6, 127.0, 127.6, 127.9, 130.1, 131.4, 131.6, 131.8, 132.5, 132.6, 132.9, 139.0, 139.4, 140.3, 140.4, 140.9, 141.3, 141.4, 142.0, 157.1, 157.3. FTIR $\nu$ = 3050, 3021, 2998, 2951, 2931, 2833, 1607, 1512, 1438, 1286, 1242, 1175, 1031, 835, 800, 758, 699 cm$^{-1}$. 
3.10 Synthesis of Dendrimer 42:

[Chemical structure image]

SK14:

To a two necked 100 mL round-bottom flask was added 1,4-diethynylbenzene (0.064 g, 0.5 mmol) and 3,4-bis(4-bromophenyl)-2,5-diphenyl-2,4-cyclopentadien-1-one (0.813 g, 1.5 mmol). The system was then sealed and purged with nitrogen to which anhydrous o-xylene (2 mL) was added. The reaction mixture was then heated to 175 ºC for 28 hours then left to cool to room temperature. The solution was then added dropwise to ethanol (125 mL) that produced a precipitate which was collected by vacuum filtration. After 3 days a solid had formed in the filtrate that was once again collected by vacuum filtration. The precipitates were combined and purified via flash column chromatography (hexane/ethyl acetate 15:1) that produced a light pink solid (0.015 g, 13%).

TLC R_f = 0.36 (hexane/ethyl acetate, 15:1); mp = more than 300 ºC; m/z: [M+Cl]^+ = 1189 g/mol; ^1H NMR (400 MHz, CDCl_3) δ 6.45-6.55 (d, 4H, J = 8.4 Hz), 6.55-6.60 (d, 4H, J = 8.4 Hz), 6.60-6.7 (m, 4H), 6.70-6.85 (m, 10H), 6.85-6.95 (d, 4H, J = 8.4 Hz), 6.95-6.96 (s, 1H), 6.96-7.05 (d, 8H, J = 8.4 Hz), 7.1-7.15 (m, 6H), 7.15-7.16 (s, 1H); ^13C NMR (100 MHz, CDCl_3) δ 118.8, 119.1, 125.0, 125.5, 125.8, 126.2, 126.7, 126.9, 128.9, 129.0, 129.3, 130.4, 130.6, 130.8, 131.9, 132.0, 136.7, 137.6, 138.0,
138.1, 138.4, 139.1, 139.8, 139.8, 139.9, 140.0. FTIR ν = 3079, 3057, 3026, 1488, 1071, 1010, 838, 798, 744, 698 cm⁻¹.
3.11 Synthesis of 1-[[3-(2-pyridinylethynyl)phenyl]ethynyl]2-pyridine:

![Chemical structure](image)

SK15

To a two necked 25 mL round bottom flask was added piperidine (0.39 mL, 4 mmol), palladium(II) chloride (0.018 g, 0.1 mmol), triphenylphosphine (0.130 g, 0.5 mmol), distilled water (3 mL) and acetone (3.80 mL). The system was sealed, purged with nitrogen and left to stir for 5 minutes. After this time diethynylbenzene (0.13 mL, 1.0 mmol) and 2-bromopyridine (0.23 mL, 2.4 mmol) was added to the reaction mixture. The reaction was heated to 60 °C for 24 hours then left to cool to room temperature. The organic products were extracted using diethyl ether (2 x 60 mL). The organic fractions were then combined, filtered, dried using magnesium sulphate and the solvent was removed. The product was purified by flash column chromatography using gradient elution (hexane/ethyl acetate 15:1 to 0:1) to yield a yellow oil (0.098 g, 35 %).

TLC R<sub>f</sub> = 0.25 (hexane/ethyl acetate, 1:1); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.1-7.15 (ddd, 2H, J = 7.6 Hz, 4.8 Hz, 1.2 Hz, pyridine), 7.2-7.25 (td, 1H, J = 7.6 Hz, 0.8 Hz, phenyl), 7.4-7.45 (ddd, 2H J = 8Hz, 1.2 Hz, 0.8 Hz, pyridine), 7.45-7.55 (dd, 2H, J = 7.6 Hz, 1.2 Hz phenyl), 7.55-7.6 (ddd, 2H, J = 8Hz, 7.6 Hz, 1.6 Hz, pyridine), 7.7-7.75 (td, 1H, J = 1.2 Hz, 0.8 Hz phenyl), 8.5-8.55 (ddd, 2H, J = 4.8 Hz, 1.6 Hz, 0.8 Hz, pyridine). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 87.0 (alkynyl), 88.3 (alkynyl), 121.7, 122.0, 126.3, 127.6, 131.4, 134.2, 135.2, 142.0, 149.0.
3.12 Synthesis of compound 43:

