Chapter 1

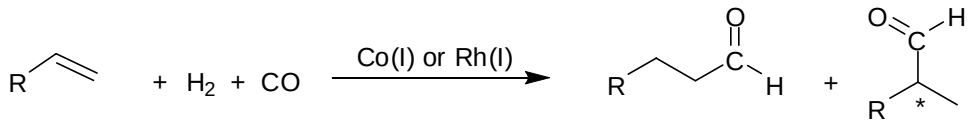
Introduction

1.1 Transition Metal Complexes as Homogeneous Catalysts

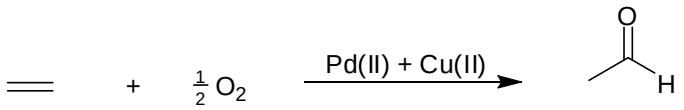
A variety of transition metals and metal complexes act as catalysts for organic reactions. The use of transition metal complexes to catalyse organic reactions is one of the most important applications of organometallic chemistry and has been the driving force in the rapid development of this field since catalysts are crucial to the turnover and selectivity in many chemical syntheses.[1*]

Organometallic complexes catalyse a wide range of reactions, both in nature and in industry. For example, the naturally occurring metalloenzymes are vital catalysts in many metabolic processes such as respiration and are crucial in the photosynthetic cycle. Transition metal catalysts are used industrially in the production of bulk materials, pharmaceuticals, agrochemicals, flavours and fragrances[2] by technological application such as; the hydroformylation of alkenes, the oxidation of alkenes, hydrocyanation of butadiene, and hydrogenation (Scheme 1.1).[3]

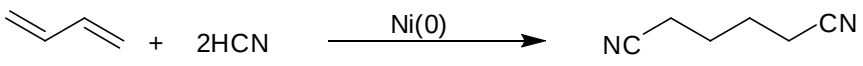
Hydroformylation of Alkenes (Oxo Process)



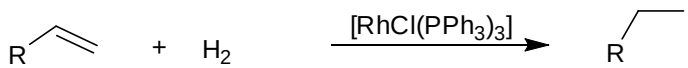
Oxidation of alkenes (Wacker Process)



Hydrocyanation of Butadiene



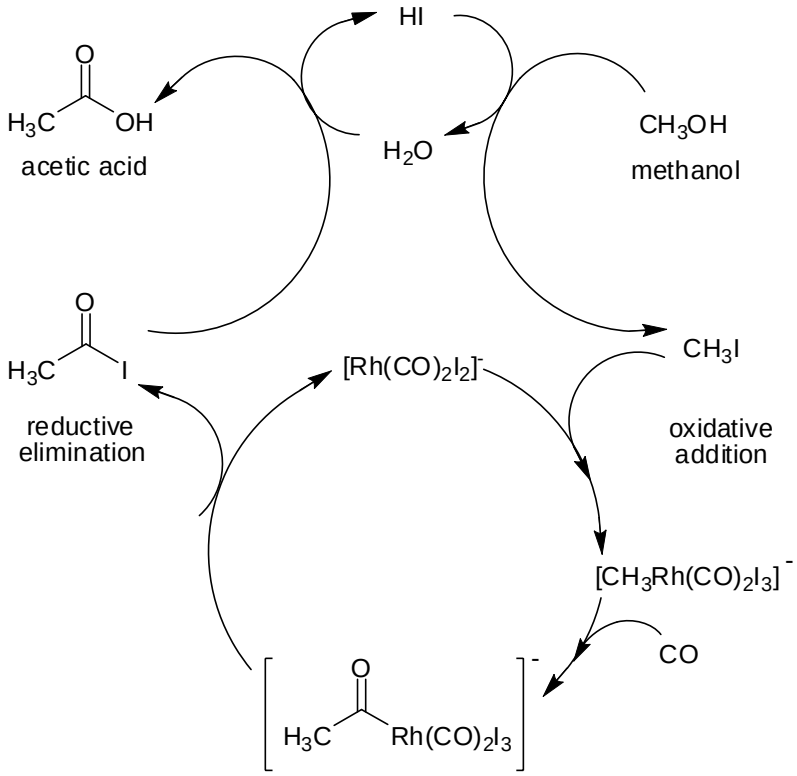
Hydrogenation (Wilkinson's Catalyst)



Scheme 0.1

[*] References begin on page 16.

One of the most important examples of homogeneous catalysis is the carbonylation of methanol to produce acetic acid, in what is known as the *Monsanto Process* (Scheme 1.2). Acetic acid is used for different purposes in the industry such as producing vinegar, food preservatives, solvents and plastics. This product is an important chemical with a world wide demand of over 6 million tons per year.



Scheme 0.2

The catalyst cycle for the Monsanto Process involves two catalyst systems. The first step involves the production of methyl iodide by treatment of methanol with hydrogen iodide. The second step involves oxidative addition of methyl iodide to the actual catalyst $[Rh(CO)_2I_2]^-$. Coordination and insertion of carbon monoxide leads to an 18-electron acyl intermediate complex which can undergo reductive elimination to yield acetyl iodide and regenerate the rhodium catalyst, that is the anionic rhodium(I) species. The final step involves hydrolysis of acetyl iodide

with water to form acetic acid and hydrogen iodide. The formation of hydrogen iodide in the final step completes the cycle. The Monsanto Process operates at a low temperature and pressure (180 °C, 30-40 atm respectively) and the reaction is extremely selective, high yielding (~99%) and very fast.[4]

1.1.1 Homogeneous and Heterogeneous Catalysis

Transition metal catalysts can be classified as either homogeneous or heterogeneous catalysts. Homogeneous catalysis occurs when both the catalyst and the substrate are in the same phase (e.g. dissolved in solution), whereas heterogeneous catalysis occurs when the catalyst is in a different phase to the reactant and the reaction usually takes place at the surface of the solid catalyst.[5]

Traditionally, heterogeneous catalysis has strongly dominated the industrial scene, and accounts for about 85% of all known catalytic processes. The attractiveness of heterogeneous catalysis is mainly due to the long life of service of the catalyst and the ease of separation from the reaction products. However there are limitations to heterogeneous catalysis and these include: (i) generally harsher reaction conditions i.e. high temperature and pressure; and (ii) characteristically low levels of activity and selectivity resulting in a mixture of products.[6]

The impact of homogeneous catalysis on the industrial process technology has grown in the past 35 years. New knowledge regarding the structure and reactivity of many organometallic compounds has created new catalytic processes in industry. In large-scale industrial processes, homogenous catalysis is attractive because it is easier to dissipate heat from a solution than from the solid bed of a heterogeneous catalyst.[6]

The advantages of homogeneous catalysis generally include high activity and selectivity under relatively mild conditions. Homogeneous catalysis presents a far better opportunity for mechanistic understanding of the catalytic cycle because it is possible to study the mechanism *in situ* where the intermediates can be

spectroscopically characterised (such as by NMR) or isolated. This is undoubtedly the striking advantage over heterogeneous catalysis where the mechanism is much more difficult to understand.[6] The history of homogeneous catalysis is the success story of process technology however there are a number of disadvantages. The greatest disadvantage of homogenous catalysis is the inherent difficulty of separating the catalyst from the product.

1.1.2 Catalysis

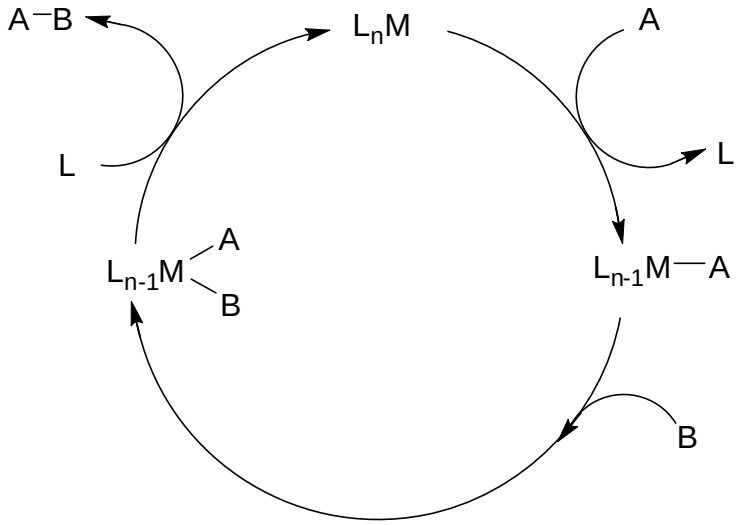
A catalyst is a compound which promotes a chemical reaction by lowering the energy of activation, thus increasing the rate of reaction and allowing the reaction to reach equilibrium more rapidly. Catalysts do not have the ability to promote a chemical reaction that is thermodynamically disfavoured, or alter the value of the equilibrium constant. The catalyst may form various reactive intermediates throughout the course of the reaction but overall it is not consumed.[5, 7]

The catalytic transformation of an organic substrate by an organometallic complex is characterised by a series of reactions through which the substrate initially coordinates to the metal catalyst to induce the catalytic reaction. A reaction takes place and the products are released and ideally, the catalyst is regenerated after the reaction is complete.[5]

The catalytic cycle constitutes a series of reactions (Scheme 1.3). In the first step of the cycle the metal centre (M) coordinates or interacts with the substrate (A). This step of the cycle is often associated with the loss of a ligand (L). For substrate coordination, the metal complex must provide a vacant coordination site.[8]

Sequential interaction of the metal complex with a second reactant (B) results in the transformation of the substrate (within the coordination sphere of the complex). The final step of the cycle involves the release of the product (A–B) from the metal centre and the catalytically active complex (L_nM) is regenerated.[9]

A metal catalyst will undergo a catalytic cycle a finite number of times before it effectively "dies" due to undesired deactivation reactions competing with the desired product-forming reactions.

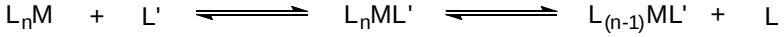


Scheme 0.3

It is necessary that the metal binds to the substrate to allow the transformation or functionalisation to occur but the metal should not bind the substrate so weakly that it fails to activate the substrate before the reaction can occur. Similarly, the product should not bind too strongly to the metal and prevent a new molecule of substrate from displacing it once the reaction is complete.

There are a number of reactions which can occur at the metal complex during a catalytic cycle. A combination of these reactions contributes to a complete catalytic cycle. The most common reactions include: (i) ligand substitution; (ii) oxidative addition and reductive elimination; (iii) migratory insertion/ β-hydride elimination; and (v) nucleophilic and electrophilic attack on ligands.[10]

Associative Exchange

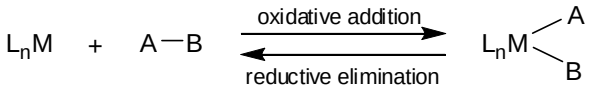


Dissociative Exchange

Scheme 0.4

The success of a metal-catalysed reaction often relies on the ability of the complex to undergo substitution reactions. The ligand substitution reaction generally occurs at the beginning and end of the catalytic cycles to bind the substrate and to release the product. The two types of ligand substitution reactions are associative and dissociative (Scheme 1.4). Coordinatively unsaturated, 16-electron complexes, typically undergo associative exchange, since the vacant site for coordination are already available for the incoming ligand.

Coordinatively saturated 18-electron complexes undergo dissociative exchange processes. Dissociated substitution is a slower reaction process since a vacant coordination site must first be created before substitution can occur. A number of factors influence the rate of substitution reactions including the size of the ligand, geometry at the metal centre, the size of the co-ligands and the ionic charge of the complex.



Scheme 0.5

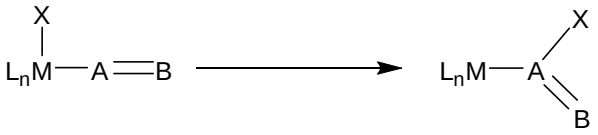
Oxidative addition, and the reverse process, reductive elimination, occur at the metal centres. In oxidative addition a substrate bond (A–B) breaks and two new bonds form (M–A and M–B) and the oxidation state of the metal increases by 2 units (Scheme 1.5). Reductive elimination involves the formation of the A–B

bonds and the oxidation state of the metal decreases by 2 units. The position of the equilibrium depends on the relative stabilities of the two oxidation states and the balance of A–B verses M–A and M–B bond strengths.

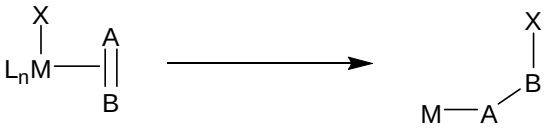
Oxidative addition often occurs at the beginning of the catalytic cycle to activate the substrate, which can then undergo reactions at the metal centre. Reductive elimination is often the last step in a catalytic cycle, and it requires the groups to be eliminated be arranged in a mutually *cis* position.

The metal centre must have two vacant coordination sites as well as two energetically accessible oxidation states, two units apart in order to undergo the oxidative addition reaction. This reaction is most commonly evident for metals such as the Ni(0)/Ni(II), Pd(0)/Pd(II), Rh(I)/Rh(III) and Ir(I)/Ir(III) redox pairs.[5]

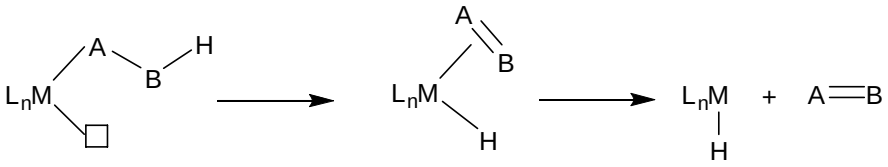
1, 1-insertion



1, 2-insertion



β-hydride elimination



Scheme 0.6

Insertion and elimination reactions transform or combine ligands within the coordination sphere of the metal, which have typically been introduced previously by oxidative addition reactions.

Migratory insertion involves the insertion of an unsaturated coordinated ligand (A=B) into an adjacent M–X bond (Scheme 1.6) and insertion can be of two types: 1, 1-insertion when the metal and X ligand are bound to the same atom of the ligand; 1, 2-insertion when the metal and X are bound to adjacent atoms. 1, 1-insertion is a common reaction for carbonyl ligands while 1, 2-insertion is seen in the reduction of a bound alkene.

The reverse reaction to migratory insertion is β-hydride elimination (Scheme 1.6). β-Hydride elimination is a common decomposition reaction for alkylmetal complexes and require a vacant coordination site positioned *cis* to the leaving group.

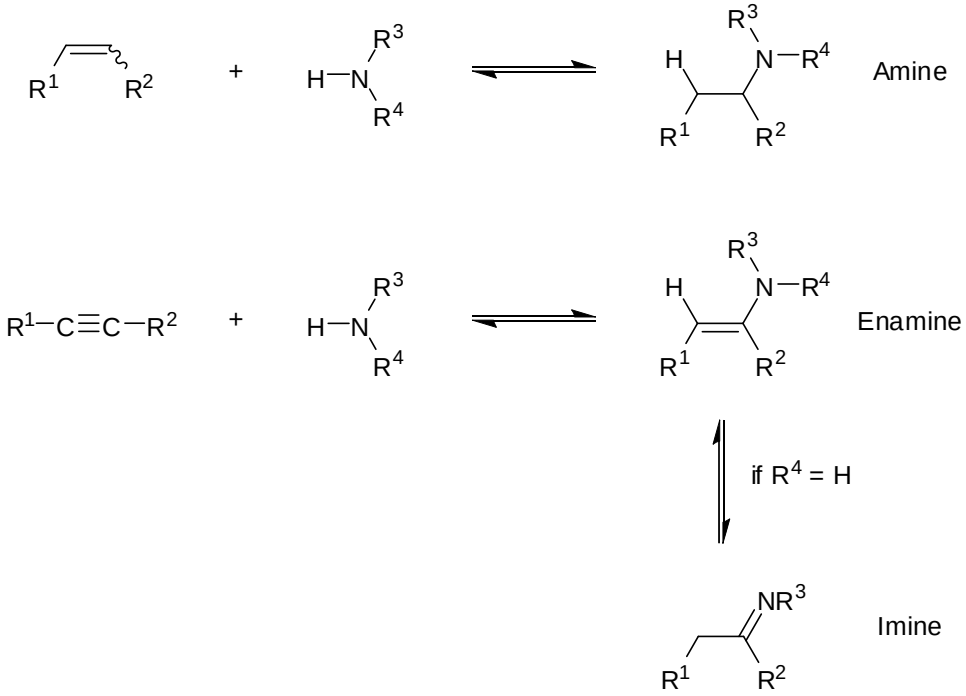
Nucleophilic or Electrophilic attack on the ligands

Another important reaction in the metal-catalysed synthesis of organic molecules is nucleophilic or electrophilic attack by an external reagent on coordinated organic molecules. Complexation of an unsaturated compound, for example, alkynes, alkenes or carbon monoxide to a metal centre can increase the susceptibility of the substrate to the direct attack of an external reagent (a nucleophile or electrophile). Nucleophilic attack is a common reaction when a substrate is coordinated to an electron deficient metal centre, i.e. a metal which bears a net positive charge and/or has electron withdrawing ligands. Electrophilic attack is far less common and is favoured when a substrate is coordinated to an electron rich metal centre, i.e. a metal which bears a net negative charge and/or has electron donating ligands.

1.1.3 Metal-Catalysed Formation of Carbon-Nitrogen Bonds

In transition metal-catalysed reactions of organic substrates, it is the chemistry of the metal that determines the course of the reaction, and the understanding of the mechanisms by which transition metal organometallic complexes react is critical to the rational use of transition metals in organic synthesis.

The addition of heteroatom-hydrogen bonds across the carbon-carbon triple bond, catalysed by transition-metal complexes, is one of the most interesting and intriguing subjects in organic chemistry. This reaction has been observed for such different types of bonds as N–H, O–H, S–H, Se–H, and P–H. The nature of the transition-metal complex also plays a key role in the reaction. All of these bond formations are very important from the synthetic point of view because, in principle, the addition reactions can be performed with 100% atom efficiency, without any waste formation, and for this reason they fulfill the requirements of green chemistry better than substitution reactions leading to the same products. Furthermore, the intramolecular version of this reaction is one of the best and most straightforward ways to obtain nitrogen- and oxygen-containing heterocycles.[11]



Scheme 0.7

Metal-catalysed hydroamination involves the formation of carbon-nitrogen bonds *via* addition of nitrogen-hydrogen across a carbon-carbon multiple bond, either in an *inter*molecular or *intra*molecular fashion. The hydroamination of alkenes and the hydroamination of alkynes are among the most desirable transformations in

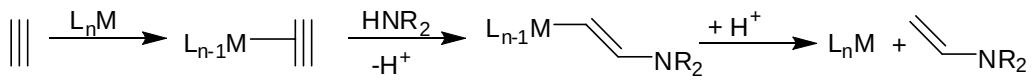
organic chemistry. They offer direct pathways to new primary, secondary and tertiary amines, as well as enamines and imines which are important bulk and fine chemicals or building blocks in organic chemistry (Scheme 1.7).[1, 12] Amines play an outstanding role as products and intermediates in the chemical industry, several million tons per year of various amines are produced worldwide.

In the absence of a metal catalyst the process is necessarily thermodynamically feasible, but a high activation barrier exists. Hydroamination reactions catalysed by metal complexes have the potential to couple non-activated alkenes and alkynes into desired products in a single reaction without the formation of side products, starting from simple and inexpensive precursors.[12, 13]

Hydroamination reactions can be assisted or catalysed by alkali metals (lithium, potassium, sodium and cesium), transition metal (iridium, ruthenium, rhodium, palladium, platinum) or *f*-element (lanthanum, lutetium) complexes. There are two basic approaches to the metal-catalysed hydroamination reaction involving activation of either alkene/ alkyne or amine.[1]

Alkene/ Alkyne Activation

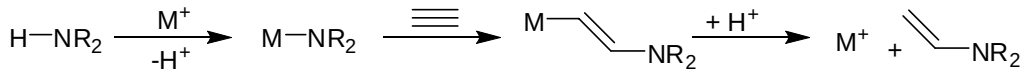
Alkene/ alkyne activation can be effected by π-coordination to late-transition metals, rendering them more susceptible towards nucleophilic attack by the amine (Scheme 1.8).



Scheme 0.8

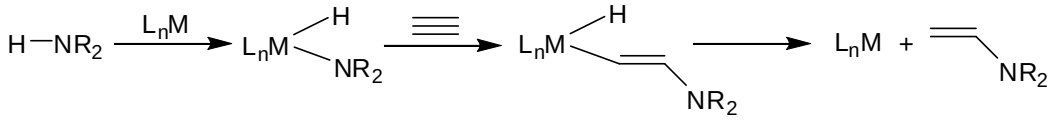
Amine Activation

One possible approach to amine activation can be by deprotonation of the amine to generate a highly nucleophilic amide species by utilizing electropositive alkali or lanthanide metals, which are then able to directly attack the carbon-carbon unsaturated bonds (Scheme 1.9).



Scheme 0.9

Alternatively, amine activation *via* oxidative addition to late transition metals has been observed. The oxidative addition of the nitrogen-hydrogen bond to a metal centre produces a hydrido-amido complex. The alkene or alkyne inserts into the metal-nitrogen (M–N) bond (Scheme 1.10) and the resulting alkylamine is reductively eliminated and regenerates the metal-catalyst.[1]



Scheme 0.10

1.1.4 The Importance of Organo-Nitrogen Compounds

The prospect of an efficient synthesis of nitrogen-containing compounds has sparked a significant research effort, due to their importance in biological systems and industrial chemicals. Amines are an important class of compounds, because many naturally occurring compounds and biologically active molecules contain amine functionalities. Amines also have many industrial applications e.g. solvents, additives for pharmaceuticals, bactericides, flotation auxiliaries, anti-foam agents, corrosion inhibitors, detergents and dyes.[14]

Classical methods for the synthesis of amines, either on laboratory or industrial scale, include transformations of alcohols or alkyl halides into amines, reductive amination of carbonyl compounds, aminoalkylation, reduction of amides, nitriles, azides or nitro compounds. All these methods have in common the necessity of refined starting materials as precursors, which are often expensive and which can be difficult to synthesise or dangerous to handle. However, the demand for

cleaner syntheses has resulted in the development for catalysed approaches to their synthesis. Hydroamination is one of the simplest synthetic approaches for the synthesis of nitrogen-containing compounds.[14]

Hydroamination has been successful in the syntheses of natural products including the alkaloid (+)-Pseudodistomin D,[15] (-)-Pinidinol,[16] the morphine derivative (-)-Dihydroisocodeine,[17] and the indolizidine alkaloid (±)-Monomorine[18] (Figure 1.1).

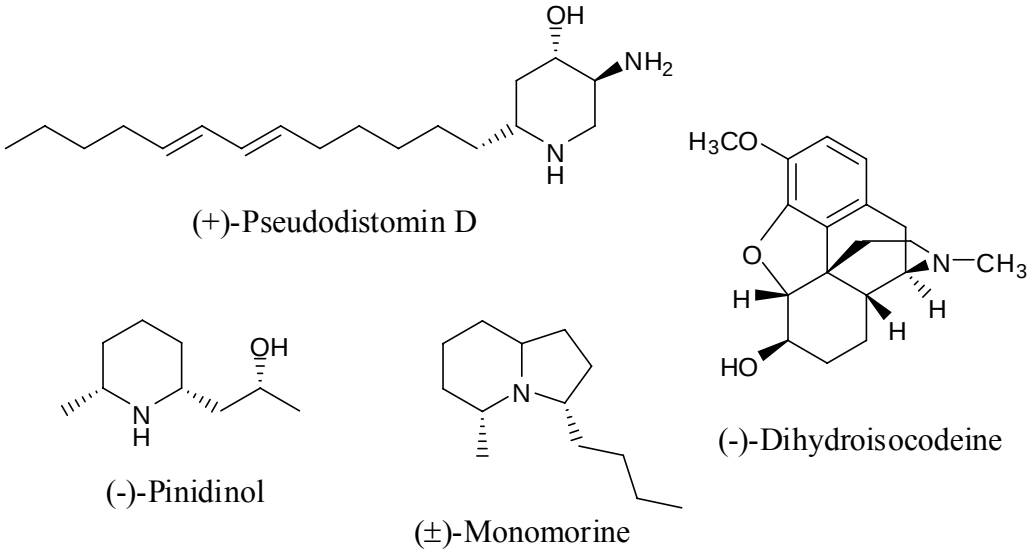


Figure 1.1

1.2 Objectives

The work described in this thesis encompasses the design and synthesis of a number of different aliphatic and aromatic aminoalkyne substrates and the exploration of the rhodium(I) complex (**1**) for further catalytic transformation. This thesis also investigates the use of organopalladium complexes with *bis*(*N*-methylimidazol-2-yl)methane (bim, **2**) nitrogen donor ligands as catalysts for the development of more efficient synthesis of imines.

The specific objectives of this work were to:

i) Synthesise and characterise 4, 5 and 6 carbon aliphatic amides as possible substrates for the formation of 4-, 5- and 6-membered cyclic amides using an intramolecular, metal-catalysed hydroamination sequence;

ii) Synthesise and characterise aromatic acetylenic amines and amides as possible precursors for substituted nitrogen-containing heterocycles *via* an intramolecular, metal-catalysed hydroamination sequence;

iii) Establish the scope of hydroamination reactions accessible with the rhodium(I) complex (**1**) as a cyclisation catalyst;

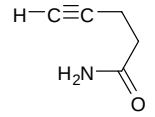
iv) Synthesise and characterise a range of possible palladium(II) complexes, analogous to the established rhodium(I) systems, and to assess the complexes as catalysts for hydroamination.

1.3 Structure of this Thesis

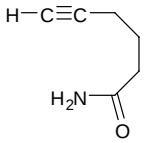
Chapter 1: Introduction to transition metal complexes as homogeneous catalysts and metal-catalysed formation of carbon-nitrogen bonds.

Chapter 2: Reports the synthesis of a series of aliphatic and aromatic amino- and amidoalkynes:

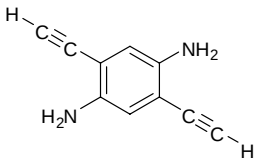
i) 4-pentyn-1-amide (**3**)



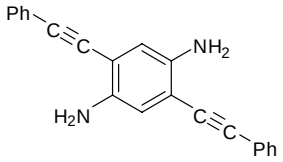
ii) 5-hexyn-1-amide (**4**)



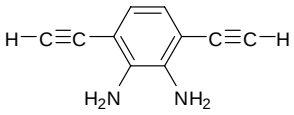
iii) 1, 4-diamino-2, 5-diethynylbenzene (**5**)



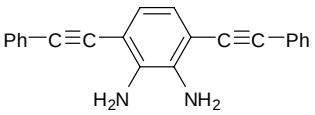
iv) 1, 4-diamino-2,5-*bis*(phenylethynyl) benzene (**6**)



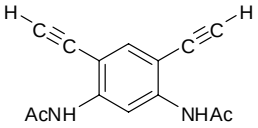
v) 2, 3-diamino-1, 4-diethynylbenzene (**7**)



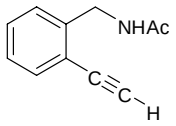
vi) 2, 3-diamino-1, 4-*bis*(phenylethynyl) benzene (**8**)



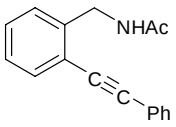
vii) 1, 5-*bis*(acetamido)-2, 4-diethynyl benzene (**9**)



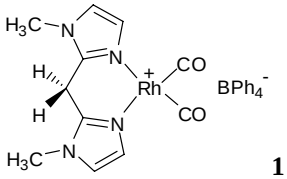
viii) *N*-(acetyl)-2-ethynylbenzylamine (**10**)



ix) *N*-(acetyl)-2-(phenylethynyl) benzylamine (**11**)



Chapter 3: Explores the scope of the hydroamination reaction catalysed by rhodium(I) complex (**1**). A series of amino- and amidoalkyne substrates (**3**-**13**, reported in Chapter 2), with both terminal and internal acetylenes are reacted with complex **1**. Cyclised products were isolated and characterised.



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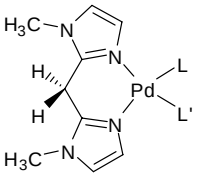
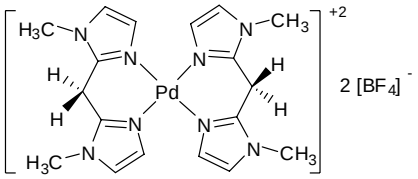
Chapter 4: Reports the synthesis of a series of four-coordinate palladium(II) cationic and neutral complexes (**14**-**20**) and the application of these complexes to the metal-catalysed cyclisation of 4-pentyn-1-amine (**21**) to 2-methyl-1-pyrroline (**22**).



L = Cl, L' = CH_3 **14**

L = L' = Cl **15**

L = $NCCH_3$, L' = Cl (anion BF_4) **16**



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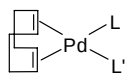
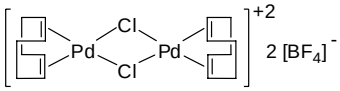


L = L' = Cl **18**

L = Cl, L' = CH_3 **19**



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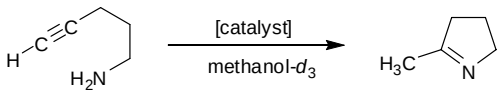
The reactivity of each complex is compared to **1** to determine the important features of a hydroamination catalyst.



21 **22**

Chapter 5: Summary, conclusions and suggestions for further work.

Chapter 6: Experimental

Appendix 1: X-ray crystallographic data

Appendix 2: Hydroamination kinetic data

1.4 References

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Chapter 2

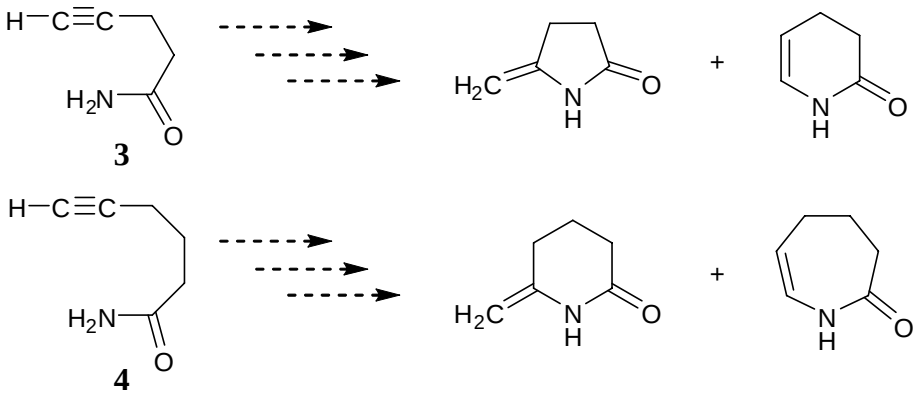
Synthesis of Substrates

2.1 Synthesis of Amino- and Amido-alkynes

2.1.1 Introduction

In order to extend the scope of substrates that can be cyclised by rhodium(I) complex (**1**) in an intramolecular hydroamination reaction, a number of potential aliphatic substrates were synthesised namely, 4-pentyn-1-amide (**3**) and 5-hexyn-1-amide (**4**).

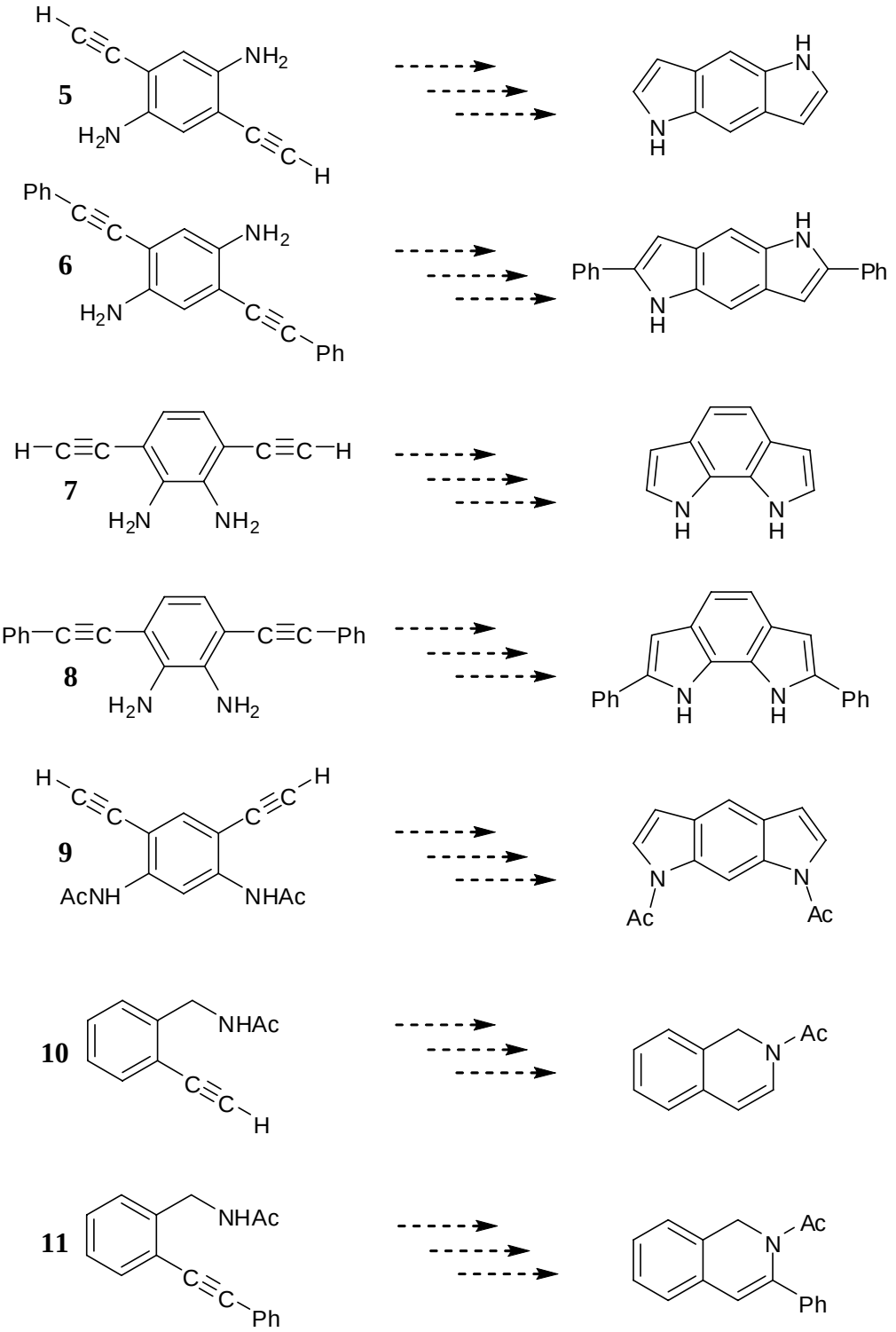
In the first part of this study, the $-NH_2$ group which is part of an amide functionality was explored for possible catalytic hydroamination. If these simple aliphatic alkynamide substrates can successfully be encouraged to undergo an intramolecular hydroamination reaction, they then provide access, in principle, to 5-, 6- and to 7-membered heterocyclic rings (Scheme 2.1).



Scheme 0.1

Secondly, a number of aromatic amino acetylene substrates were also synthesised namely: 1, 4-diamino-2, 5-diethynylbenzene (**5**), 1, 4-diamino-2, 5-*bis*(phenylethynyl)benzene (**6**), 2, 3-diamino-1, 4-diethynylbenzene (**7**), 2, 3-diamino-1, 4-*bis*(phenylethynyl)benzene (**8**), 1, 5-*bis*(acetamido)-2, 4-diethynylbenzene (**9**), *N*-(acetyl)-2-ethynylbenzylamine (**10**) and *N*-(acetyl)-2-(phenylethynyl)benzylamine (**11**).

All of these aromatic substrates are specific alkynamines which, in principle, provide access to indoles and condensed indoles if they can undergo intramolecular hydroamination reactions (Scheme 2.2).



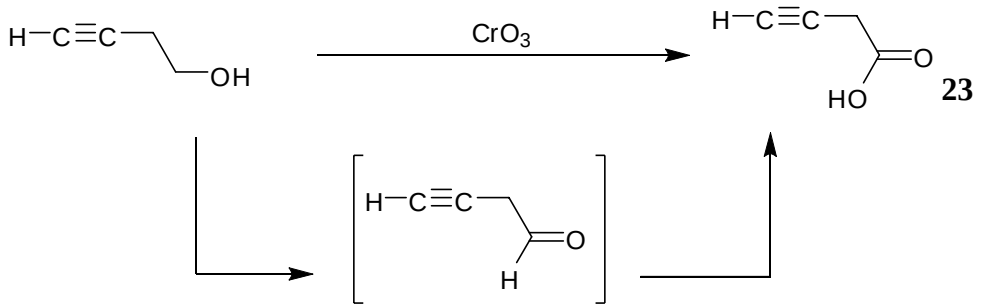
Scheme 0.2

2.2 Synthesis of Aliphatic Alkynamides

The starting materials 3-butyn-1-ol, 4-pentyn-1-ol and 5-hexyn-1-ol were commercially available and were used to prepare the corresponding alkynoic acids and subsequently the alkynamides.

2.2.1.1 3-Butynoic acid (23)

There are only a few published methods for the oxidation of alkynols to alkynoic acids and the method used followed a procedure described by Holland and Gilman.[1*] 3-Butynoic acid (**23**) was prepared from 3-butyn-1-ol (Scheme 2.3) using chromium(VI) oxide (CrO_3, Jones' reagent) in aqueous sulfuric acid as the oxidising agent. The procedure used was identical to the literature with the exclusion of the aqueous sodium hydroxide workup step as these conditions resulted in isomerisation of the alkyne to the corresponding allene (but-2, 3-dienoic acid (**24**), Scheme 2.5).[2] The reaction was performed on a relatively large scale (15 g) to compensate for the poor yields of the reaction. Compound **23** was isolated by distillation (kugelrohr) to give white plates in 12% yield.



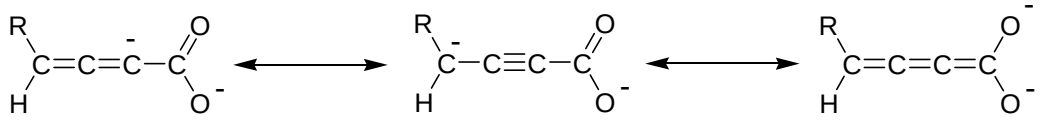
Scheme 0.3

The synthesis of **23** firstly involves the well-established oxidation of an alcohol by chromium(VI) oxide. The reaction proceeds via a chromate ester to produce an aldehyde which is further oxidised to the carboxylic acid.[3]

[*] References begin on page 55.

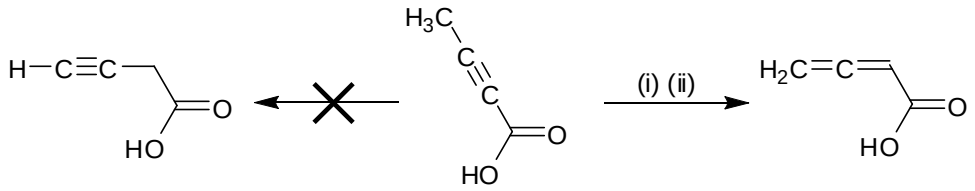
^{1}H NMR analysis identified the expected resonances in the aliphatic region from δ 3.37-2.24 ppm which were clearly distinguishable from the starting material. In chloroform-*d* solvent, the hydroxyl group of the carboxylic acid was identified in the ^{1}H NMR as a single broad resonance at δ 9.78 ppm. ^{13}C{^{1}H} NMR analysis of **23** showed that the carbon bound to the alcohol group was no longer present and a new resonance at δ 174.3 ppm confirmed the presence of a carboxyl functionality in the product. The negative electrospray mass spectrum showed the presence of the $(M–H)^-$ ion consistent with product **23**. Compound **23** has been reported in the literature[2, 4] and the ^{1}H NMR values corresponded to those reported.[4]

The synthesis of 3-butynoic acid (**23**) was also attempted from 2-butynoic acid (**25**, Scheme 2.5) by migration of the triple bond to the terminal position through an allene intermediate, in the presence of a base.[5] Previous work[6] demonstrated that the addition of a 2-alkynoic acid to a solution of sodium amide in liquid ammonia initially gave a solution of the sodium salt of the carboxylic acid. If an excess of sodium amide was present, the weakly basic salt was further deprotonated at the carbon next to the triple bond. The alkynoic acid-dianion is highly delocalised and resonance stabilised (Scheme 2.4).



Scheme 0.4

The protonation with ammonium chloride was apparently highly regioselective, since the product obtained after acidic work-up gave pure 3-alkynoic acid.[6] Using this alternative approach, only the allene but-2, 3-dienoic acid (**24**) was obtained in 18% yield rather than the expected 3-butynoic acid (**23**, Scheme 2.5).



23 **25** **24**

Scheme 0.5 (i) sodium amide, ammonia (liquid), -78 °C; (ii) ammonium chloride, room temperature.

^{1}H NMR analysis identified the resonances in the allene region from δ 5.53-5.15 ppm which were clearly distinguishable from the starting material and target product. ^{13}C{^{1}H} NMR analysis of **24** showed a new resonance at δ 216.3 ppm which confirmed the presence of the quaternary allenic carbon in compound **24**. These NMR values correspond to reported values for **24**.[7]

2.2.1.2 4-Pentynoic acid (26)

4-Pentynoic acid (**26**) was prepared from 4-pentyn-1-ol according to the procedure described by Holland and Gilman.[1] Workup was followed according to the synthesis of **23** with the inclusion of the aqueous sodium hydroxide step. 4-pentynoic acid was isolated in 15% yield after recrystallisation from diethyl ether/ hexane. Despite repeated attempts, literature yields of 48%[1] and 69%[8] could not be replicated.

Aliphatic resonances were observed in the region from δ 2.60-1.98 ppm in the ^{1}H NMR spectrum with the acetylenic proton resonance at δ 1.98 ppm. ^{13}C{^{1}H} NMR analysis of **26** also showed a new resonance at δ 177.0 ppm, confirming the presence of a carboxyl functionality in the product. The negative electrospray mass spectrum was also consistent with reported values for product **26**.[1]

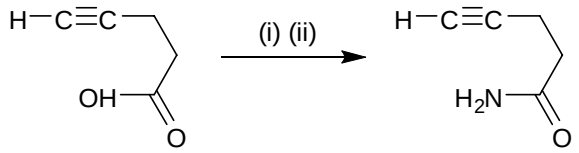
2.2.1.3 5-Hexynoic acid (27)

5-Hexynoic acid (**27**) was prepared from 5-hexyn-1-ol. The procedure used was identical to that for the synthesis of **26**. The reaction was performed on a larger scale (15 g) due to the relative poor yield of the reaction. The product (**27**) was a colourless oil which was distilled under vacuum and isolated in 32% yield. ^{1}H and $^{13}C\{^{1}H\}$ NMR chemical shifts for compound **27** were consistent with literature values.[1, 9]

Aliphatic resonances were observed in the region δ 2.49-1.85 ppm in the ^{1}H NMR spectrum. The resonance of the protons α to the alcohol functional group in the starting material was no longer present. The acetylenic and the hydroxyl protons resonance were identified at δ 1.91 and 9.97 ppm respectively. The hydroxyl proton resonance shifted upfield with respect to that of the starting material (δ 2.10 ppm). The $^{13}C\{^{1}H\}$ NMR spectrum was also consistent with the proposed structure for **27** with acetylenic resonances at δ 83.1 and 69.4 ppm.

2.2.2 4-Pentyn-1-amide (3)

4-Pentyn-1-amide was prepared in one step from 4-pentynoic acid (**26**) by reaction with ammonia using morpho-CDI (*N*-cyclohexyl-*N*′-(2-morpholinoethyl)carbodiimide methyl-*p*-toluenesulfonate) as a coupling reagent (Scheme 2.6).