SK17:

To a 5 mL round bottom flask was added 1-\{3-(2-pyridinylethynyl)phenyl|ethynyl|2-pyridine (0.073 g, 0.26 mmol) and 3,4-bis(4-methoxyphenyl)-2,5-diphenyl-2,4-cyclopentadien-1-one (0.231 g, 0.52 mmol). The system was sealed and purged with nitrogen to which anhydrous o-xylene (1 mL) was added. The reaction mixture was heated to 175 °C for 7 days then left to cool to room temperature. The solvent was removed and the products were purified via flash column chromatography (hexane/ethyl acetate 1:1) to yield the solid monoadduct (0.023 g, 13 %).

TLC R\_f = 0.26 (hexane/ethyl acetate, 1:1); m/z: [M+H]\^+: 697 g/mol; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 3.5–3.6 (s, 6H, 2 x OMe), 6.25-6.4 (d, 4H, J = 8 Hz), 6.5-6.9 (m, 18H), 6.95-7.05 (dd, 2H, J = 8.8 Hz, 1.2 Hz), 7.05-7.2 (m, 2H), 7.3-7.4 (s, 1H), 7.5-7.6 (td, 1H, J = 8 Hz, 1.2 Hz), 8.05-8.15 (m, 1H), 8.4-8.55 (m, 1H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \delta 53.9 (OMe), 86.9 (alkynyl), 88.5 (alkynyl), 111.2, 119.5, 121.5, 124.3, 124.4, 125.7, 126.1, 130.3 131.2, 131.6, 131.8, 135.1, 137.8, 139.0, 139.2, 139.3, 139.6, 142.6, 148.9, 156.0. FTIR ν = 3051, 3022, 2997, 2970, 2950, 2931, 2905, 2832, 1512, 1285, 1242, 1175, 1031, 779, 748, 698 cm\textsuperscript{-1}. 

82
3.13 Synthesis of dendrimer 44:

![Dendrimer 44](image)

SK17:

To a 5 mL round bottom flask was added 2-[[3-(2-pyridinylethynyl)phenyl]ethynyl]pyridine (0.073 g, 0.26 mmol) and 3,4-di(4-methoxyphenyl)-2,5-diphenyl-2,4-cyclopentadien-1-one (0.231 g, 0.52 mmol). The system was sealed and purged with nitrogen to which anhydrous o-xylene (1 mL) was added. The reaction mixture was heated to 175 °C for 7 days then left to cool to room temperature. The solvent was removed and the products were purified via flash column chromatography (hexane/ethyl acetate 1:1) to yield the target compound as a white solid (0.135 g, 47%).

TLC $R_f = 0.41$ (hexane/ethyl acetate, 1:1); m/z: [M+H]+: 1113 g/mol; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.5-3.6 (s, 12H, 4 x OMe), 5.4-5.5 (d, 1H, J = 6 Hz), 6.1-7.1 (m, 45H), 8.0-8.1 (s, 1H), 8.1-8.2 (s, 1H).
3.14 Synthesis of 1-(2-nitrophenyl)piperidine:

![Structure of 1-(2-nitrophenyl)piperidine]

SK18:  

To a two-necked 100 mL round bottom flask was added palladium(II) chloride (0.0887 g, 0.5 mmol, 10%), triphenylphosphine (0.437 g, 1.66 mmol, 20%), piperidine (1.97 mL, 20 mmol), distilled water (15 mL) and acetone (19 mL). The system was sealed and purged with nitrogen prior to the reaction being stirred for 5 minutes. To this was added 1-chloro-2-nitrobenzene (1.275 g, 8.3 mmol) and 1,3-diethynylbenzene (0.664 mL, 5 mmol) before being heated to 60 °C for 50 hours. The reaction was then left to cool to room temperature before being extracted with diethyl ether (400 mL). The organic layers were combined, dried with magnesium sulphate and the solvent was removed. The crude product was then purified utilizing flash column chromatography (hexane/ethyl acetate 20:1) providing 1-(2-nitrophenyl)piperidine as orange needles.