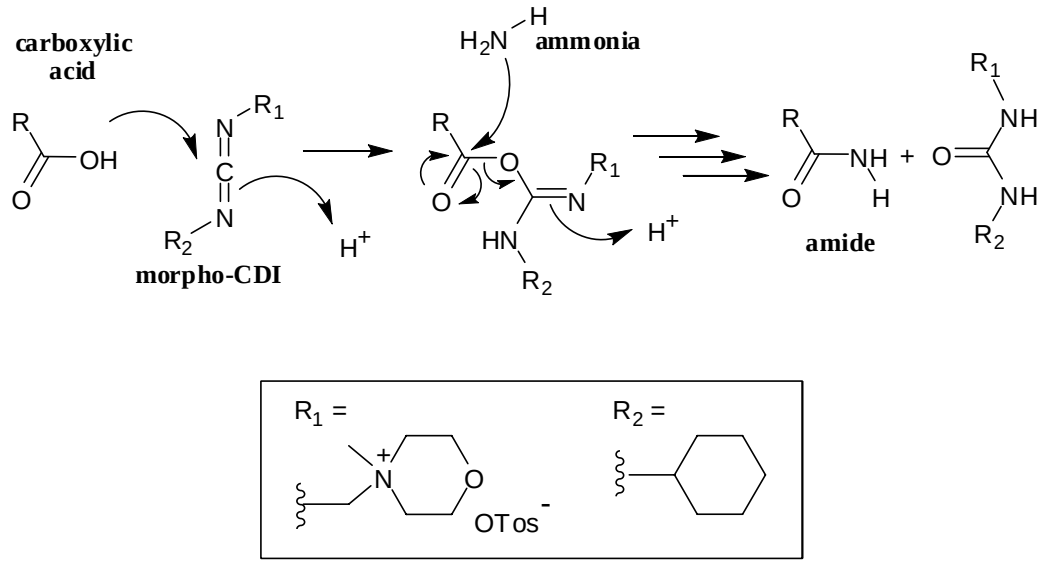


26 **3**

Scheme 0.6 (i) morpho-CDI; (ii) ammonia (liquid), room temperature.

4-Pentynoic acid was treated with morpho-CDI to form a reactive ester intermediate which then reacts with ammonia to give 4-pentyn-1-amide in

moderate yield (47%). The coupling reagent and the urea byproducts are both water soluble and are easily removed during aqueous/ organic extraction (Scheme 2.7).

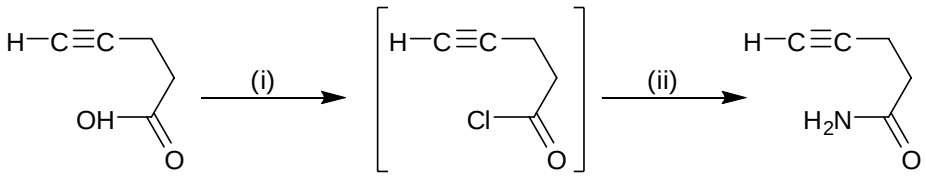


Scheme 0.7

^{1}H NMR analysis in tetrahydrofuran-d_8 identified the expected resonances in the aliphatic region between δ 2.41-2.33 ppm although the multiplicities of the aliphatic protons were overlapping and difficult to assign. The acetylenic proton resonance at δ 2.22 ppm was slightly shifted downfield with respect to the starting material. The amine protons gave rise to two separate broad signals in the NMR spectrum separated by 76 Hz at 300 K and this is probably due to restricted rotation about the carbon-nitrogen bond. When the temperature was increased to 320 K a single resonance was observed for the amine protons. ^{13}C{^{1}H} NMR analysis supported the presence of an amide with a new carbonyl resonance at δ 172.2 ppm. All spectral data for compound **3** were consistent with literature values.[10]

2.2.3 4-Pentyn-1-amide (3) *via* Acid Chloride Intermediate (28)

The synthesis of 4-pentyn-1-amide was initially attempted following a procedure described by Jacobi *et al.*[10] The carboxylic acid **26** was treated with thionyl chloride to form the intermediate acid chloride **28** which was then treated with liquid ammonia to form the amide (Scheme 2.8). This reaction sequence only resulted in low yields of the product due to extensive decomposition of the starting material to a black insoluble tarry residue.



26 **28** **3**

Scheme 0.8 (i) thionyl chloride, reflux 1 h; (ii) ammonia (liquid), room temperature.

The best yield obtained using this method was 7% and this was difficult to reproduce reliably. The reaction of thionyl chloride with carboxylic acids produces hydrochloric acid as a reaction byproduct and this probably promotes secondary condensation and polymerisation reactions at the remote acetylenic functionality.

2.2.4 5-Hexyn-1-amide (4)

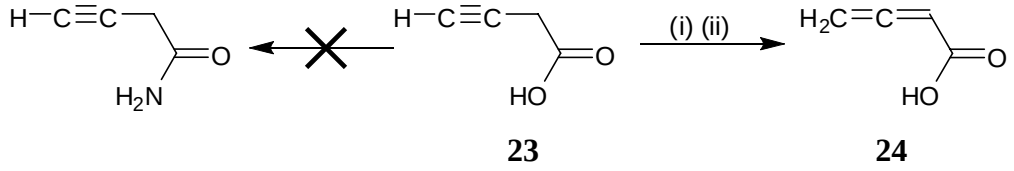
5-Hexyn-1-amide (**4**) was prepared from the reaction of 5-hexynoic acid (**27**) with ammonia using morpho-CDI as a coupling reagent. The procedure used was identical to that for the synthesis of **3** (Scheme 2.6). The product (**4**) was purified by recrystallisation to give 5-hexyn-1-amide as a white solid in 47% yield.

Compound **4** has not been reported in the literature and thus was characterised as a new compound. ^{1}H NMR analysis identified the expected resonances of the product in the aliphatic region from δ 2.22-1.80 ppm. The acetylenic proton

resonance was located at δ 2.14 ppm at 330 K. At 300 K, the resonance overlapped with the other aliphatic protons and could not be clearly seen in the spectrum. The amine protons gave rise to two separate broad signals in the NMR spectrum separated by 68 Hz at 300 K. When the temperature was increased to 340 K a single resonance was observed. $^{13}C\{^{1}H\}$ NMR analysis of **4** showed a new resonance at δ 174.8 ppm confirming the presence of an amide. Microanalysis, positive electrospray and high resolution mass spectrometry confirmed the elemental formula of **4**. The infrared spectrum also contained absorbances at 3184s ν (N–H), 2115w ν (C≡C) and 1661s, 1634s ν (C=O) cm^{-1} consistent with the presence of the functional groups in the molecule.

2.2.4.1 Attempted Synthesis of 3-Butyn-1-amide

An attempt to form 3-butyn-1-amide from 3-butynoic acid (**23**) was undertaken following the procedure for the synthesis of **4**. The reaction was unsuccessful and the only product that was isolated was the isomeric allene, but-2, 3-dienoic acid (**24**, Scheme 2.9). The structure of compound **24** was confirmed by ^{1}H and $^{13}C\{^{1}H\}$ NMR.

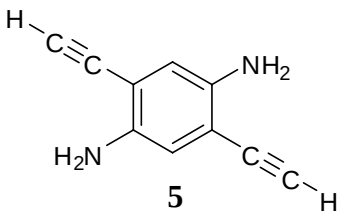


23 **24**

Scheme 0.9 (i) morpho-CDI; (ii) ammonia (liquid), room temperature.

2.3 Synthesis of Aromatic Alkynamines

1, 4-Diamino-2, 5-diethynylbenzene (**5**) and 1, 4-diamino-2, 5-*bis*(phenylethynyl)benzene (**6**) were prepared in 6 and 5 steps respectively. Both **5** and **6** have two amino groups in mutually *para* positions and two acetylene groups also in mutually *para* positions. Substrate **5** has terminal acetylenes whilst **6** has internal acetylenes. Both of these substrates are potential precursors for tricyclic pyrrolo[2, 3-*f*]indoles.



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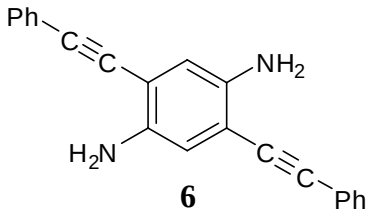
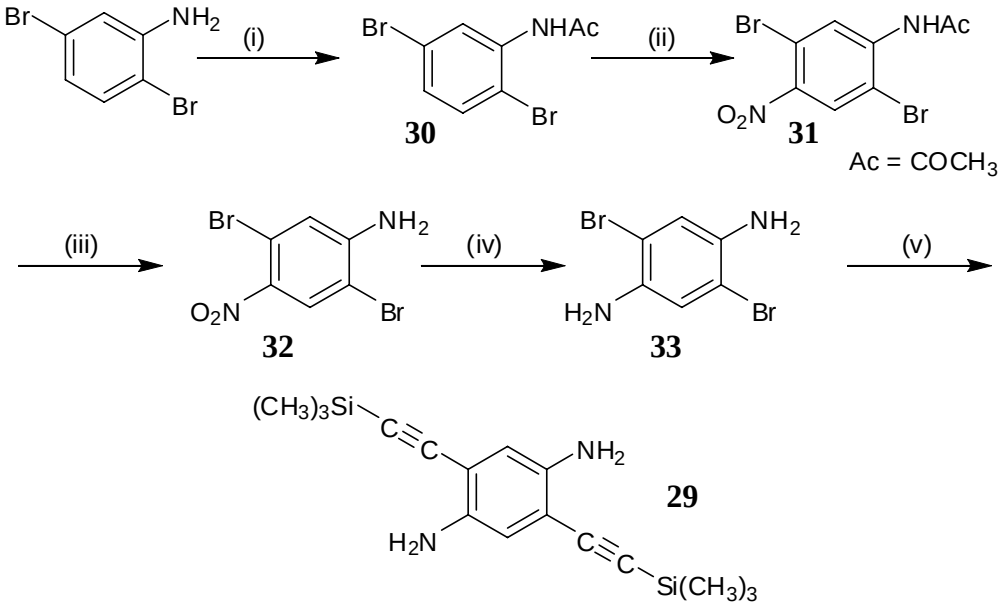


6

2.3.1.1 1, 4-Diamino-2, 5-*bis*(trimethylsilylethynyl)benzene (29)

1, 4-Diamino-2, 5-*bis*(trimethylsilylethynyl)benzene (**29**) was prepared following the procedure described by Moroni *et al*.[11] (Scheme 2.10).



Scheme 0.10 (i) acetic anhydride, water, reflux, 4h; (ii) concentrated nitric acid and sulfuric acid; (iii) hydrochloric acid (1M), reflux, 66 h; (iv) tin powder, concentrated hydrochloric acid, ethanol, 6 h; (v) palladium(II) chloride, copper(II) acetate, triphenylphosphine, (trimethylsilyl)acetylene (2 equivalents), triethylamine, 85 °C, 8 h.

2, 5-Dibromoacetanilide (**30**) was prepared from commercially available 2, 5-dibromoaniline by treatment with acetic anhydride in a yield of 92%. This compound was nitrated at the 4-position using a 1:1 mixture of concentrated sulfuric acid and nitric acid. The crude material was purified by column chromatography and 2, 5-dibromo-4-nitroacetanilide (**31**) was isolated in good yield (81%).

2, 5-Dibromo-4-nitroaniline (**32**) was formed in good yield (87%) by hydrolysis of 2, 5-dibromo-4-nitroacetanilide (**31**) in refluxing dilute hydrochloric acid for 66 h. 1, 4-Diamino-2, 5-dibromobenzene (**33**) was synthesised in 76% yield by reducing the nitro group in 2, 5-dibromo-4-nitroaniline (**32**) with tin powder and concentrated hydrochloric acid followed by a mild basic workup. Compound **33** was isolated rapidly and used immediately in the next step. The compound is air and light sensitive and easily oxidises from a white to a brown crystalline solid within hours. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra for compounds **30**, **31**, **32** and **33** all correspond to literature values reported by Moroni *et al*.[11]

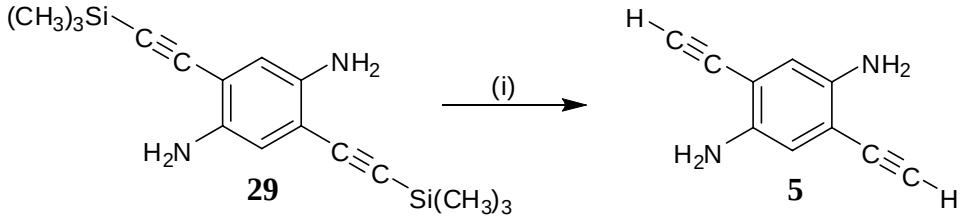
1, 4-Diamino-2, 5-*bis*(trimethylsilylethynyl)benzene (**29**) was formed from a coupling reaction of 1, 4-diamino-2, 5-dibromobenzene (**33**) with (trimethylsilyl)acetylene (2 equivalents) by stirring with a solution of palladium(II) chloride, copper(II) acetate and triphenylphosphine in dry and degassed triethylamine under nitrogen. Purification was achieved by column chromatography to give **29** in 60% yield. As it has not been reported in the literature, compound **29** was characterised as a new compound.

In the ^{1}H NMR spectrum, the amine protons appeared as a broad singlet at δ 3.78 ppm whilst the singlet at δ 0.22 ppm was due to the trimethylsilyl group. The acetylenic carbons were observed at δ 101.5 and 101.2 ppm in the $^{13}C\{^{1}H\}$ NMR spectrum. The electron impact mass spectrum showed the presence of the (M^{+}) ion in agreement with the proposed product (**29**). The composition of the compound was also confirmed by high resolution mass

spectrometry.

2.3.2 1, 4-Diamino-2, 5-diethynylbenzene (5)

1, 4-Diamino-2, 5-diethynylbenzene (**5**) was prepared by desilylating 1, 4-diamino-2, 5-*bis*(trimethylsilylethynyl)benzene (**29**) with tetrabutylammonium fluoride (TBAF) (Scheme 2.11). Purification by column chromatography gave compound **5** in 60% yield.



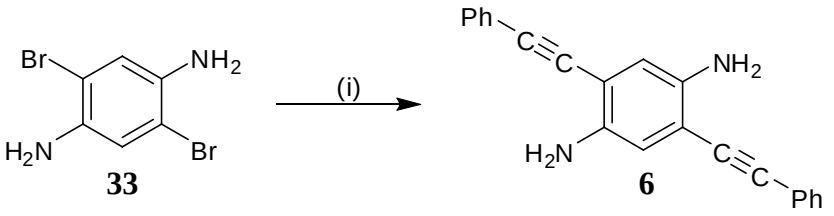
Scheme 0.11 (i) TBAF (1M) in tetrahydrofuran, room temperature.

Compound **5** has not been reported in the literature. The ^{1}H NMR resonance of the amine appeared at δ 3.82 ppm and the aromatic proton resonance at δ 6.73 ppm, both resonances were shifted slightly downfield compared to the starting material (**29**). The acetylenic proton resonance was identified at δ 3.39 ppm. The $^{13}C\{^{1}H\}$ NMR spectrum showed the resonance of the non-terminal acetylenic carbon at δ 84.0 ppm and the terminal acetylenic carbon at δ 81.8 ppm.

Both the electron impact mass spectrum and high resolution mass spectrum confirmed the composition of the compound. The infrared spectrum also contained acetylenic stretching vibrations which were identified at 2100ν (C≡C–H) cm^{-1}, consistent with the presence of the terminal acetylene functional group in the molecule.

2.3.3 1, 4-Diamino-2, 5-*bis*(phenylethynyl)benzene (6)

1, 4-Diamino-2, 5-*bis*(phenylethynyl)benzene (**6**) was prepared from 1, 4-diamino-2, 5-dibromobenzene (**33**), using an analogous synthetic method to that used for the preparation of **29** but using phenylacetylene (2 equivalents) in place of (trimethylsilyl)acetylene (Scheme 2.12). The product was purified by column chromatography to give 1, 4-diamino-2, 5-*bis*(phenylethynyl)benzene (**6**) as an orange powder in relatively poor yield (13%).

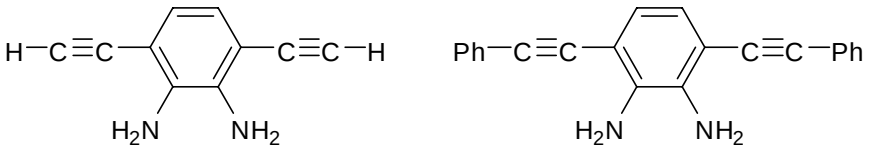


Scheme 0.12 (i) palladium(II) chloride, copper(II) acetate, triphenylphosphine, phenylacetylene (2 equivalents), triethylamine, 85 °C, 8 h.

Compound **6** is a new compound. In the ^{1}H NMR spectrum, the amine resonance was identified at δ 4.35 ppm and the singlet aromatic proton resonance at δ 6.70 ppm, both resonances shifted slightly downfield compared with the starting material (**33**). The coupled phenylacetylene protons exhibited multiplet resonances between δ 7.52-7.31 ppm. The structure of compound **6** was also supported by ^{13}C{^{1}H} NMR and infrared spectroscopy as well as electron impact and high resolution mass spectrometry.

2.3.4 2, 3-Diamino-1, 4-diethynylbenzene (7)

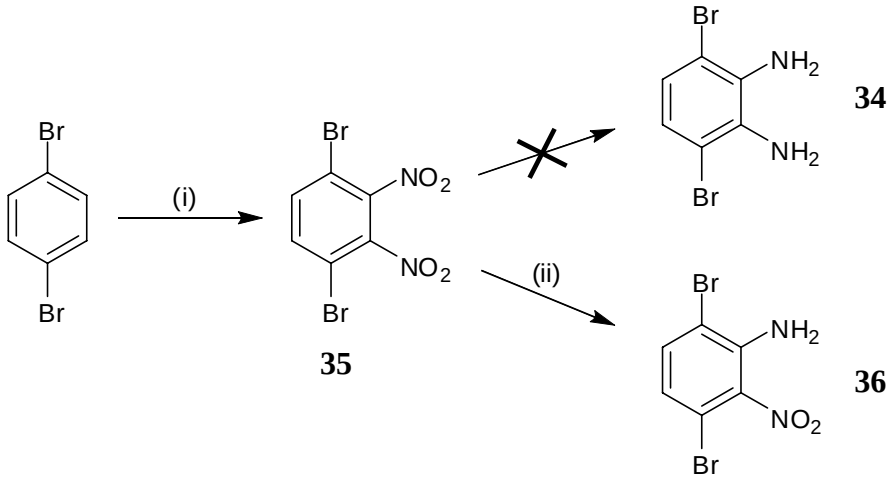
In contrast to the previous compounds (**5** and **6**), 2, 3-diamino-1, 4-diethynylbenzene (**7**) and 2, 3-diamino-1, 4-*bis*(phenylethynyl)benzene (**8**) were prepared in order to obtain alternative isomers where the amines are now *ortho* to each other. The acetylenes remain in *para* positions. Both of these substrates are potential precursors for tricyclic pyrrolo[2, 3-*g*]indoles.



7 **8**

2.3.4.1 Attempted Synthesis of 2, 3-Diamino-1, 4-dibromobenzene (34)

1, 4-Dibromo-2, 3-dinitrobenzene (**35**) is a known compound and was prepared from commercially available 1, 4-dibromobenzene and a 1:1 mixture of concentrated sulfuric acid and concentrated nitric acid at reflux (Scheme 2.13).[12-16] Purification was achieved by recrystallisation from glacial acetic acid to give **35** in 6.5% yield. The literature procedure also reported a low yield of 12.6% from this reaction.[13]



Scheme 0.13 (i) concentrated sulfuric acid and concentrated nitric acid (1:1), reflux (ii) iron powder and acetic acid, reflux.

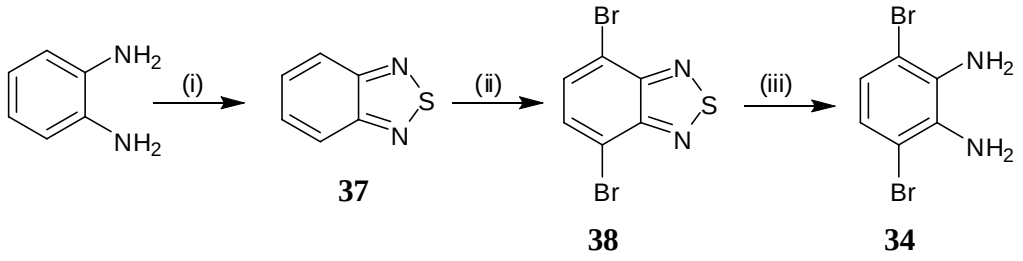
^{1}H NMR analysis identified the expected singlet resonance in the aromatic region at δ 7.75 ppm which was clearly distinguishable from the starting material. ^{13}C{^{1}H} NMR analysis of **35** confirmed the presence of 3 new carbon environments. The new resonance at δ 144.9 ppm confirmed the presence of nitro functionality in the product. The electron impact mass spectrum showed the presence of the (M^{+}) ion in agreement with product **35**.

Most attempts to reduce compound **35** to **34** were unsuccessful. Both tin(II) chloride dihydrate in ethanol[17] and zinc in hydrochloric acid[18] proved unsuccessful and there was no spectral evidence (by ^{1}H NMR) for the formation of the desired product or starting material.

The reduction was also attempted with iron powder and acetic acid[19] with heating for 4 days whilst the reaction was monitored by TLC. The ^{1}H NMR spectrum identified an amine resonance at δ 5.22 ppm and the aromatic protons were identified in the aromatic region at δ 7.39 and 6.90 ppm as doublets of doublets. The coupling constant between these aromatic protons (8.5 Hz) indicated that these protons were *ortho* to each other and were clearly distinct from the corresponding resonances of the starting material and target product (**34**). This is evidence for the possible formation of partially reduced product (**36**) (Scheme 2.13). This compound was not purified or isolated in the course of this work.

2.3.4.2 2, 3-Diamino-1, 4-dibromobenzene (34)

2, 3-Diamino-1, 4-dibromobenzene (**34**) is a known compound and was prepared in 3 steps from 2-phenylenediamine (Scheme 2.14). 2, 1, 3-Benzothiadiazole (**37**) was prepared from 1, 2-phenylenediamine and thionyl chloride.[20-22] Purification was achieved by recrystallisation from hexane to give **37** in 54% yield. Compound **37** was characterised by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy. The intermediate, 4, 7-dibromo-2, 1, 3-benzothiadiazole (**38**) was formed almost quantitatively by the slow addition of bromine in a solution of hydrobromic acid (47%) at reflux.[23-25] The 4, 7-dibromo-2, 1, 3-benzothiadiazole, **38** was characterised by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy. The electron impact mass spectrum showed the presence of the (M^{+}) ion consistent with compound **38**.



37 **38** **34**

Scheme 0.14 (i) thionyl chloride, triethylamine, reflux, 15 min; (ii) hydrobromic acid (47%), bromine, reflux; (iii) sodium borohydride, 0 °C.

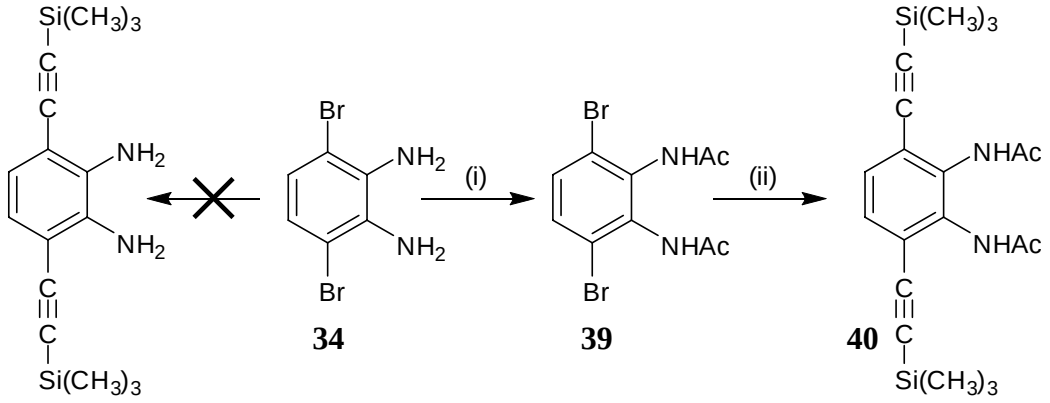
2, 3-Diamino-1, 4-dibromobenzene (**34**) was prepared by reducing 4, 7-dibromo-2, 1, 3-benzothiadiazole (**38**) with sodium borohydride which gave **34** in 68% yield.[24] Compound **34** was examined by ^{1}H NMR spectroscopy where the amine resonance appeared at δ 3.90 ppm and the aromatic proton resonance appeared at δ 6.84 ppm. ^{13}C{^{1}H} NMR chemical shifts were consistent with **34**. The electron impact mass spectrum showed the presence of the (M^{+}) ion in agreement with product **34**. Compound **34** has also been synthesised from **38** by using zinc and acetic acid as the reagents.[26] Both procedures were high yielding and gave a clean product.

2.3.4.3 Attempted Acetylenic Coupling Reactions

Attempts to couple 2, 3-diamino-1, 4-dibromobenzene (**34**) with (trimethylsilyl)acetylene (2 equivalents) by stirring with a solution of palladium(II) chloride, copper(II) acetate, triphenylphosphine under standard Sonogashira conditions were unsuccessful (Scheme 2.15). The product mixture showed no evidence by ^{1}H NMR for either the expected product or the starting material so the starting material is unstable under the reaction conditions employed.

The isomeric 1, 4-diamino-2, 5-*bis*(trimethylsilylethynyl)benzene (**29**, Section 2.3.1.1) was successfully prepared from 2, 5-dibromo-4-aminoaniline (**33**) by coupling with (trimethylsilyl)acetylene (2 equivalents). However, isomer **29** does have the amino groups *para* to each other and the failure of **34** to couple may be due to a strong "bidentate" coordination between the two amines in *ortho*

positions in compound **34** and the catalyst in the Sonogashira coupling reaction, thus inhibiting the coupling with the acetylenes.



Scheme 0.15 (i) acetic anhydride, dichloromethane, reflux; (ii) palladium(II) chloride, copper(II) acetate, triphenylphosphine, (trimethylsilyl)acetylene (2 equivalents), triethylamine, 85 °C, 24 h.

2, 3-*Bis*(acetamido)-1, 4-dibromobenzene (**39**) was prepared by treating 2, 3-diamino-1, 4-dibromobenzene (**34**) with acetic anhydride in dichloromethane. After workup, the crude solid was recrystallised from ethanol to give **39** in 31% yield. Compound **39** has not been reported in the literature and was examined by ^{1}H NMR spectroscopy where the methyl resonance was identified at δ 2.01 ppm. Compound **39** was also fully characterised by ^{13}C{^{1}H} NMR spectroscopy.

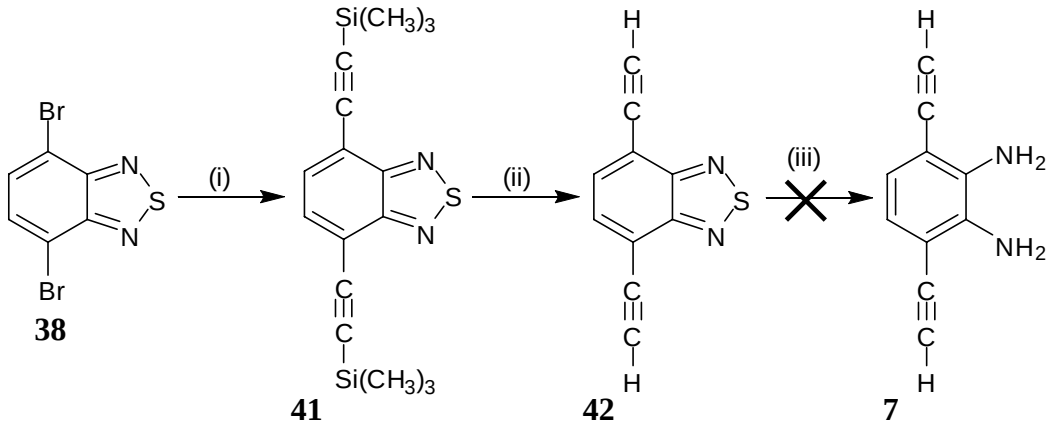
2, 3-*Bis*(acetamido)-1, 4-*bis*(trimethylsilylethynyl)benzene (**40**) was formed by coupling **39** with (trimethylsilyl)acetylene (2 equivalents). Purification was achieved by column chromatography to give **40** in 11% yield. Compound **40** is a new compound. The ^{1}H NMR analysis identified the broad amine resonance at δ 7.87 ppm and the trimethylsilyl resonance at δ 0.25 ppm. ^{13}C{^{1}H} NMR analysis confirmed the presence of the acetylenic carbons at δ 102.9 and 100.8 ppm. The electrospray mass spectrum showed the presence of the $(2M+Na)^{+}$ ion in agreement with product (**40**). The composition of the compound was confirmed by high resolution mass spectrometry.

Compound **40** was only isolated in a low yield and 2 more steps were required in order to obtain the final product; the removal of the trimethylsilyl and acetyl functional groups. An alternative synthesis was investigated in order to optimise the yield.

2.3.4.4 4, 7-*Bis*(trimethylsilylethynyl)-2, 1, 3-benzothiadiazole (41)

4, 7-*Bis*(trimethylsilylethynyl)-2, 1, 3-benzothiadiazole (**41**) was prepared according to literature methods (Scheme 2.16).[27] Compound **41** was formed by coupling dibromobenzothiadiazole (**38**) with (trimethylsilyl)acetylene (2 equivalents). Purification was achieved by column chromatography to give **41** as a yellow brown solid in 79% yield. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra for compound **41** corresponded to literature values reported by Khan *et al*.[28] The synthesis of compound **41** had a significant improvement in yield compared to the synthesis of compound **40** (Section 2.3.4.3) and so the synthesis of compound **7** was pursued according to the benzothiadiazole pathway (Schemes 2.16 and 2.17).

Previous work,[28, 29] reported the synthesis of a series of poly(aryleneethynylene)s with aryl heterocyclic structure and different long side chains using transition metals. These polymers were photoluminescent and electrochemically active and showed metallic lustre in solid state. Poly(aryleneethynylene) polymers are expected to be the key material in future electronic and optical devices such as nonlinear optical devices for rapid switching and manipulation of light (e.g. to construct effective optical communication systems).



Scheme 0.16 (i) palladium(II) chloride, copper(II) acetate, triphenylphosphine, (trimethylsilyl)acetylene (2 equivalents), diisopropylamine/ tetrahydrofuran (1:4), reflux, 2 h; (ii) potassium fluoride; (iii) sodium borohydride.

2.3.4.5 4, 7-*Bis*(ethynyl)-2, 1, 3-benzothiadiazole (42)

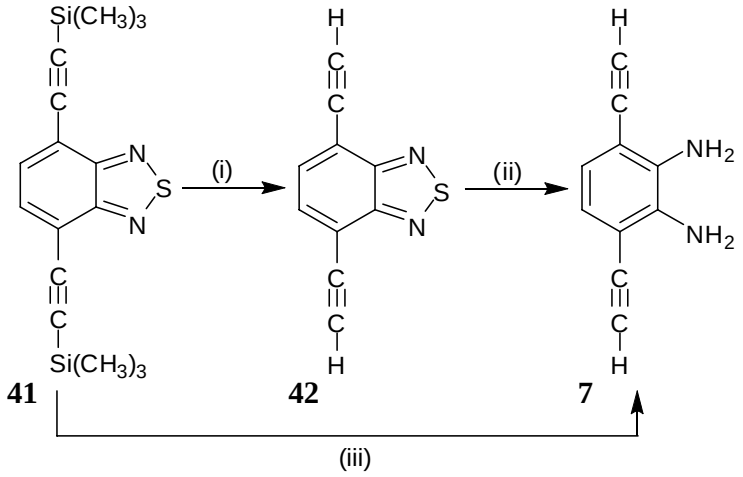
4, 7-*Bis*(ethynyl)-2, 1, 3-benzothiadiazole (**42**) was prepared by desilylating 4, 7-*bis*(trimethylsilylethynyl)-2, 1, 3-benzothiadiazole (**41**) with potassium fluoride. Purification by column chromatography gave compound **42** in 12% yield.

Compound **42** is light sensitive and easily oxidises from an orange to a dark brown crystalline solid within hours in air. The ^{1}H NMR resonance of the aromatic proton resonance appeared at δ 7.75 ppm and was shifted slightly downfield compared to compound **41**. The acetylenic proton resonance was identified at δ 3.68 ppm. The ^{13}C{^{1}H} NMR spectrum showed the resonance of the non-terminal acetylenic carbon at δ 79.0 ppm and the terminal acetylenic carbon at δ 85.5 ppm. Desilylation of compound **41** was reported by Khan *et al*.[28] and this was achieved with aqueous potassium hydroxide. However in our hands, desilylation by this method was unsuccessful and only starting material was recovered.

2.3.5 2, 3-Diamino-1, 4-diethynylbenzene (7)

Attempts to reduce the *bis*-alkynylbenzothiadiazole (**42**) to the corresponding *bis*-amine (**7**) using a range of standard conditions were unsuccessful. The use of zinc and acid acetic[26] and sodium borohydride,[24] as employed for the synthesis of compound **34** (Section 2.3.4.2) were unsuccessful and there was no spectral evidence for the formation of the desired product (**7**). Attempted reduction with tin(II) chloride dihydrate[30] and reduction with magnesium in methanol[31] also proved unsuccessful and only unreacted starting material was recovered.

2, 3-Diamino-1, 4-diethynylbenzene (**7**) was prepared successfully by directly treating a crude sample of 4, 7-*bis*(trimethylsilylethynyl)-2, 1, 3-benzothiadiazole (**41**) with an excess amount of sodium borohydride in ethanol. The crude benzothiadiazole (**41**) still contained palladium(II) chloride and copper(II) acetate residues from the previous Sonogashira coupling step in the reaction sequence. The removal of the trimethylsilyl group and the reduction of compound **41** were achieved in a single step by treatment with sodium borohydride providing that the reaction mixture still contained residual amounts of the palladium(II) and copper(II) reagents. This pathway provided compound **7** in only 5% yield (Scheme 2.17, (iii)).



Scheme 0.17 (i) potassium fluoride; (ii) sodium borohydride, palladium(II) chloride (10%), copper(II) acetate (10%) 0 °C; (iii) sodium borohydride.

A purified sample of 4, 7-*bis*(ethynyl)-2, 1, 3-benzothiadiazole (**42**) can also be

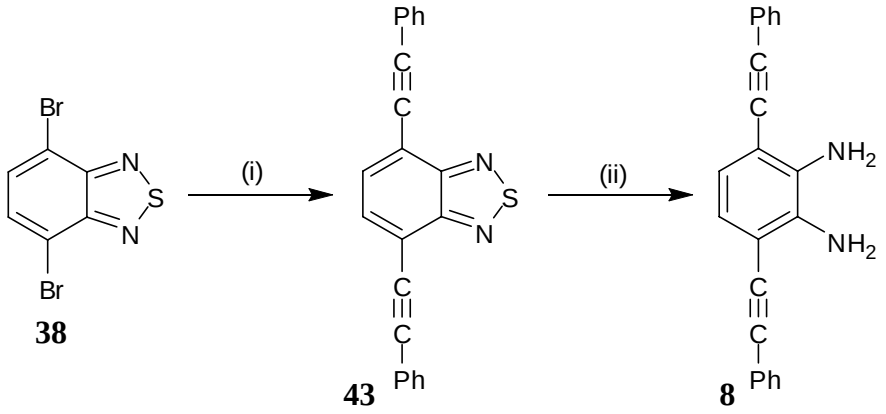
reduced successfully providing a catalytic amount of palladium(II) chloride and copper(II) acetate are used with an excess amount of sodium borohydride (Scheme 2.17, (ii)). The use of the palladium(II) and copper(II) combination gives a cleaner and higher yield of the final product compared to the single step method starting from crude **41**. Compound **7** was isolated by column chromatography as a dark red solid in 43% yield. In this reaction, it is essential to have catalytic amounts of both palladium(II) and copper(II) reagents to achieve the desired reduction. The addition of either palladium(II) or copper(II) reagent alone is insufficient for the reaction to proceed and no product is formed.

The scope and utility of this combination of reagents for carrying out reductions of this type was beyond the scope of this thesis and was not investigated further. However the results obtained here suggest that borohydride reducing agents, used in conjunction with palladium(II) and copper(II) species may provide a new and useful reducing agent. The scope and nature of this reduction deserves further research.

Compound **7** has not been reported in the literature and was fully characterised. ^{1}H NMR analysis identified the aromatic protons at δ 6.77 ppm and a broad amine resonance at δ 4.72 ppm. The acetylenic proton resonance appeared at δ 3.98 ppm. ^{13}C{^{1}H} NMR analysis confirmed the presence of a terminal acetylenic carbon at δ 84.7 ppm and a non-terminal acetylenic carbon at δ 82.5 ppm. The electron impact mass spectrum showed the presence of the $(M+H)^{+}$ ion consistent with product **7**. The composition of the compound was confirmed by high resolution mass spectrometry. Infrared absorbances at 3417m, 3336m (N–H), 2093w (C≡C) cm^{-1} confirmed the presence of the correct functional groups in the molecule.

2.3.5.1 4, 7-*Bis*(phenylethynyl)-2, 1, 3-benzothiadiazole (43)

4, 7-*Bis*(phenylethynyl)-2, 1, 3-benzothiadiazole (**43**) was prepared from **38**, using the same synthetic method for preparing **41** but using phenylacetylene (2 equivalents) in place of (trimethylsilyl)acetylene (Scheme 2.18). The product was purified by column chromatography to give 4, 7-*bis*(phenylethynyl)-2, 1, 3-benzothiadiazole (**43**) as a yellow brown solid in 79% yield. Spectroscopic data for compound **43** corresponded to literature values reported by Dupont *et al*.[25]



Scheme 0.18 (i) palladium(II) chloride, copper(II) acetate, triphenylphosphine, (trimethylsilyl)acetylene (2 equivalents), diisopropylamine/ tetrahydrofuran (1:4), reflux, 2 h; (ii) sodium borohydride, palladium(II) chloride (10%), copper(II) acetate (10%), 0 °C.

In the ^{1}H NMR spectrum of **43**, the singlet at δ 7.78 ppm was due to the protons of the benzothiadiazole ring whilst the multiplets at δ 7.67-7.39 ppm were due to the aromatic rings of the arylacetylene substituents. Compound **43** was also characterised by $^{13}C\{^{1}H\}$ NMR and infrared spectroscopy as well as electron impact and high resolution mass spectrometry.

2.3.6 2, 3-Diamino-1, 4-*bis*(phenylethynyl)benzene (8)

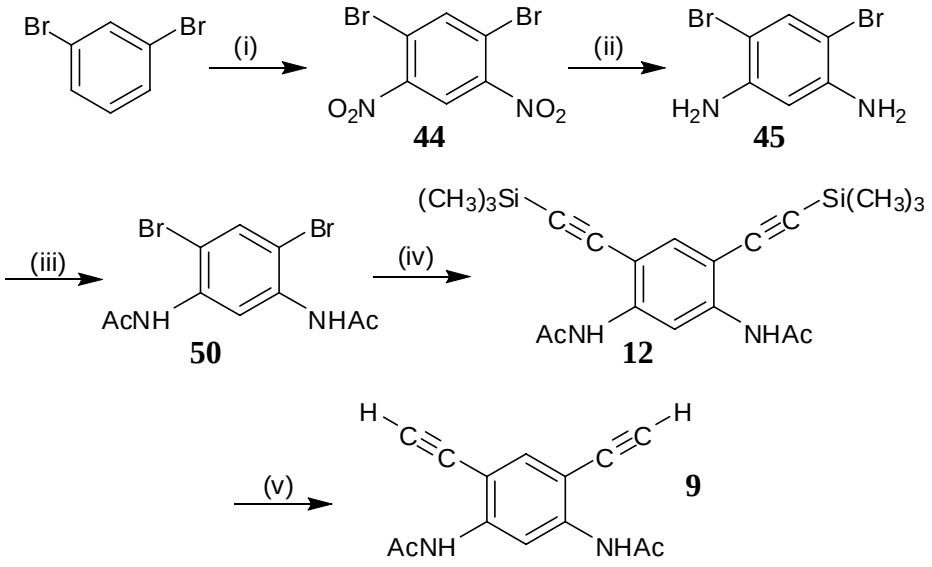
2, 3-Diamino-1, 4-*bis*(phenylethynyl)benzene (**8**) was prepared from the substituted benzothiadiazole **43**, when either the crude sample of compound **43** was treated with an excess amount of sodium borohydride or a purified sample of **43** was reacted with a catalytic amount of palladium(II) chloride, copper(II) acetate and an excess amount of sodium borohydride. Purification by column chromatography gave compound **8** as a brown solid in 92% yield.

Compound **8** has not been reported in the literature and was characterised spectroscopically. In the ^{1}H NMR spectrum, the amine resonance appeared at δ 4.04 ppm and the central aromatic proton resonance was identified at δ 6.93 ppm. The aromatic rings of the arylacetylene substituents produced multiplet resonances between δ 7.56-7.33 ppm. Compound **8** was also characterised by ^{13}C{^{1}H} NMR and the resonances at δ 95.8 and 86.2 ppm were attributed to the acetylenic carbons in **8**. The infrared spectrum also confirmed the presence of the acetylenic functional group in the molecule with ν (C≡C) at 2198w cm^{-1}.

2.4 Synthesis of Aromatic Alkynamides

2.4.1 1, 5-*Bis*(acetamido)-2, 4-diethynylbenzene (9)

The syntheses of 1, 5-*bis*(acetamido)-2, 4-*bis*(trimethylsilylethynyl)benzene (**12**) and 1, 5-*bis*(acetamido)-2, 4-diethynylbenzene (**9**) were achieved in 4 and 5 steps respectively from 1, 3-dibromobenzene (Scheme 2.19). Compound **9** contains amide functional groups whereas previous aromatic substrates (**5**, **6**, **7** and **8**) contain primary amines. In addition, the amides and acetylene are in *meta* positions ultimately providing potential access to the pyrrolo[3, 2-*f*]indole skeleton.

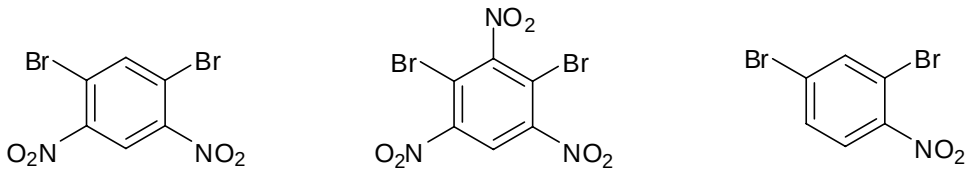


Scheme 0.19 (i) fuming nitric acid and concentrated sulfuric acid; (ii) iron powder, acetic acid, reflux, 5.5 h; (iii) acetic anhydride, dichloromethane, room temperature; (iv) palladium(II) chloride, copper(II) acetate, triphenylphosphine, (trimethylsilyl)acetylene (2 equivalents), triethylamine, 85 °C, 8 h; (v) potassium fluoride.

2.4.1.1 1, 5-Dibromo-2, 4-dinitrobenzene (44)

1, 5-Dibromo-2, 4-dinitrobenzene (**44**, Scheme 2.19) was formed by the reaction of 1, 3-dibromobenzene with a cooled 1:1 mixture of fuming nitric acid (90%) and concentrated sulfuric acid. The crude product was examined by ^{1}H NMR

spectroscopy and three singlet resonances were observed with chemical shifts of δ 8.44, 8.21 and 7.83 ppm. The mixture consisted of two products, the desired product (**44**) and a byproduct 1, 5-dibromo-2, 4, 6-trinitrobenzene (**46**) (Figure 2.1) in a ratio of approximately 2:1 of di- and tri- substituted nitrobenzene respectively.



44 **46** **47**

Figure 0.1

Attempts to separate **44** and **46** by column chromatography were unsuccessful however recrystallisation of the crude material from a mixture of absolute ethanol and acetone afforded pure 1, 5-dibromo-2, 4-dinitrobenzene (**44**) in 60% yield. The ^{1}H, $^{13}C\{^{1}H\}$ NMR spectra and electron impact mass spectrum were consistent with literature values reported for compound **44**.[16]

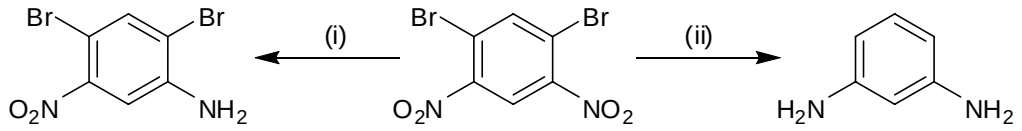
1, 5-Dibromo-2, 4, 6-trinitrobenzene (**46**) in a pure dry solid state is known to be an explosive product and safety procedures were taken to avoid any incidents. In particular compound **46** was left in the mother liquor after recrystallisation of compound **44** and not isolated in dry powdered form.

Nitration of 1, 3-dibromobenzene under milder conditions (a mixture of concentrated nitric acid (75%) and concentrated sulfuric acid in a 1:1 ratio), afforded only 1, 3-dibromo-4-nitrobenzene (**47**, Figure 2.1). Both the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectrum were consistent with compound **47**.

2.4.1.2 1, 5-Diamino-2, 4-dibromobenzene (45)

1, 5-Diamino-2, 4-dibromobenzene **(45)** was prepared by treating 1, 5-dibromo-2, 4-dinitrobenzene **(44)** with iron powder and acetic acid which gave compound **45** in near quantitative yield (98%). This isomer of diaminodibromobenzene was significantly more stable than **33** (Section 2.3.1.1) and showed little tendency to darken on standing.