TLC $R_f = 0.59$ (hexane/ethyl acetate, 5:1); m/z: [M+H]$^+$: 207 g/mol, [M+Na]$^+$: 229 g/mol; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.45-1.55 (m, 2H, piperidine), 1.55-1.7 (m, 4H, piperidine), 2.85-3.0 (m, 4H, piperidine), 6.85-6.95 (ddd, 1H, J = 8.16 Hz, 7.2 Hz, 1.2 Hz, nitrophenyl), 7.0-7.1 (dd, 1H, J = 8.33 Hz, 1.2 Hz, nitrophenyl), 7.3-7.4 (ddd, 1H, J = 8.33 Hz, 7.2 Hz, 1.6 Hz, nitrophenyl), 7.6-7.7 Hz, (dd, 1H, J = 8.16 Hz, 1.6 Hz, nitrophenyl). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 24.0 (CH$_2$), 26.0 (CH$_2$), 53.0 (CH$_2$ – N), 120.6, 120.8, 126.0, 133.4, 142.6, 147.0.
3.15 Synthesis of 
({3,5-bis([trimethylsilyl]ethynyl)phenyl}ethynyl)(trimethyl)silane\textsuperscript{56}:

![Chemical structure](image)

**SK26:**

A two-necked 100 mL round bottom flask was charged with 1,3,5-tribromobenzene (1.78 g, 5.68 mmol), copper iodide (0.01 g, 0.05 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.08 g, 0.11 mmol) and diethylamine (47 mL). To this was added ethynyltrimethylsilane (2.9 mL, 20.4 mmol) and the reaction mixture was heated to 50\(^\circ\)C for 7 hours. The resulting light brown precipitate of diethylamine hydrobromide was separated via vacuum filtration and washed with diethylether. The organic solvents were removed and the product was purified via flash column chromatography (petroleum ether) to yield a light yellow solid (0.77 g, 37\%).

TLC \(R_f = 0.65\) (petroleum ether); \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta 0.2-0.3\) (s, 27H, 3 x SiMe\(_3\)), 7.45-7.55 (s, 3H, phenyl); \(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)) \(\delta 96.4\) (C-C-Si), 103.3 (C-C-phenyl), 123.8 (phenyl C), 135.6 (CH of phenyl).
3.16 Synthesis of 1,3,5-triethynylbenzene:

SK28:

To (\(\text{[3,5-bis(trimethylsilyl)ethynyl]phenyl} \text{ethynyl)(trimethyl)silane}\) (0.696 g, 1.9 mmol) in a 150 mL round bottom flask was added anhydrous potassium carbonate (0.078 g, 0.51 mmol). The reaction vessel was sealed with a septum and the system was purged with nitrogen prior to anhydrous methanol (6 mL) being added through a syringe. The reaction was left to stir for 3 hours followed by the removal of the organic solvent under reduced pressure. Distilled water (50 mL) was added to the resulting solid and the product was extracted using diethyl ether (50 mL). The organic phases were combined, dried using magnesium sulphate, filtered and the solvent was removed to yield a brown solid (0.27 g, 95 %).

TLC \(R_f = 0.70\) (petroleum ether/dichloromethane 5:1); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.0-3.1 (s, 3H, terminal group), 7.45-7.55 (s, 3H, phenyl); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 78.7 (alkynyl–H), 81.6 (alkynyl–phenyl), 122.9 (aryl C–C), 135.7 (aryl C–H).
3.17 Synthesis of 1-((3,5-bis[(6-methoxy-2-naphthyl)ethynyl]phenyl)ethynyl)-6-methoxynaphthalene:

To a 100 mL round bottom flask was added 1,3,5-triethynylbenzene (0.263 g, 1.75 mmol), 1-bromo-6-methoxynapthalene (1.43 g, 6.13 mmol), palladium(II) chloride (0.046 g, 0.26 mmol), triphenylphosphine (0.482 g, 1.84 mmol), piperidine (1 mL, 10.5 mmol), distilled water (5 mL) and acetone (7mL). The reaction vessel was purged with nitrogen prior to being heated to 60 °C and left for 24 hours. The reaction mixture was left to cool to room temperature before being extracted with diethyl ether. The organic material was dried using magnesium sulphate that was then filtered out and the solvent was removed from the filtrate to yield a light yellow solid. The product was purified by flash column chromatography (hexane/ethyl acetate 4:1) that have

1-((3,5-bis[(6-methoxy-2-naphthyl)ethynyl]phenyl)ethynyl)-6-methoxynapthalene (0.11g, 10%).

TLC Rf = 0.42 (hexane/ethyl acetate, 3:1); 1H NMR (400 MHz, CDCl3) δ 3.3-3.4 (s, 9H, OMe), 7.0-7.1 (s, 3H), 7.1-7.2 (dd, 3H, J = 8.8 Hz, 2.4 Hz), 7.4-7.5 (dd, 3H, J = 8.4 Hz, 1.6 Hz), 7.6-7.65 (s, 3H), 7.65-7.7 (d, 3H, J = 8.4 Hz), 7.65-7.7 (d, 3H, J = 8.8 Hz), 7.9-8.0 (s, 3H). 13C NMR (100 MHz, CDCl3) δ 55.4 (OMe), 87.7 (alkynyl), 91.1 (alkynyl), 105.7, 105.8, 117.7, 119.5, 119.8, 124.3, 127.0, 128.1, 128.4, 128.5, 129.0, 129.5, 129.6, 131.6, 133.9, 134.3, 158.5.
3.18 Synthesis of 1-ethynyl-3-[(4-nitrophenyl)ethynyl]benzene:

![Chemical Structure]

**SK33:**

To a two-necked 50 mL round bottom flask was added palladium(II) chloride (0.107 g, 0.6 mmol), triphenylphosphine (0.377 g, 1.4 mmol), distilled water (18 mL) and acetone (23 mL). The reaction vessel was purged with nitrogen and N,N-diisopropylethylamine (2 mL, 12 mmol) was added by syringe. The reaction mixture was allowed to stir for 5 minutes before 1,3-diethynylbenzene (0.4 mL, 3 mmol) and 1-bromo-4-nitrobenzene (1.45 g, 7.2 mmol) was added. The brown mixture was heated to 60 °C whilst stirring and left for 12 hours. The reaction mixture was then left to cool to room temperature and the brown solid formed was filtered off before the product was extracted with diethyl ether. The organic phase was then dried using magnesium sulphate that was later filtered and the solvent was removed from the filtrate. The product was purified using column chromatography (hexane/ethyl acetate 10:1) to yield a creamy yellow solid (0.24g, 33%).

\[\text{H NMR (400 MHz, CDCl}_3\text{)} \delta \text{ 3.0-3.1 (s, 1H, terminal hydrogen), 7.2-7.3 (m, 1H), 7.4-7.5 (m, 2H), 7.55-7.6 (d, 2H, J = 8.8 Hz), 7.6-7.65 (s, 1H), 8.1-8.2 (d, 2H, J = 8.8 Hz).} \]

\[\text{C NMR (100 MHz, CDCl}_3\text{)} \delta \text{ 78.2 (alkynyl–H), 82.4 (alkynyl), 88.1 (alkynyl), 93.5 (alkynyl), 122.5, 122.8, 123.7, 128.7, 130.0, 132.0, 132.4, 132.8, 135.3, 147.2.} \]
4 References


5 Appendices
Appendix 1: A $^1$H NMR spectrum of a mixture containing compound 25 and 1-(4-nitrophenyl)piperdine.
Appendix 2: A $^1$H NMR spectrum of the product formed from a rhodium catalysed reaction between 2-(phenylethynyl)pyridine 14 and 1,3-diphenylcyclopropenone 28.
Appendix 3: A COSY NMR spectrum of the product formed from a rhodium catalysed reaction between 2-(phenylethynyl)pyridine 14 and 1,3-diphenylcyclopropenone 28.
Appendix 4: A $^{13}$C NMR spectrum of the product formed from a rhodium catalysed reaction between 2-(phenylethynyl)pyridine 14 and 1,3-dipheynylcyclopropenone 28.
Appendix 5: The $^1$H NMR spectrum published by Wender et al for compound 31. Taken from\textsuperscript{20}.
Appendix 6: The $^1$H NMR spectrum of 3,4-bis(4-methoxyphenyl)-2,5-diphenyl-2,4-cyclopentadien-1-one 41.
## Appendix 7

Table 1. Crystal data and structure refinement for 1-(2-nitrophenyl)piperidine.

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<th>Value</th>
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<td>Empirical formula</td>
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</tr>
<tr>
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<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
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<td></td>
<td>b = 10.4595(6) Å, β = 90°</td>
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<td></td>
<td>c = 12.8750(9) Å, γ = 90°</td>
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<td>R indices (all data)</td>
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<td>Absolute structure parameter</td>
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<td>Largest diff. peak and hole</td>
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Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) U(eq) is defined as one third of the trace of the orthogonalized U$_{ij}$ tensor.

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Table 3. Bond lengths [Å] and angles [°] for 1-(2-nitrophenyl)piperdine.

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C(6)-C(1)-N(1)         | 122.2(5)     |
C(6)-C(1)-C(2)         | 115.8(5)     |
N(1)-C(1)-C(2)         | 121.9(5)     |
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Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å\(^2\) x 10\(^{3}\)) for 1-(2-nitrophenyl)piperidine. The anisotropic displacement factor exponent takes the form: -2\(\pi^2\)\(h^2a^*a^*U^{11} + \ldots + 2hkab^{*}b^{*}U^{12}\).

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