Compound **45** was identified as a new compound and characterised spectroscopically. In the ^{1}H NMR spectrum, the broad singlet at δ 5.09 ppm was attributed to the amine resonances and the singlets at δ 7.22 and 6.24 ppm were due to the aromatic proton resonances. $^{13}C\{^{1}H\}$ NMR spectroscopy identified the presence of two identical quaternary carbons bound to the amine at δ 145.6 ppm. Both the electron impact mass spectrum and the microanalysis confirmed the elemental formula.



48 **44** **49**

Scheme 0.20 (i) iron powder, acetic acid, reflux, 2 h; (ii) tin powder, concentrated hydrochloric acid, room temperature, 6 h.

When the reaction was halted after 2 h, the partially reduced product, 1-amino-2, 4-dibromo-5-nitrobenzene (**48**, Scheme 2.20, (i)) was isolated. Compound **48** was examined by ^{1}H NMR spectroscopy, the amine resonance appeared at δ 4.42 ppm and the aromatic protons were observed as 2 singlets at δ 7.74 and 7.25 ppm. Compound **48** was also characterised by $^{13}C\{^{1}H\}$ NMR and the six different resonances were consistent with the structure of compound **48**. 1-Amino-2, 4-dibromo-5-nitrobenzene **(48)** was further reduced to produce **45** in good yield.

A number of alternative reaction conditions were attempted to reduce **44** to **45**. The reduction of **44** using tin powder and concentrated hydrochloric acid as for the synthesis of compound **33** (Section 2.3.1.1) was unsuccessful, in that the nitro groups were reduced, however, under these conditions, the bromine groups were lost to give 1, 3-diaminobenzene (**49**, Scheme 2.20, (ii)) which was identified by ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy. Other methods for reduction including hydrogenation of **44** with palladium-on-charcoal in ethanol and reduction with tin(II) chloride dihydrate in ethanol[17] also proved unsuccessful and there was no spectral evidence (^{1}H NMR) for the formation of the desired product (**45**).

2.4.1.3 1, 5-*Bis*(acetamido)-2, 4-dibromobenzene (50)

1, 5-*Bis*(acetamido)-2, 4-dibromobenzene (**50**) was prepared by treating 1, 5-diamino-2, 4-dibromobenzene (**45**) with acetic anhydride in dichloromethane. After workup, the crude solid was recrystallised from ethanol to give **50** in 61% yield. Compound **50** has not been reported in the literature and was examined by ^{1}H NMR spectroscopy, the methyl resonance appeared at δ 2.07 ppm. The compound was also characterised by $^{13}C\{^{1}H\}$ NMR spectroscopy.

2.4.1.4 1, 5-*Bis*(acetamido)-2, 4-*bis*(trimethylsilylethynyl)benzene (12)

1, 5-*Bis*(acetamido)-2, 4-*bis*(trimethylsilylethynyl)benzene (**12**) was formed from a Sonogashira coupling reaction of **50** with (trimethylsilyl)acetylene (2 equivalents). Purification was achieved by column chromatography to give **12** in 50% yield.

Compound **12** has not been reported in the literature and was fully characterised. The trimethylsilyl resonance appeared at δ 0.27 ppm in the ^{1}H NMR spectrum. $^{13}C\{^{1}H\}$ NMR analysis showed the presence of the acetylenic carbons at δ 102.1 and 99.4 ppm. The composition of the compound was confirmed by both microanalysis and high resolution mass spectrometry. Infrared absorbances at 2155m ν (C≡C), 1671s ν (C=O) cm^{-1} confirmed the presence of the correct functional groups in the molecule.

2.4.2 1, 5-*Bis*(acetamido)-2, 4-diethynylbenzene (9)

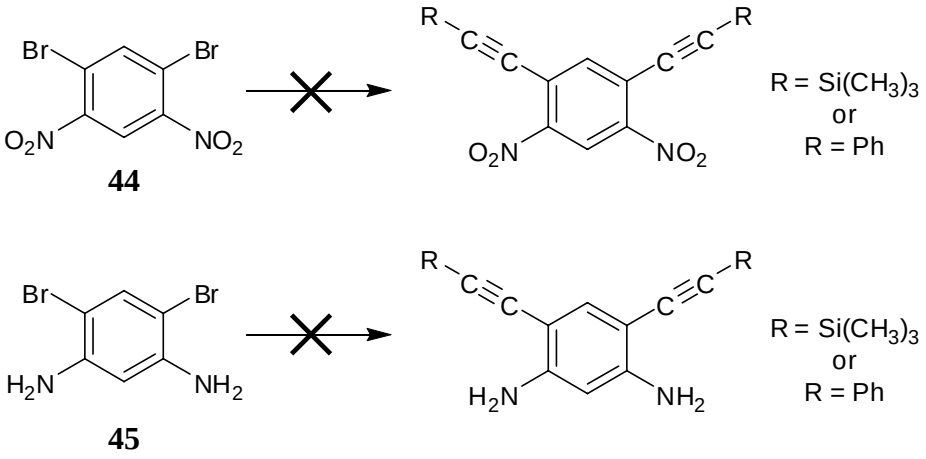
1, 5-*Bis*(acetamido)-2, 4-diethynylbenzene (**9**) was prepared by desilylation of 1, 5-*bis*(acetamido)-2, 4-*bis*(trimethylsilylethynyl)benzene (**12**) with potassium fluoride. After workup, compound **9** was obtained in 39% yield and characterised as a new compound.

The ^{1}H NMR analysis identified the acetylenic proton resonance at δ 3.92 ppm whilst the $^{13}C\{^{1}H\}$ NMR analysis confirmed the presence of the acetylenic carbons at δ 84.8 and 79.3 ppm. The electron impact mass spectrum showed the presence of the (M^{+}) ion in agreement with product (**9**). The composition of the compound was also confirmed by high resolution mass spectrometry.

The removal of the trimethylsilyl group was initially attempted by using tetrabutylammonium fluoride as in the synthesis of **5** (Section 2.3.2). The reaction was monitored by TLC and was complete in minutes. However, the purification of the compound by chromatography was significantly more difficult.

2.4.2.1 Attempted Acetylenic Coupling Reactions

Numerous attempts to couple (trimethylsilyl)acetylene or phenylacetylene to compounds **44** and **45** were undertaken (Scheme 2.21). Attempts to couple the aromatic bromides of compound **44** to (trimethylsilyl)acetylene and phenylacetylene according to procedures reported by Moroni *et al*[11] and Ma *et al*[32] were unsuccessful. The product mixtures were complex and showed no resonances for either the expected products or the starting material. Attempts to couple compound **45** to (trimethylsilyl)acetylene and phenylacetylene according to procedures reported by Roesch and Larock,[33] and Arcadi *et al*.[34] were also unsuccessful and the starting materials were recovered. The presence of nitro or amino groups (compound **44** and **45** respectively) in *meta* positions to each other appear to have hindered the coupling of the aryl bromides to (trimethylsilyl)acetylene or phenylacetylene.



Scheme 0.21

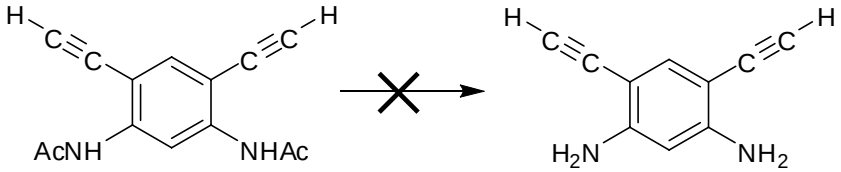
1, 5-*Bis*(acetamido)-2, 4-dibromobenzene (**50**) successfully coupled to (trimethylsilyl)acetylene to give compound **12** (Section 2.4.1). The amine functional groups in compound **45** were protected with acetic anhydride and the amide was formed. The amide functional groups in compound **50** minimised the possibility of the nitrogen coordination with the catalysts in the Sonogashira coupling reaction. Whereas, compounds **44** and **45** were probably more susceptible to coordination with the catalysts, thus inhibiting the coupling of the acetylenes.

Numerous attempts to couple the aromatic bromides in compound **50** to phenylacetylene, propargyltrimethylsilane and propyne to form internal acetylenes were undertaken.[11, 32, 33, 35] However, ^{1}H NMR analysis of the product mixtures showed no resonances for the expected product only a mixture of starting materials.

2.4.2.2 Attempted Hydrolysis of 1, 5-*Bis*(acetamido)-2, 4-diethynylbenzene (9)

1, 5-*Bis*(acetamido)-2, 4-diethynylbenzene (**9**) was treated with dilute hydrochloric acid (1M) under reflux to remove the acetyl functional group (Scheme 2.22) as for the synthesis of compound **32** (Section 2.3.1.1). The reaction was monitored by TLC and after workup a crystalline white solid was

isolated. Although the starting material was consumed, the product was not the expected *bis*-amine since the ^{1}H, $^{13}C\{^{1}H\}$ NMR and mass spectra did not correspond to the expected product. Positive electrospray mass spectrometry in methanol/ dichloromethane showed the major species to have an *m/z* value of 579. The product has not yet been identified or further characterised.



9

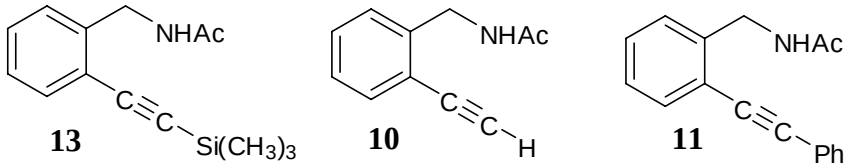
Scheme 0.22

Attempted hydrolysis of 1, 5-*bis*(acetamido)-2, 4-diethynylbenzene (**9**) with higher concentrations of dilute hydrochloric acid (5M) led only to decomposition of the starting material.

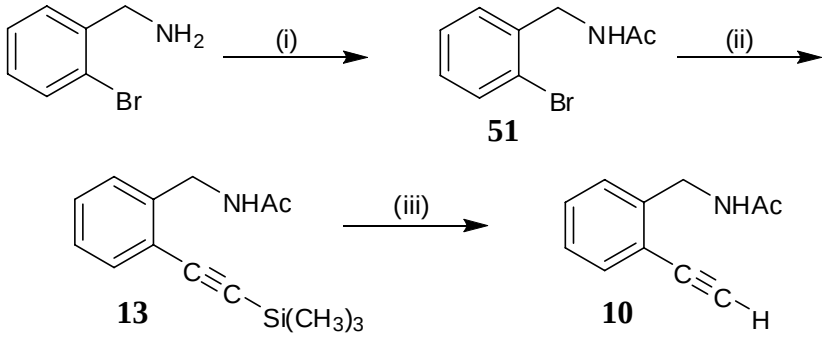
Further attempts to remove the acetyl functional group were undertaken when 1, 5-*bis*(acetamido)-2, 4-*bis*(trimethylsilylethynyl)benzene (**12**) was treated with different concentrations of dilute hydrochloric acid (2M and 4M) under reflux. After workup ^{1}H NMR spectral analysis showed starting material in the case when 2M hydrochloric acid was used and only desilylation of the starting material in the case of 4M hydrochloric acid.

2.4.3 *N*-(Acetyl)-2-ethynylbenzylamine (10)

N-(Acetyl)-2-(trimethylsilylethynyl)benzylamine (**13**), *N*-(acetyl)-2-ethynylbenzylamine (**10**) and *N*-(acetyl)-2-(phenylethynyl)benzylamine (**11**) were synthesised in 2 steps for **13** and **11** and 3 steps for **10**. Compounds **13**, **10** and **11** have CH_2 groups linking the amide functionalities to the aromatic rings. These compounds are all potential precursors for the isoquinoline nucleus if they successfully undergo an intramolecular hydroamination reaction.



N-(Acetyl)-2-ethynylbenzylamine (**10**) was isolated in 3 steps by following literature procedures.[36-38] The first step involved the synthesis of *N*-(acetyl)-2-bromobenzylamine (**51**) by treating 2-bromobenzylamine hydrochloride in triethylamine with acetic anhydride at 0 °C (Scheme 2.23). After workup, the acetamide **51** was obtained as a white solid in 91% yield.



Scheme 0.23 (i) acetic anhydride, triethylamine; (ii) palladium(II) chloride, copper(II) acetate, triphenylphosphine, (trimethylsilyl)acetylene, triethylamine, 85 °C, 8 h; (iii) TBAF (1M) in tetrahydrofuran, room temperature.

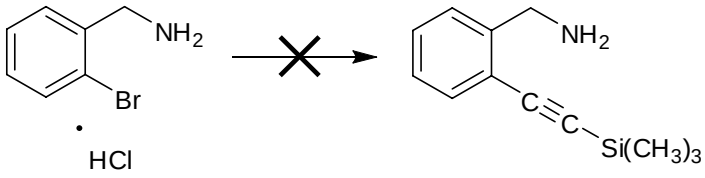
N-(Acetyl)-2-(trimethylsilylethynyl)benzylamine (**13**) was formed by coupling *N*-(acetyl)-2-bromobenzylamine (**51**) to (trimethylsilyl)acetylene. Purification was achieved by column chromatography to give **13** as a brown solid in 18% yield.

The target compound, *N*-(acetyl)-2-ethynylbenzylamine (**10**) was prepared by treating *N*-(acetyl)-2-(trimethylsilylethynyl)benzylamine (**13**) with tetrabutylammonium fluoride to deprotect the acetylene by removal of the trimethylsilyl group. Purification by column chromatography gave compound **13** as yellow crystals in 49% yield. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectral analysis for

compounds **51**, **13** and **10** all corresponded to literature values.[36-38]

2.4.3.1 Attempted Synthesis of 2-Ethynylbenzylamine

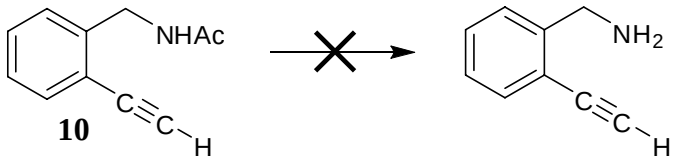
Attempts to couple (trimethylsilyl)acetylene to 2-bromobenzylamine hydrochloride under standard Sonagashira coupling conditions were undertaken (Scheme 2.24).[11] However the product mixtures were complex and showed no evidence for the expected product or starting material.



Scheme 0.24

2.4.3.2 Attempted Hydrolysis of *N*-(Acetyl)-2-ethynylbenzylamine (10)

N-(Acetyl)-2-ethynylbenzylamine (**10**) was treated with dilute hydrochloric acid under reflux to remove the acetyl functional group (Scheme 2.25) as for the synthesis of compound **32** (Section 2.3.1.1). After workup, an orange coloured oil was isolated. Although the starting material was consumed, none of the target products was formed based on the ^{1}H NMR spectrum.

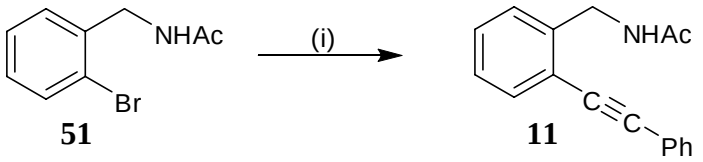


Scheme 0.25

2.4.4 *N*-(Acetyl)-2-(phenylethynyl)benzylamine (11)

N-(Acetyl)-2-(phenylethynyl)benzylamine (**11**) was prepared from **51,** using an analogous synthetic method to that used for the preparation of **13** but using phenylacetylene (excess) in place of (trimethylsilyl)acetylene (Scheme 2.26). The product was purified by column chromatography to give

N-(acetyl)-2-(phenylethynyl)benzylamine (**11**) as an orange solid in 79% yield and characterised as a new compound.



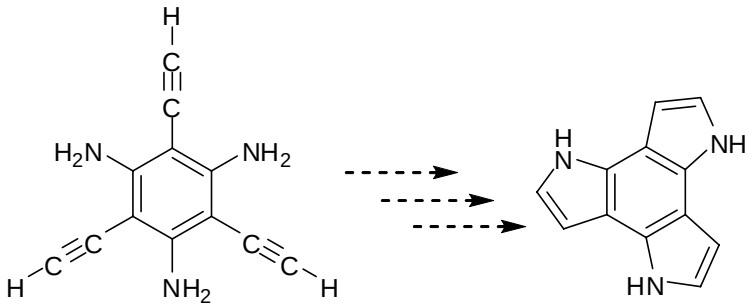
51 **11**

Scheme 0.26 (i) palladium(II) chloride, copper(II) acetate, triphenylphosphine, phenylacetylene, triethylamine, 85 °C, 8 h.

In the ^{1}H NMR spectrum, the amine resonance was identified at δ 6.42 ppm whilst the multiplets at δ 7.55-7.23 ppm were due to the aromatic protons. The benzyl protons were identified at δ 4.64 ppm as a doublet with a coupling constant of 5.8 Hz. The ^{13}C{^{1}H} NMR, electron impact and high resolution mass spectra were all consistent with compound **11**.

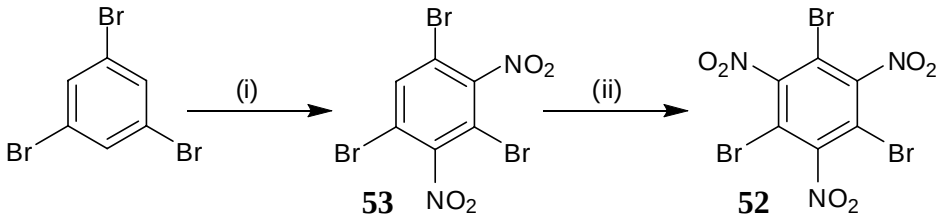
2.5 Attempted Synthesis of 1, 3, 5-Triamino-2, 4, 6-tribromobenzene

Numerous attempts to prepare 1, 3, 5-triamino-2, 4, 6-tribromobenzene were undertaken. It was proposed that (trimethylsilyl)acetylene or phenylacetylene could be coupled to the three aromatic bromides once 1, 3, 5-triamino-2, 4, 6-tribromobenzene was isolated. These acetylene coupled substrates are potential precursors for tetracyclic dipyrrolo[2, 3-*e*, 2', 3'- *f*]indoles.



2.5.1 1, 3, 5-Tribromo-2, 4, 6-trinitrobenzene (52)

1, 3, 5-Tribromo-2, 4, 6-trinitrobenzene (**52**) was prepared in two steps according to the procedure described by Hill and Taylor.[39] 1, 3, 5-Tribromo-2, 4-dinitrobenzene (**53**, Scheme 2.27) was prepared by treating 1, 3, 5-tribromobenzene with concentrated sulfuric acid and fuming nitric acid.[40] After workup, the solid was recrystallised from chloroform to give **53** in 95% yield. 1, 3, 5-Tribromobenzene was easily nitrated as the reaction proceeded at 60 °C and was complete in less than 1 h. Spectroscopic data for compound **53** was consistent with literature values.[39]



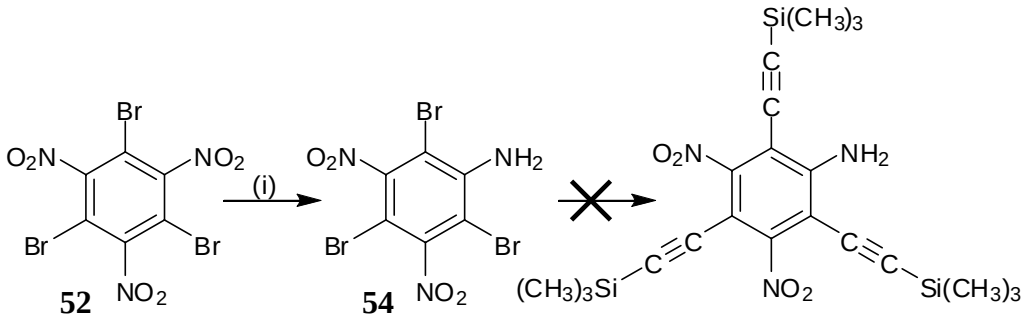
Scheme 0.27 (i) concentrated sulfuric acid, fuming nitric acid; (ii) potassium nitrate, fuming sulfuric acid (20% oleum), 125 °C, 9 h.

Nitration of the sixth position in 1, 3, 5-tribromo-2, 4-dinitrobenzene (**53**) required more drastic conditions because of the intense deactivation effect of the nitro groups and the steric hindrance of the bromine atoms *ortho* to the open position. Low yields and extensive decomposition were encountered by previous work[41, 42] in nitrating with mixed acids for the synthesis of compound **53**. Hill and Taylor[39] reported the synthesis of 1, 3, 5-tribromo-2, 4, 6-trinitrobenzene (**52**) by nitration of compound **53** in a solution of potassium nitrate dissolved in fuming sulfuric acid in yields of up to 74% without excess bromine migration or decomposition. The rate of nitration was also sharply affected by the reaction temperature. Optimum reaction was obtained at 125-127 °C for a reaction period of 8-9 h. In this work, compound **52** was prepared according to the literature procedure with fuming sulfuric acid 20% oleum rather than the 30% oleum reported in the literature. After workup, the crude solid was recrystallised from ethyl acetate to

give compound **52**. Compound **52** was characterised by $^{13}C\{^{1}H\}$ NMR spectroscopy. The electron impact mass spectrum showed the presence of the (M^+) ion in agreement with product (**52**). The best yield obtained using this method was 7%. Attempts to optimise this reaction often gave unidentified low melting byproducts which were not readily separable by recrystallisation.

2.5.1.1 Attempted Reduction and Acetylenic Coupling Reaction

Attempts to completely reduce compound **52** to 1, 3, 5-triamino-2, 4, 6-tribromobenzene were unsuccessful. The reduction of **52** using iron powder and acetic acid was unsuccessful; only one of the three nitro groups was reduced to give 2, 4, 6-tribromo-3, 5-dinitroaniline (**54**, Scheme 2.28) as the reaction product which was identified by ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy and electron impact mass spectrometry. Other methods for reduction including hydrogenation of **52** with palladium-on-charcoal in ethanol and reduction with tin(II) chloride dihydrate in ethanol[17] proved unsuccessful and there was no spectral evidence (by ^{1}H NMR) for the formation of the desired product.

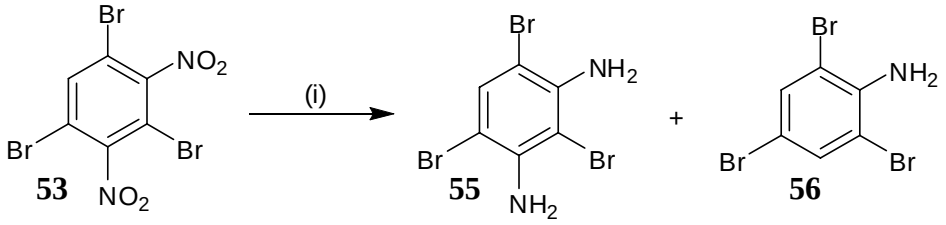


Scheme 0.28 (i) iron powder, acetic acid, reflux, 24 h.

Attempted Sonogashira coupling of (trimethylsilyl)acetylene (3 equivalents) to the tribromo compound **54** was also undertaken (Scheme 2.28). However the product mixture was complex and showed no resonances for either the expected product or the starting material.

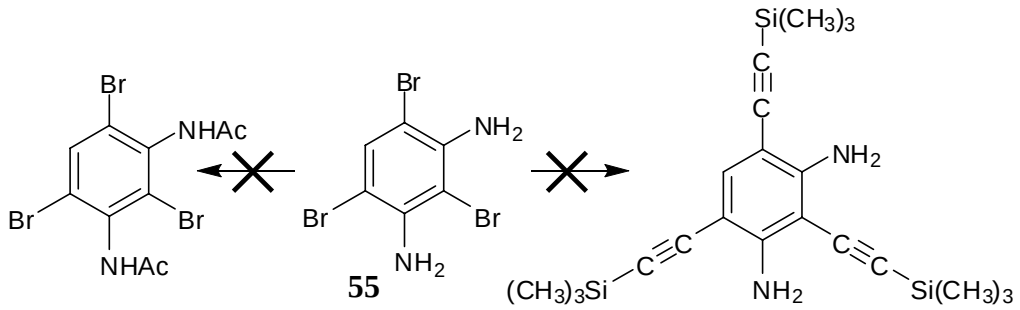
2.5.1.2 2, 4-Diamino-1, 3, 5-tribromobenzene (55)

Alternate pathways to synthesise 1, 3, 5-triamino-2, 4, 6-tribromobenzene were also explored. 2, 4-Diamino-1, 3, 5-tribromobenzene (**55**) was prepared by treating 1, 3, 5-tribromo-2, 4-dinitrobenzene (**53**) with iron powder and acetic acid which gave the fully reduced diamino compound **55** in 68% yield (Scheme 2.29). The reaction was monitored by TLC and the compound was formed in 15 mins. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectral data for compound **55** corresponded to literature values.[43] The electron impact mass spectra showed the presence of the (M^{+}) ion in agreement with product (**55**). 2, 4, 6-Tribromoaniline (**56**) was also isolated when the synthesis of compound **55** was halted after 16 h. ^{1}H NMR and electron impact mass spectra for compound **56** corresponded to literature data.[44]



Scheme 0.29 (i) iron powder, acetic acid, reflux, 1h.

Nitration at the vacant position on the aromatic ring in compound **55** was required in order to become one step closer to the desired product 1, 3, 5-triamino-2, 4, 6-tribromobenzene. Prior to the nitration step, the amines in compound **55** needed to be protected. An attempt to protect the amines by forming the amide was undertaken. An excess amount of acetic anhydride was added to a solution of compound **55** as for the amine protection of compound **50** (Section 2.4.1). The reaction was monitored by TLC and ^{1}H NMR and neither showed evidence for a new product and the starting material was recovered (Scheme 2.30).



Scheme 0.30

An attempt to couple the aromatic bromides of compound **55** to (trimethylsilyl)acetylene were undertaken according to the procedure reported by Moroni *et al*.[11] However the product mixture was complex and showed no resonances for either the expected product or the starting material (Scheme 2.30).

2.6 Summary of the Synthesis of Substrates

The aliphatic compounds synthesised and characterised included 4-pentyn-1-amide (**3**) and 5-hexyn-1-amide (**4**). Both were prepared using morpho-CDI with modification of literature procedure and both isolated in 47% yield. The synthesis of 3-butyn-1-amide was unsuccessful since but-2, 3-dienoic acid (**24**) was isolated rather than the expected product.

The aromatic compounds synthesised and characterised included 1, 4-diamino-2, 5-diethynylbenzene (**5**) and 1, 4-diamino-2, 5-*bis*(phenylethynyl)benzene (**6**) which were prepared in 6 and 5 steps respectively and were isolated in 60% and 13% yields respectively. 2, 3-Diamino-1, 4-diethynylbenzene (**7**) and 2, 3-diamino-1, 4-*bis*(phenylethynyl)benzene (**8**) were also synthesised in 4 and 3 steps respectively in 43% and 92% yield. Three aromatic amides were prepared and characterised, 1, 5-*bis*(acetamido)-2, 4-diethynylbenzene (**9**), *N*-(acetyl)-2-ethynylbenzylamine (**10**) and *N*-(acetyl)-2-(phenylethynyl)benzylamine (**11**) which were isolated in 39%, 49% and 79% yield respectively.

2.7 References

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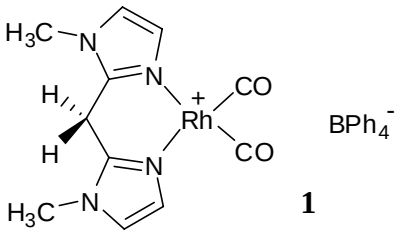
Chapter 3

Hydroamination of Substrates

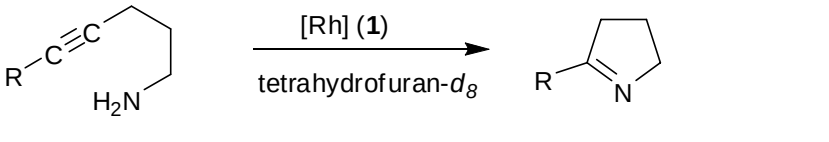
3.1 Introduction

The rhodium(I) complex (**1**) was established as a hydroamination catalyst for a series of aminoalkyne substrates.[1*]

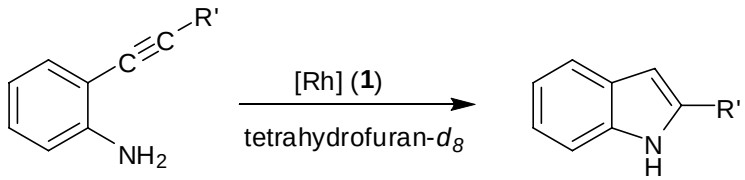


1

The rhodium(I) catalyst (**1**) catalytically and regioselectively cyclised 4-pentyn-1-amine (**21**) to 2-methyl-1-pyrroline (**22**), as well as 4-hexyn-1-amine (**57**) to 2-ethyl-1-pyrroline (**58**), 2-ethynylaniline (**59**) to indole (**60**) and 2-(2-phenylethynyl)aniline (**61**) to 2-phenylindole (**62**) (Scheme 3.1).[1]



R = H (**21**) R = CH_3 (**57**) R = H (**22**) R = CH_3 (**58**)



R' = H (**59**) R' = Ph (**61**) R' = H (**60**) R' = Ph (**62**)

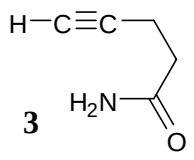
Scheme 0.1

The hydroamination reaction catalysed by the rhodium(I) complex (**1**) was studied in depth by Burling *et al.*[1-3] Based on the results established for rhodium(I) complex (**1**), eleven substrates were synthesised (Chapter 2) to assess the scope for the hydroamination of more complex amino- and amidoalkyne substrates.

A series of aromatic and aliphatic amino- and amidoalkynes with both terminal and internal acetylene bonds, and different carbon chain lengths, were

[*] References begin on page 83.

investigated to assess the selectivity and limitations for intramolecular hydroamination reactions. The cyclisation of aromatic and aliphatic aminoalkynes would lead to indoles, isoquinolines, cyclic amides and other classes of nitrogen-containing heterocycles. The aliphatic compounds synthesised for this study were 4-pentyn-1-amide (**3**) and 5-hexyn-1-amide (**4**). In this study the amine group which is part of an amide functionality was explored for possible catalytic hydroamination. In addition, a number of aromatic substrates were also synthesised namely, 1, 4-diamino-2, 5-diethynylbenzene (**5**), 1, 4-diamino-2, 5-*bis*(phenylethynyl)benzene (**6**), 2, 3-diamino-1, 4-diethynylbenzene (**7**), 2, 3-diamino-1, 4-*bis*(phenylethynyl)benzene (**8**), 1, 5-*bis*(acetamido)-2, 4-diethynylbenzene (**9**), 1, 5-*bis*(acetamido)-2, 4-*bis*(trimethylsilylethynyl)benzene (**12**), *N*-(acetyl)-2-ethynylbenzylamine (**10**), *N*-(acetyl)-2-(trimethylsilylethynyl)benzylamine (**13**) and *N*-(acetyl)-2-(phenylethynyl)benzylamine (**11**).



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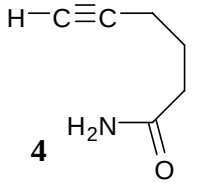

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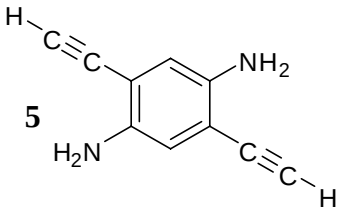

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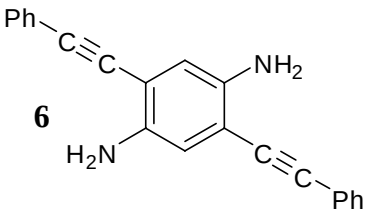

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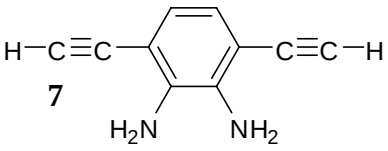

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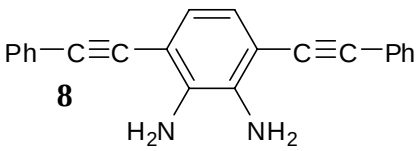

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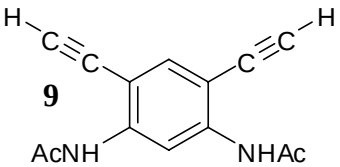

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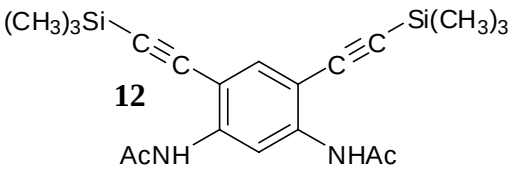

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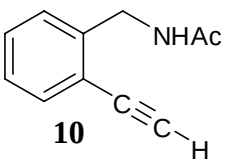

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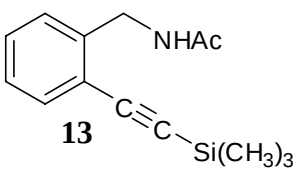

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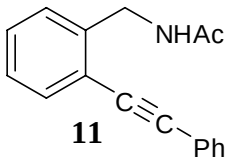

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3.2 Metal-Catalysed Intramolecular Hydroamination of Aminoalkynes

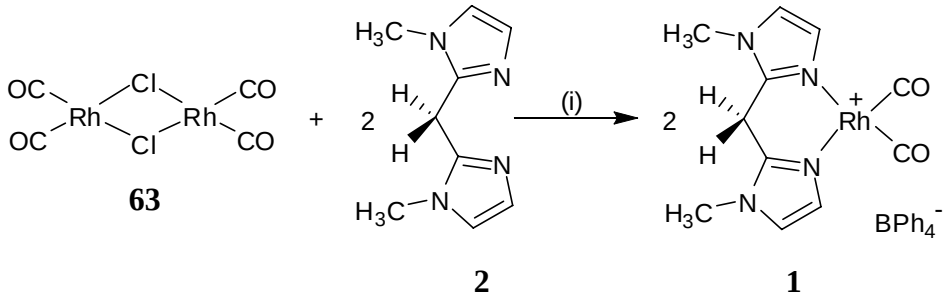
3.2.1 General procedures for catalytic reactions

The metal-catalysed cyclisation of the aminoalkynes was typically performed on a small scale in NMR tubes fitted with concentric Teflon valves in tetrahydrofuran-d_8 at 60 °C with a catalytic amount of the rhodium(I) complex (**1**). All of the substrates were solids and therefore a typical procedure required that the substrate was weighed out into an NMR tube, followed by addition of the solvent by vacuum transfer. The tube was then placed under an atmosphere of nitrogen and a pre-weighed amount of rhodium(I) catalyst (**1**) was added to the NMR tube.

The reactions were monitored by ^{1}H NMR spectroscopy at regular intervals and the conversion of starting material to product was determined by integration of selected resonances. Products were identified and confirmed by comparison of the ^{1}H and ^{13}C{^{1}H} NMR data with literature values or data from authentic samples where possible or products were isolated and characterised.

3.3 [Rh(bim)(CO)$_2$][BPh$_4$] (1)

Rhodium(I) complex (**1**) was synthesised by combining the chloride-bridged rhodium dimer di-μ-chloro-tetracarbonyldirhodium (**63**) and *bis*(*N*-methylimidazol-2-yl)methane (bim; **2**) ligand (see Chapter 4 for detailed synthesis).



63 **2** **1**

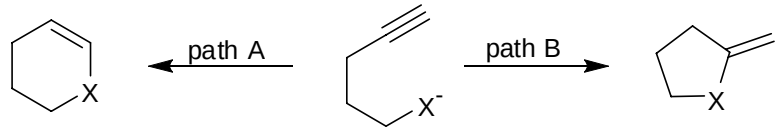
Scheme 0.2 (i) sodium tetraphenylborate, methanol, room temperature.

The rhodium bridged dimer (**63**) was prepared by the method of McCleverty and Wilkinson[4] where rhodium trichloride hydrate was heated at 100 °C in a stream of carbon monoxide for 3-4 h, during which time bright red needles of **63** formed and were isolated by a hexane extraction.

The synthetic method for preparing **1** required the addition of bim ligand (**2**) (2 equivalents) in methanol to a methanol solution of **63** under an atmosphere of nitrogen at room temperature. The bridging chlorides of the rhodium precursor were selectively displaced by the bim (**2**) nitrogen donors to produce the target four-coordinate cation. After 30 min, an excess of the counterion, tetraphenylborate, was added as a methanol solution to the mixture (Scheme 3.2). The rhodium(I) complex (**1**) was prepared in high yield (91%) by the method outlined above. The complex exhibited identical spectroscopic properties to those reported previously.[5] The complex was stable in air as a solid but decomposed in solution after several days.

3.4 Intramolecular Cyclisation

The intramolecular ring closure reaction between a heteroatom and the carbon-carbon multiple-bond in the same molecule is one of the most useful methods for constructing cyclic compounds and has been used for natural product synthesis. The ring size of the products from the ring closure reaction depend on a number of competing stereoelectronic effects as well as specific requirements which may be imposed by any catalyst used. For example, substrate (a) can undergo either a '6-*endo*' cyclisation *via* path A or '5-*exo*' cyclisation *via* path B ring closure (Scheme 3.3).



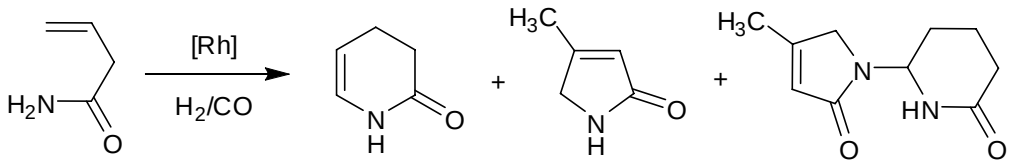
(a)

Scheme 0.3

3.4.1 Cyclisation of 4-Pentyn-1-amide (3) to 3, 4-Dihydro-2-pyridone (64)

The dihydro-2-pyridone and 2-pyrrolinone skeletons are important nitrogen-containing heterocycles for pharmaceutical and agrochemical agents. Dihydro-2-pyridone and 2-pyrrolinone also serve as key intermediates for the synthesis of biologically active alkaloids. Simple dihydro-2-pyridones have been synthesised by the direct reaction of 2, 4-pentadienoic acid or sorbic acid with ammonia to give a mixture of 3, 6-dihydro- and 5, 6-dihydro-2-pyridones[6] and by sodium borohydride reduction of glutarimide to yield 3, 4-dihydro-2-pyridones selectively.[7]

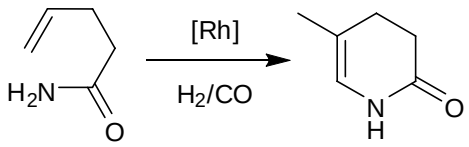
There are a few literature reports of metal-catalysed cyclisation of aliphatic amides and amines by intramolecular amidocarbonylation.[8-10] Ojima and Korda reported the intramolecular amidocarbonylation of 3-buten-1-amide (**65**) which was carried out using rhodium catalysts ($RhCl(PPh_3)_3$, $RhCl(CO)(PPh_3)_2$ or $Rh_4(CO)_{12}$) in the presence of carbon monoxide/ hydrogen gas (1200 psi) at 80-100 °C to give a mixture of 3, 4-dihydro-2-pyridone (**64**), methyl-3-pyrrolin-2-one (**66**) and a heterodimer 6-(4-methyl-3-pyrrolin-2-on-1-yl)-2-piperidone (**67**) (Scheme 3.4).



65 **64** **66** **67**

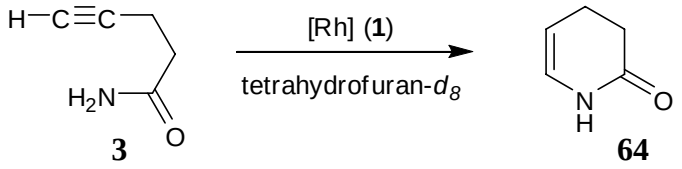
Scheme 0.4

Whereas, the amidocarbonylation of 4-penten-1-amide with rhodium complexes ($RhCl(PPh_3)_3$, $RhCl(CO)(PPh_3)_2$, $HRh(CO)(PPh_3)_3$ and $Rh_4(CO)_{12}$) gave 4-methyl-3, 4-dihydro-2-pyridone (Scheme 3.5) as the sole product in excellent yield (88-92%).[9]



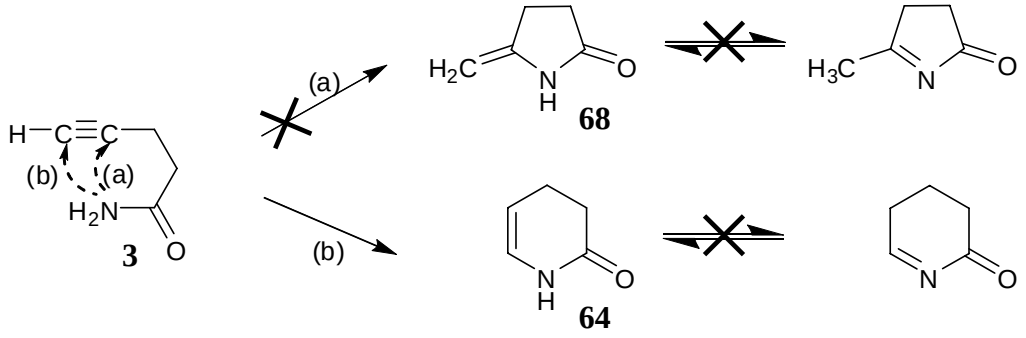
Scheme 0.5

The cyclisation of 4-pentyn-1-amide (**3**) to 3, 4-dihydro-2-pyridone (**64**) was catalysed by rhodium(I) complex (**1**) (10 mol%) (Scheme 3.6). The reaction was monitored by ^{1}H NMR spectroscopy and halted after 40 h by which time 100% conversion had been achieved. Product **64** was isolated by column chromatography in 11% yield. The low isolated yield was probably due to the fact that the reaction was carried out on a small scale. In addition some of the product could have coordinated to the rhodium metal and been lost during the column chromatography step.



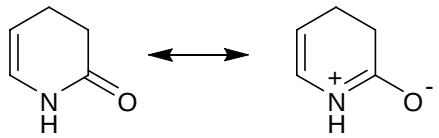
Scheme 0.6

Compound **64** was characterised by ^{1}H, ^{13}C{^{1}H} NMR spectroscopy and a ^{13}C DEPT experiment showed the molecule had 2 CH and 2 CH_2 groups. The electron impact mass spectrum showed the presence of the (M^+) ion and the positive electrospray mass spectrum showed the presence of the ($5M^+$) ion both of which were in agreement with product **64**. The composition of the compound was confirmed by high resolution mass spectrometry.



Scheme 0.7 Possible ring-closing pathways for the rhodium(I) catalysed cyclisation of 4-pentyn-1-amide (**3**): (a) *exo*-cyclisation (b) *endo*-cyclisation.

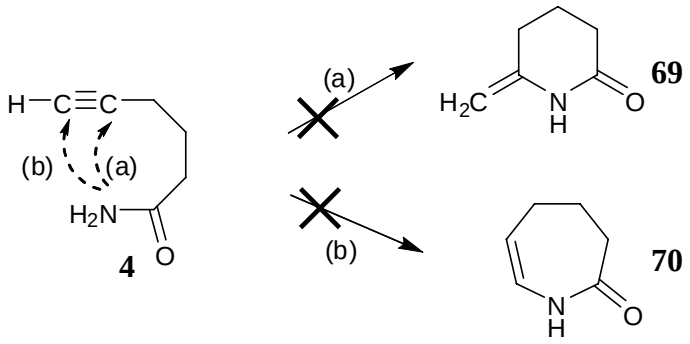
Intramolecular cyclisation *via* hydroamination of 4-pentyn-1-amide (**3**) may give two possible isomers resulting from either 5-*exo* or 6-*endo* ring closures. *Exo*-cyclisation of **3** would lead to 5-methylenepyrrolidin-2-one (**68**) (Scheme 3.7, (a)), a 5-membered ring, while *endo*-cyclisation would lead to 3, 4-dihydro-2-pyridone (**64**) a 6-membered ring (Scheme 3.7, (b)). However, in the cyclisation reaction described above compound **64** was the only product isolated. The intramolecular hydroamination of aliphatic alkynamines produces enamines in the first instance, which then tautomerise to the more stable imine products.[2] However, for the cyclisation of aliphatic amides, the C=C–NH tautomer is stable and this is probably due to interaction with the amide group.



3.4.1.1 The Attempted Cyclisation of 5-Hexyn-1-amide (4)

5-Hexyn-1-amide (**4**) is a similar substrate to 4-pentyn-1-amide (**3**), with an additional carbon in the chain. The expected products from intramolecular hydroamination in this case would see the 6-*exo* and 7-*endo* ring-closing pathways apply. *Exo* ring-closure would result in the formation of 6-methylenepiperidin-2-one (**69**) (Scheme 3.8, (a)), while *endo*-cyclisation would

afford 4, 5-dihydroazepin-2-one (**70**) (Scheme 3.8, (b)). A 7-membered ring is not uncommon since Li and Marks reported the production of a 7-membered heterocycle (92%) *via* the intramolecular hydroamination of 7-phenylhept-6-yn-1-amine.[11]



Scheme 0.8 Possible ring-closing pathways for the rhodium(I) catalysed cyclisation of 5-hexyn-1-amide (**4**): (a) *exo*-cyclisation (b) *endo*-cyclisation.

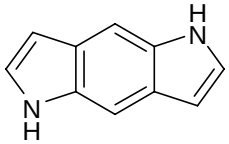
The cyclisation of 5-hexyn-1-amide (**4**) was initially attempted with 20 mol% and 30 mol% of the rhodium(I) complex (**1**) in tetrahydrofuran-d_8 at 60 °C. The high catalyst loading led to extensive decomposition of the starting material. However, when the cyclisation of **4** was undertaken using 6, 10 and 15 mol% of the rhodium(I) complex in tetrahydrofuran-d_8 at both 60 °C and at reflux, no cyclisation products (**69** or **70)** were produced. The ^{1}H NMR spectrum showed some evidence for the formation of a cyclic product with vinyl resonances in the same region as **64** however the concentration of this product was calculated to be less than 1% after 36 h and the structure of the product was not identified conclusively. Isolation of the cyclic product was attempted by column chromatography however this was unsuccessful and only the starting material was isolated.

3.5 Cyclisation of Aromatic Aminoalkynes

The catalytic cyclisation of *ortho* amino- and *ortho* amidoethynylbenzenes to indoles has now been established for a number of simple substrates.[1-3] The challenge in this work was to see if this metal-catalysed cyclisation could be used to generate more highly condensed polynuclear heterocycles. The cyclisation of substrates **5-9** and **12** were examined to further explore the scope of the double cyclisation of terminal and internal alkynes. Similarly, the catalytic cyclisations of *ortho*-acetylethynylbenzylamines **10**, **11** and **13** were also explored.

3.5.1 Cyclisation of 1, 4-Diamino-2, 5-*bis*(ethynyl)benzene (5) to 1, 5-Dihydro-pyrrolo[2, 3-*f*]indole (71)

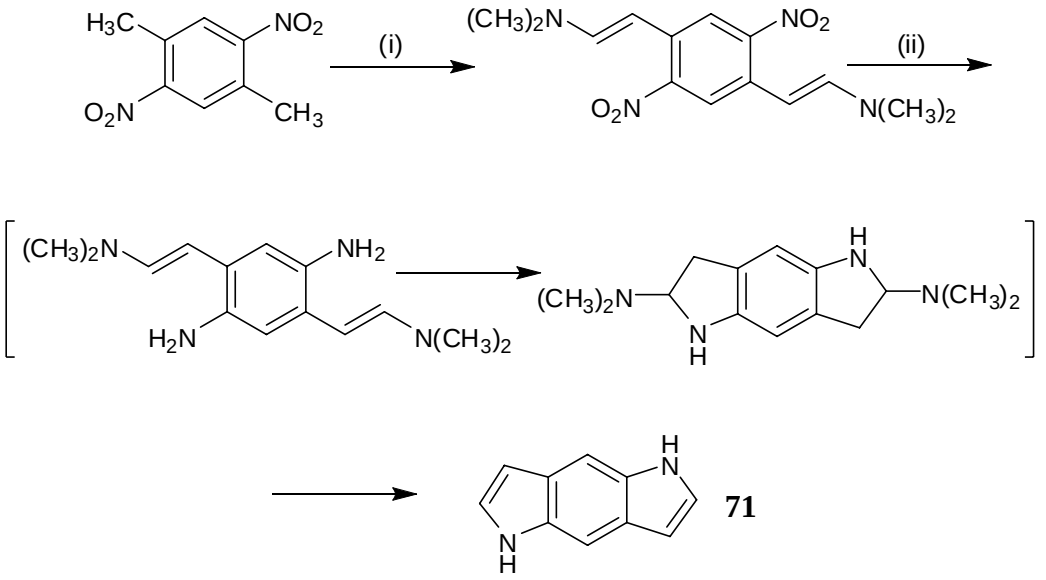
The indole nucleus is a common structural feature of many biologically interesting compounds and therefore the preparation of substituted indole derivatives are of considerable interest.



71

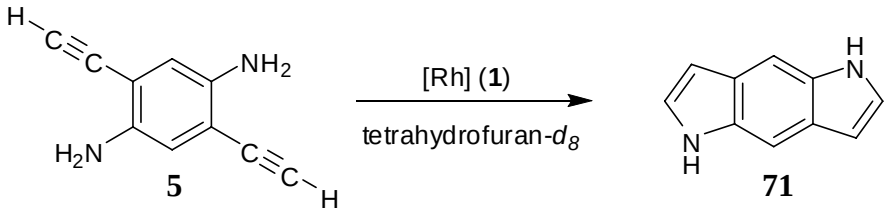
There are a few reports for the synthesis of the 1, 5-dihydro-pyrrolo[2, 3-*f*]indole (**71**) skeleton. In the literature, one method utilises the electrophilic substitution of 5-aminoindoles and employs the indolization strategy developed by Norlander and co-workers.[12] Berlin *et al.*[13] have also reported the synthesis of benzodipyrroles by a double condensation of *N*, *N*-dimethylformamide diethyl acetal with a suitable dinitro-xylene, followed by catalytic reduction. The catalytic reduction (hydrogen gas/ palladium-on-charcoal) converts the nitro groups into amino functionalities *in situ* and these immediately cyclise to give the desired benzodipyrrole derivatives without isolation of the enamine intermediates (Scheme 3.9). This isomeric pyrrolo-[2, 3-*f*]indole system has been of interest as a possible precursor to conducting polymers because of its good electronic properties and environmental

stability.[12, 14]



Scheme 0.9 (i) *N*, *N*-dimethylformamide diethyl acetal in *N*, *N*-dimethylformamide 90-120 °C, 5-20 h; (ii) hydrogen gas, 10% palladium-on-charcoal in ethyl acetate, room temperature, atm. pressure.

The cyclisation of 1, 4-diamino-2, 5-*bis*(ethynyl)benzene (**5**) to 1, 5-dihydro-pyrrolo[2, 3-*f*]indole (**71**) was catalysed by the rhodium(I) complex (**1**) (30 mol%) (Scheme 3.10). The reaction was monitored by ^{1}H NMR spectroscopy (Figure 3.1) and **71** was isolated by column chromatography in 20% yield. The product was identified by comparison of the ^{1}H NMR spectroscopy data with literature values[13] and further characterised by ^{13}C{^{1}H} NMR spectroscopy.



Scheme 0.10

The conversion rate of **5** to **71** was measured by integration of the ^{1}H NMR

signals of the starting material and the product. Complex **1** (30 mol%) produced quantitative conversion to 1, 5-dihydro-pyrrolo[2, 3-*f*]indole (**71**) in 7.2 h with heating at 60 °C in tetrahydrofuran-d_8.

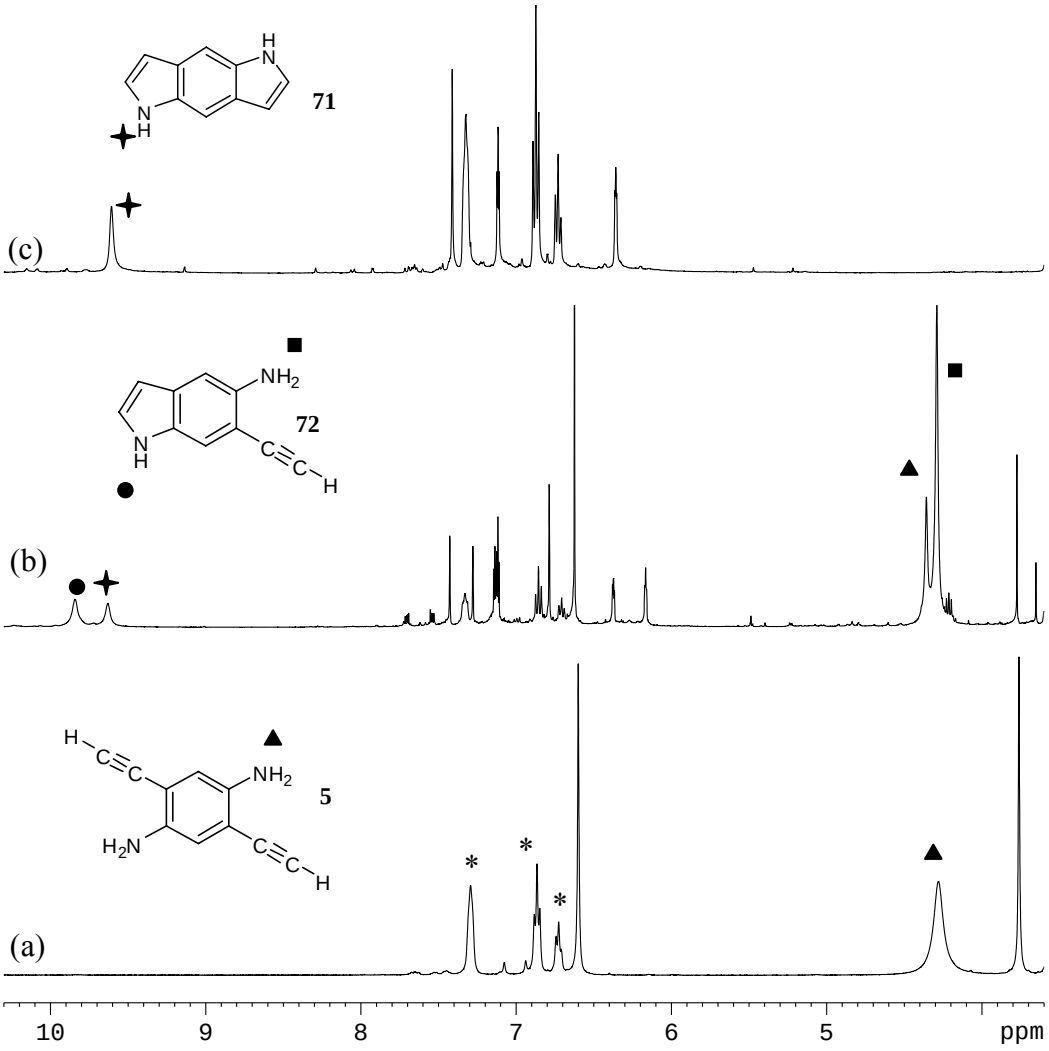
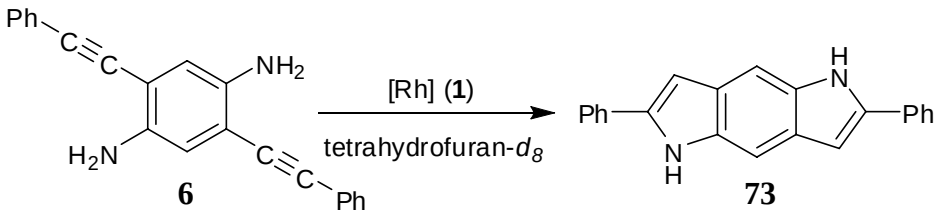


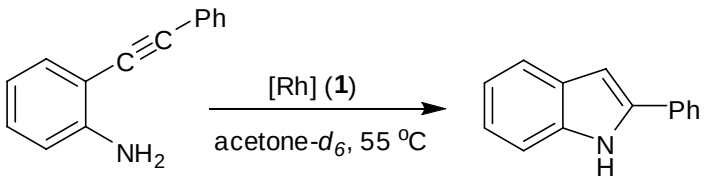
Figure 0.1 ^{1}H NMR spectra (400 MHz, tetrahydrofuran-d_8, 60 °C) of the cyclisation of 1, 4-diamino-2, 5-*bis*(ethynyl)benzene (**5**) to 1, 5-dihydro-pyrrolo[2, 3-*f*]indole (**71**): (a) starting material and complex **1** only (*) (b) a mixture of starting material (**5**), singly (**72**) and doubly cyclised (**71**) products (c) complete reaction to 1, 5-dihydro-pyrrolo[2, 3-*f*]indole (**71**).

3.5.2 Cyclisation of 1, 4-Diamino-2, 5-*bis*(phenylethynyl)benzene (6) to 1, 5-Dihydro-2, 6-diphenyl-pyrrolo[2, 3-*f*]indole (73)



Scheme 0.11

The potential for achieving metal-catalysed intramolecular hydroamination of a *bis*-alkynylaniline substrate with internal acetylenes was assessed using 1, 4-diamino-2, 5-*bis*(phenylethynyl)benzene (**6**) as a substrate. The cyclisation of 1, 4-diamino-2, 5-*bis*(phenylethynyl)benzene (**6**) to 1, 5-dihydro-2, 6-diphenyl-pyrrolo[2,3-*f*]indole (**73**) was catalysed by **1** (26 mol%) (Scheme 3.11). The reaction was monitored by ^{1}H NMR spectroscopy and the product (**73**) crystallised directly from the reaction mixture and was isolated by filtration in 24% yield. After 36 min quantitative conversion of the substrate was achieved as no signals for the starting material or product were observed in the ^{1}H NMR spectrum. The time required for completion was significantly shorter than that required for the cyclisation of 1, 4-diamino-2, 5-*bis*(ethynyl)benzene (**5**) to 1, 5-dihydro-pyrrolo[2, 3-*f*]indole (**71**) (Section 3.5.1). Burling *et al.*[2] reported the cyclisation of 2-(2-phenylethynyl)aniline with the rhodium(I) complex (**1**) (1.6 mol%) to give 2-phenylindole as the sole cyclised product after 40 h at 55 °C in acetone-d_6 (Scheme 3.12).

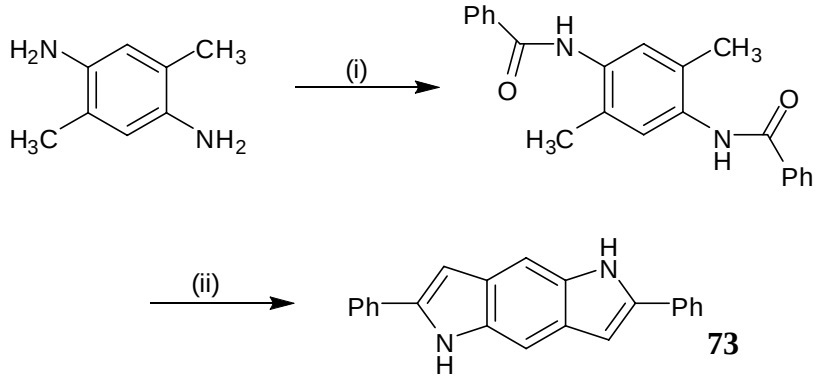


Scheme 0.12

Compound **73** was examined by ^{1}H NMR spectroscopy, the resonance for the amine protons appeared at δ10.10 ppm and those for the aromatic protons between δ 7.83-6.81 ppm. Compound **73** was also characterised by $^{13}C\{^{1}H\}$ NMR, where all the chemical shifts were consistent with the structure proposed.

The electron impact mass spectrum showed the presence of the (M^{+}) ion in agreement with product **73**. The composition of the compound was also confirmed by microanalysis.

Geise *et al*.[15] reported the synthesis of compound **73** in 17% yield by means of a classical Madelung indole synthesis starting from 2, 5-dimethyl-1, 4-phenylenediamine (Scheme 3.13).



Scheme 0.13 (i) benzoyl chloride (ii) potassium *tert*-butoxide, 320-330 °C.

3.5.3 X-ray Crystal Structure of 1, 5-Dihydro-2, 6-diphenyl-pyrrolo[2, 3-*f*]indole (73)

A pale yellow blade like crystal suitable for X-ray crystal structure determination was obtained from the reaction mixture. An ORTEP depiction of the molecule, with an atom numbering system is given in Figure 3.2. Selected bond lengths and angles are listed in Table 3.1. Crystallographic data is presented in Appendix 1.

Compound **73** has a planar geometry and as expected the single carbon-carbon bond at C(1)-C(11) and C(6)-C(17) are significantly longer compared with the rest of the bonds in the molecule.

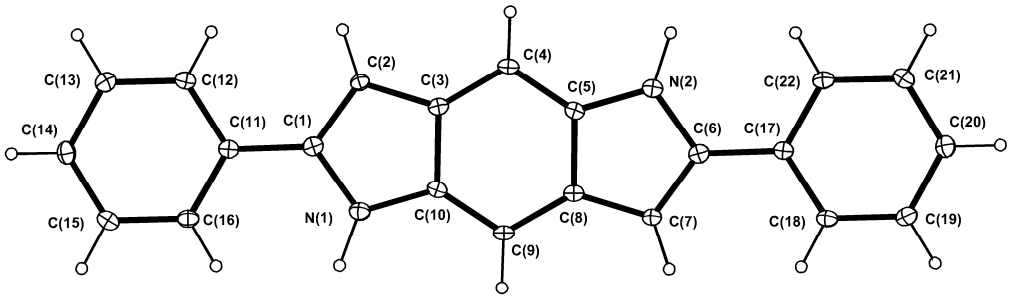


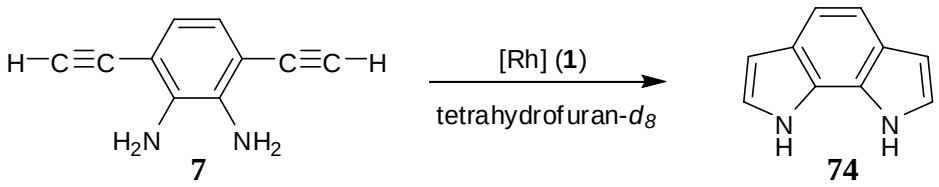
Figure 0.2 ORTEP plot and crystal structure numbering of compound **73**

Table 0.1 Selected bond distances and bond angles of compound **73**

1, 5-Dihydro-2, 6-diphenyl-pyrrolo[2, 3-*f*]indole (73)			
Atoms	**Bond Distance (Å)**	**Atoms**	**Bond Angle (°)**
N(1)-C(1)	1.389(3)	C(1)-N(1)-C(10)	109.41(14)
N(2)-C(6)	1.381(3)	C(6)-N(2)-C(5)	109.58(17)
N(1)-C(10)	1.391(3)	C(2)-C(1)-N(1)	108.23(17)
N(2)-C(5)	1.398(3)	C(7)-C(6)-N(2)	108.25(17)
C(1)-C(2)	1.369(3)	C(1)-C(2)-C(3)	109.14(17)
C(6)-C(7)	1.372(3)	C(6)-C(7)-C(8)	109.04(17)
C(1)-C(11)	1.460(3)	N(1)-C(1)-C(11)	123.60(18)
C(6)-C(17)	1.463(3)	N(2)-C(6)-C(17)	123.43(18)

3.5.4 Cyclisation of 2, 3-Diamino-1, 4-diethynylbenzene (7) to 1, 8-Dihydro-pyrrolo[2, 3-*g*]indole (74)

The cyclisation of 2, 3-diamino-1, 4-diethynylbenzene (**7**) to 1, 8-dihydro-pyrrolo[2, 3-*g*]indole (**74**) was catalysed by the rhodium(I) complex (**1**) (16 mol%) (Scheme 3.14). The reaction was monitored by ^{1}H NMR spectroscopy and **74** was isolated by column chromatography in 31% yield. The product was identified by comparison of the ^{1}H NMR spectroscopy data with literature values[13] and further characterisation by ^{13}C{^{1}H} NMR spectroscopy.

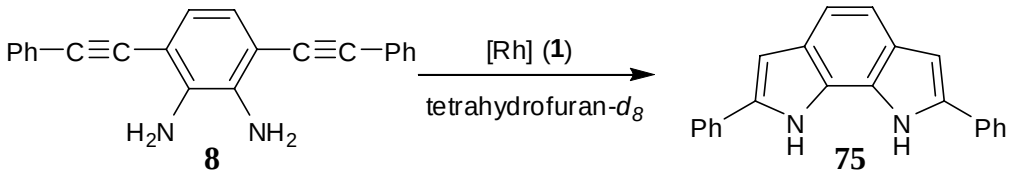


Scheme 0.14

The conversion rate of **7** to **74** was measured by integration of the ^{1}H NMR signals of the starting material and the product. After 34 h quantitative conversion of the substrate was achieved.

3.5.5 Cyclisation of 2, 3-Diamino-1, 4-*bis*(phenylethynyl)benzene (8) to 1, 8-Dihydro-2, 7-diphenyl-pyrrolo[2, 3-*g*]indole (75)

The cyclisation of 2, 3-diamino-1, 4-*bis*(phenylethynyl)benzene (**8**) to 1, 8-dihydro-2, 7-diphenyl-pyrrolo[2, 3-*g*]indole (**75**) was catalysed by the rhodium(I) complex (**1**) (20 mol%) (Scheme 3.15). The reaction was monitored by ^{1}H NMR spectroscopy and **75** was isolated by column chromatography in 31% yield.

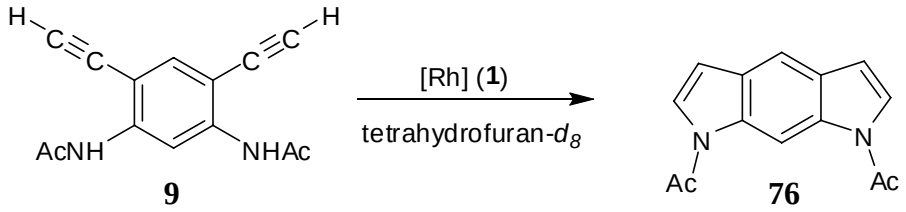


Scheme 0.15

Compound **75** has not been reported in the literature. In the ^{1}H NMR spectrum, the amine resonance appeared at δ10.12 ppm and the aromatic protons between δ 7.70-6.91 ppm. Compound **75** was also characterised by $^{13}C\{^{1}H\}$ NMR, where all the chemical shifts were consistent with the structure proposed. Both the electron impact and high resolution mass spectra confirmed the composition of the compound.

3.5.6 Cyclisation of 1, 5-*Bis*(acetamido)-2, 4-diethynylbenzene (9) to 1, 7-Diacetyl-pyrrolo[3, 2-*f*]indole (76)

The cyclisation of 1, 5-*bis*(acetamido)-2, 4-diethynylbenzene (**9**) to 1, 7-diacetyl-pyrrolo[3, 2-*f*]indole (**76**) was catalysed by rhodium(I) complex (**1**) (30 mol%) (Scheme 3.16). The reaction was monitored by ^{1}H NMR spectroscopy and was halted after 72 h as no further conversion was observed. The rate of the reaction for the cyclisation of the substituted aromatic amide **9** was considerably slower than that for the primary amines **5**, **6**, **7** and **8**. Compound **76** was isolated as the sole product by column chromatography in 36% yield.

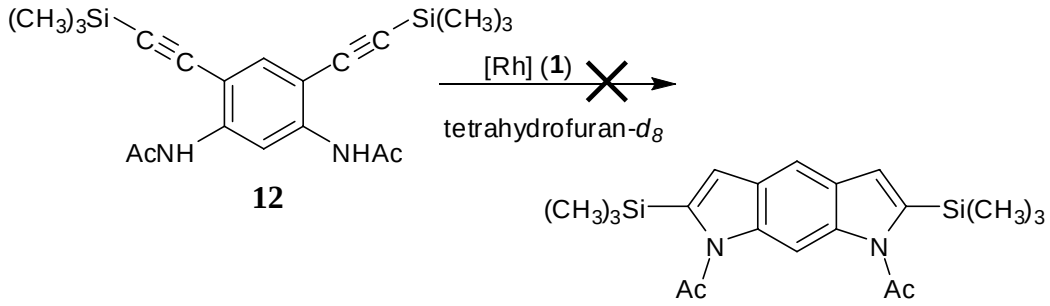


9 **76**

Scheme 0.16

Compound **76** is a new compound. In the ^{1}H NMR spectrum, the signals for the aromatic protons appeared between δ 9.47-6.67 ppm and those for the methyl resonances was as expected at δ 2.67 ppm. Compound **76** was also characterised by $^{13}C\{^{1}H\}$ NMR and all the chemical shifts were consistent with the structure proposed for the molecule. Both the electron impact and high resolution mass spectra confirmed the elemental formula.

3.5.6.1 Attempted Cyclisation of 1, 5-*Bis*(acetamido)-2, 4-*bis*(trimethylsilylethynyl)benzene (12)



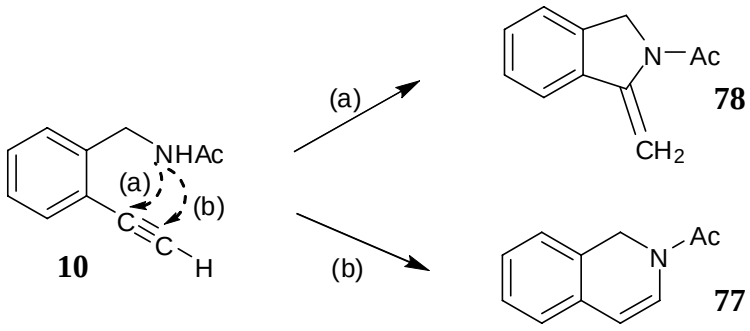
12

Scheme 0.17

The rhodium(I) complex (**1**) successfully cyclised **9**, a terminal acetylene (Section 3.5.6) and attempts to cyclise an internal acetylene were undertaken. The cyclisation of 1, 5-*bis*(acetamido)-2, 4-*bis*(trimethylsilylethynyl)benzene (**12**) (from the second last step of the synthesis of **9**, Section 2.4.1) was initially attempted with 30 mol%, 15 mol% and 5 mol% of the rhodium(I) complex (**1**) in tetrahydrofuran-d_8 at 60 °C (Scheme 3.17). All three catalyst loadings appeared to have cyclised and desilylated **12** although a complex mixture was obtained and not purified further. 1, 7-Diacetyl-pyrrolo[3, 2-*f*]indole (**76**) was identified by ^{1}H NMR to be one of the many cyclised products by comparison with an authentic sample formed from the cyclisation of **9** (Section 3.5.6). The cyclisation of **12** was extremely slow varying between 6 days with high catalyst loading and 30 days with low catalyst loading. An attempt to prepare an alternative internal acetylene of this type i.e. 1, 5-*bis*(acetamido)-2, 4-*bis*(phenylethynyl)benzene was discussed in Chapter 2 (Section 2.4.2.1) however the synthesis undertaken was unsuccessful.

3.5.7 Cyclisation of *N*-(Acetyl)-2-ethynylbenzylamine (10) to *N*-(Acetyl)-1, 2-dihydroisoquinoline (77)

Intramolecular cyclisation of *N*-(acetyl)-2-ethynylbenzylamine (**10**) *via* hydroamination may give two possible isomers resulting from either 5-*exo* or 6-*endo* ring closure. *Exo*-cyclisation of **10** would lead to a the 5-membered ring, while *endo*-cyclisation would lead to *N*-(acetyl)-1, 2-dihydroisoquinoline (**77**) a 6-membered ring (Scheme 3.18). However, compound **77** (Scheme 3.18, (b)) was the only product isolated for the cyclisation reaction described above.



Scheme 0.18 Possible ring-closing pathways for *N*-(acetyl)-2-ethynylbenzylamine (**10**): (a) *exo*-cyclisation (b) *endo*-cyclisation.

The intramolecular cyclisation of *N*-(acetyl)-2-ethynylbenzylamine (**10**) by Cid *et al*.[16] underwent a 5-*exo* ring closure upon treatment with sodium hydride in dimethylformamide and gave *N*-(acetyl)-1-methyleneisoindole (**78**) (Scheme 3.18, (a)) after 3 h in 87% yield.

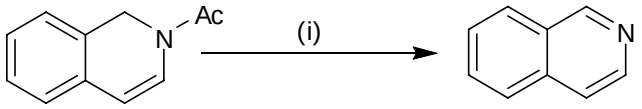
Compound **77** was determined by ^{1}H NMR spectroscopy to consist of a mixture of two isomers due to the restricted rotation about the amide bond in a ratio of 84:16 which was consistent with literature values.[17] Compound **77** was further characterised by $^{13}C\{^{1}H\}$ NMR spectroscopy.

The electron impact mass spectrum showed the presence of the (M^{+}) ion in agreement with product **77**. The composition of the compound was confirmed by

high resolution mass spectrometry.

3.5.7.1 Isoquinoline (79) from *N*-(Acetyl)-1, 2-dihydroisoquinoline (77)

Isoquinoline **79** was identified by ^{1}H NMR spectroscopy after *N*-(acetyl)-1, 2-dihydroisoquinoline (**77**) was allowed to stand in chloroform-*d* at room temperature for several days. Compound **79** was formed directly when **77** was treated with DDQ (2, 3-dichloro-5, 6-dicyano-benzoquinone) as an aromatizing agent.[18] The reaction occurred immediately upon addition of DDQ and was accompanied by a colour change (Scheme 3.19).

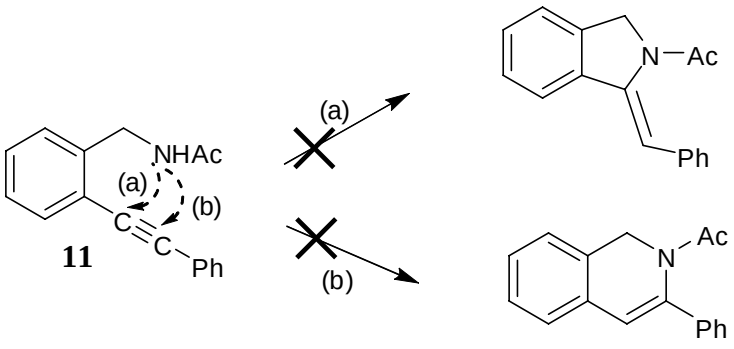


77 **79**

Scheme 0.19 (i) DDQ.

Compound **79** was identified by comparison of the ^{1}H and ^{13}C{^{1}H} NMR spectroscopy data with those of an authentic sample. The electron impact mass spectrum showed the presence of the (M^{+}) ion in agreement with product **79**.

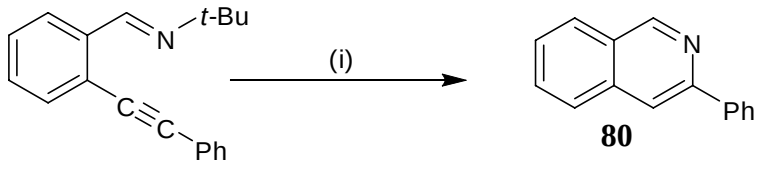
3.5.7.2 Attempted Cyclisation of *N*-(Acetyl)-2-(phenylethynyl)benzylamine (11)



Scheme 0.20 Possible ring-closing pathways for the rhodium(I) catalysed cyclisation of *N*-(acetyl)-2-(phenylethynyl)benzylamine (**11**): (a) *exo*-cyclisation (b) *endo*-cyclisation.

The rhodium(I) complex (**1**) was successful in catalytically cyclising substrates with an internal acetylene (**6** and **8**) (Section 3.5.2 and 3.5.5), and *N*-substituted acetamide derivatives (**9** and **10**) (Section 3.5.6 and 3.5.7). These two functionalities were incorporated in a single substrate, *N*-(acetyl)-2-(phenylethynyl)benzylamine (**11**) and reacted with 12 mol% and 30 mol% of complex **1** in tetrahydrofuran-d_8 at 60 °C (Scheme 3.20). Complex **1** failed to produce any cyclic products for both attempts. There was no spectral evidence (by ^{1}H NMR) for the formation of the desired product only unreacted starting material was observed.

Roesch and Larock[19] reported the synthesis of monosubstituted isoquinolines in excellent yields *via* copper-catalysed cyclisation of iminoalkynes. 3-Phenylisoquinoline (**80**) was prepared in 100% yield (Scheme 3.21) by this method.



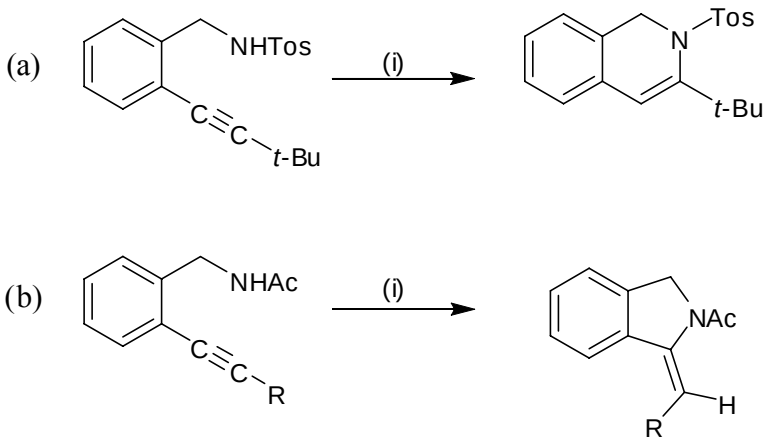
80

Scheme 0.21 (i) 10 mol% of copper(I) iodide in 5 mL of *N, N*-dimethylformamide, 3h, 100 °C.

The cyclisation reaction[19] was dependent upon the nature of the acetylene employed for example; aryl-, vinylic-, and alkyl-substituted acetylenes underwent palladium-catalysed coupling and subsequent copper-catalysed cyclisation in excellent yields. However propargylic, hydroxyl and highly hindered iminoalkyne groups were not tolerated in the reaction.

Tetrabutylammonium fluoride (TBAF) is a well known reagent for the cleavage of silyl functional groups, however Jacobi and Rajeswari reported the first TBAF promoted 5-*exo* cyclisation reaction.[20] Hiroya *et al.*[21] also explored the application of TBAF promoted cyclisation towards other heterocyclic ring systems. Hiroya *et al*. reported the high regioselectivity of the cyclisation was

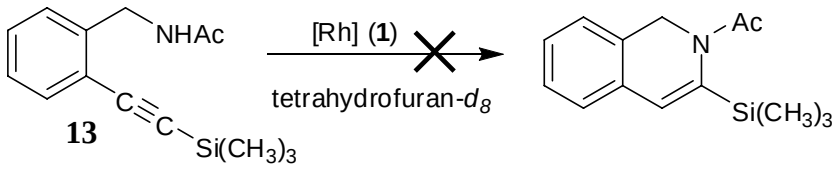
dependent on the substituents on the end of the acetylene bond of the 2-ethylnylbenzylamine derivatives. That is, 6-membered ring derivatives were obtained from the compounds which have a *t*-butyl group on the acetylene bond (Scheme 3.22 (a)). Whereas 5-membered ring products were afforded from the substrates having hydrogen or aromatic substituents on the acetylene (Scheme 3.22 (b)). It was found that the regioselectivity was due to the steric bulkiness of the functional groups and both tetrabutylammonium cation and fluoride anion were essential for the efficient cyclisation reaction.[21]



Scheme 0.22 (a) (i) TBAF.3H_2O, dioxane, reflux, 24 h, reflux, 84% (b) (i) (R = Ph) TBAF, tetrahydrofuran, 3 h, reflux, 56%.

3.5.7.3 Attempted Cyclisation of *N*-(Acetyl)-2-(trimethylsilylethynyl)benzylamine (13)

Attempts to cyclise an alternative internal acetylene were undertaken since substrate **11** produced no product. The cyclisation of *N*-(acetyl)-2-(trimethylsilylethynyl)benzylamine (**13**) was attempted with 10 mol% of the rhodium(I) complex (**1**) in tetrahydrofuran-d_8 at 60 °C. The rhodium(I) complex (**1**) cyclised and desilylated substrate **13** although a complex mixture was obtained and not purified further. *N*-(acetyl)-1, 2-dihydroisoquinoline (**77**) was identified by ^{1}H NMR to be one of the many cyclised products formed and not the desired cyclised product as illustrated in Scheme 3.23. The cyclised product **77** was characterised by ^{1}H NMR spectroscopy only (literature values reported by Katayama *et al*.[17]).



Scheme 0.23

3.6 Summary of the Catalysed Intramolecular Hydroamination of Aminoalkynes

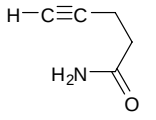
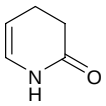
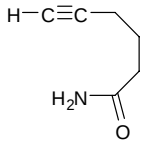
The cyclisation reactions described in this chapter report the catalytic reactivity of rhodium(I) complex (**1**) for the intramolecular hydroamination reaction. The rhodium(I) complex (**1**) has successfully fulfilled its potential to catalyse hydroamination in both terminal and internal acetylenic amine and amide substrates, to give pyridones, indoles and isoquinolines. The scope of the reactions investigated using **1** as a catalyst are summarised in Table 3.2.

The catalytic potential of the rhodium(I) complex (**1**) was explored for the formation of carbon-nitrogen bonds. The rhodium(I) complex (**1**) regioselectively produced a 6-membered ring, by 6-*endo* cyclisation of 4-pentyn-1-amide (**3**) which led to 3, 4-dihydro-2-pyridone (**64**). Attempts to cyclise 5-hexyn-1-amide (**4**) to produce a 6- or 7-membered ring were unsuccessful.

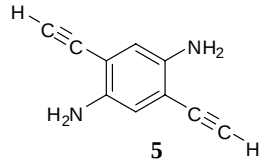
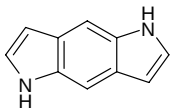
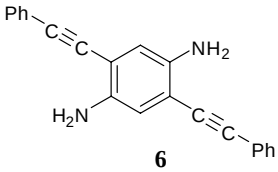
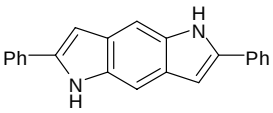
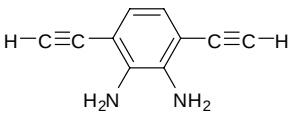
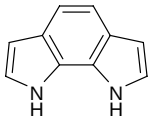
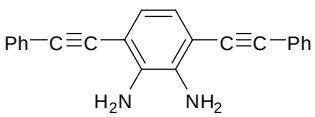
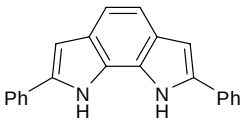
The hydroamination of both terminal and internal acetylenic amines were achieved using **1**. Compounds **5**, **6**, **7** and **8** were catalytically cyclised to **71**, **73**, **74** and **75** respectively. Similarly, the hydroamination of the aromatic amides with terminal acetylenes **9** and **10** cyclised to give **76** and **77** respectively. The substrates with trimethylsilylacetylene groups **12** and **13** resulted in the cyclisation and removal of the trimethylsilyl groups as well.

Table 0.2 Summary of the rhodium(I) complex (**1**) catalysed intramolecular hydroamination of amino- and amidoalkynes.

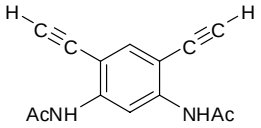
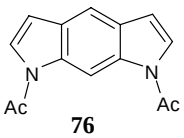
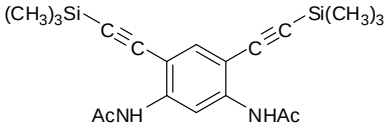
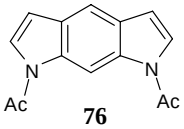
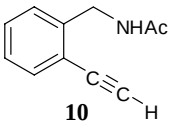
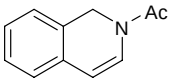
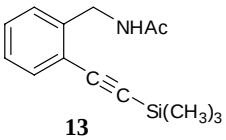
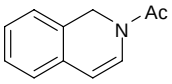
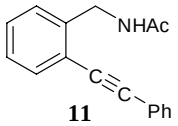
Alphatic Amides

Substrates	Products	Mol% of Catalyst	Time (h) at 100% Conversion	Isolated Yield %
 **3**	 **64**	10	40	11
 **4**	—			

Aromatic Amines

Substrates	Products	Mol% of Catalyst	Time at 100% Conversion	Isolated Yield %
 **5**	 **71**	30	7.2	20
 **6**	 **73**	26	0.6	24
 **7**	 **74**	16	34	31
 **8**	 **75**	20	44	41

Aromatic Amides

Substrates	Products	Mol% of Catalyst	Time (h) at 100% Conversion	Isolated Yield %
 **9**	 **76**	30	72	36
 **12**	 **76**	30	6[a]	[b]
 **10**	 **77**	10	48	62
 **13**	 **77**	10	15[a]	[b]
 **11**	—			

[a] Days

[b] Major product identified and characterised by ^{1}H NMR spectroscopy only

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Chapter 4

Palladium Complexes and the Cyclisation of 4-Pentyn-1-amine

4.1 Transition Metal-Catalysed Hydroamination

4.1.1 Intramolecular Hydroamination

Hydroamination (see Chapter 1) is a highly atom-economical process in which an amine functionality is added to a carbon-carbon double bond or triple bond. There has been a considerable increase in the number of reports of *intra*molecular hydroamination (cyclisation) reactions by metal complexes. Unlike *inter*molecular reactions, *intra*molecular processes are generally more facile and therefore the cyclisation of aliphatic and aromatic aminoolefins and aminoalkynes has received much attention. The nitrogen-containing compounds which are formed as products are frequently valuable components of biologically important compounds. For example, the total synthesis of the anti-fungal agent (+)-Preussin incorporated an intramolecular cyclisation step, producing a pyrroline ring (Figure 4.1).[1, 2*]

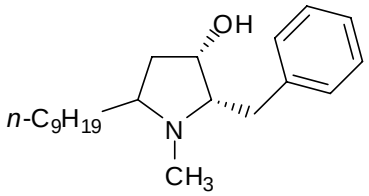


Figure 4.1

There are a number of thermodynamic and kinetic barriers that hinder the direct hydroamination reaction, these include:[3, 4]

i) An inherent electrostatic repulsion between the nitrogen lone pairs of the approaching amine and the π-bond of the electron-rich unsaturated non-activated carbon-carbon bond resulting in a high activation barrier;

ii) A [2+2] addition of the nitrogen-hydrogen bond to the alkene is unfavourable process due to the large difference in energy between the carbon-carbon π-bond and the nitrogen-hydrogen σ-bond orbitals;

* References begin on page 123.

iii) The reaction entropy is highly negative and the equilibrium is shifted toward the starting material so promotion of the reaction by increasing the temperature is limited.

Uncatalysed hydroamination additions are generally observed only for activated, electron-deficient alkenes. A catalyst is generally incorporated for the hydroamination reaction to overcome the activation barrier. Increasing research effort has led to the development of many catalyst systems, including early transitions metals, lanthanides, actinides and late transition metals.[3] Despite the interest in this research area there is still no general and simple method to apply this transformation, particular at an industrial scale to the wide variety of alkynes and amines.[5]

This chapter is concerned primarily with the intramolecular hydroamination of a model compound, 4-pentyn-1-amine (**21**), which cyclises to 2-methyl-1-pyrroline (**22**), a cyclic imine. 4-Pentyn-1-amine (**21**) is a common substrate used to test catalytic activity for the hydroamination of alkynes.

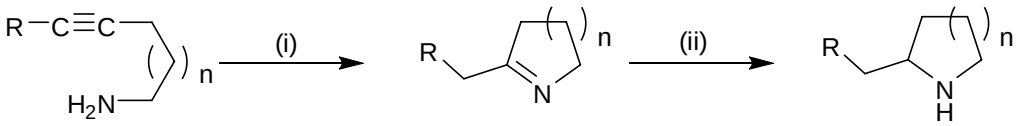
Early Transition Metal Catalysts

Early transition metal complexes, in particular titanium[6] and zirconium[4, 7] complexes have proved successful for the hydroamination of aminoalkynes, as well as aminoalkenes and aminoallenes. Early work focussed on complexes with cyclopentadienyl (Cp) ligands, while more recent work has shown that non-metallocene complexes are very efficient catalysts for hydroamination.[8, 9]

Livinghouse *et al.*[1] utilised $CpTiMe_2Cl$ and $CpTiCl_3$ as catalyst precursors for a variety of intramolecular hydroamination reactions leading to the construction of dihydropyrrole and tetrahydropyridine rings and functionalised tetrahydropyrrole rings. All compounds were synthesised under mild reaction conditions and in high yields (88-94%). 4-Pentyn-1-amine (**21**) was completely converted to the cyclic imine in less than 1 minute using 10 mol% of $CpTiCl_3$ at 25 °C in

benzene-d_6. The total synthesis of anti-fungal agent (+)-Preussin (Figure 4.1) and the indolizidine alkaloid (±)-Monomorine (Chapter 1, Figure 1.1) utilised $CpTiMe_2Cl$ and $CpTiCl_3$ respectively, producing their target compounds.[5]

Doye *et al*.[10] have reported the intramolecular hydroamination/ cyclisation of a range of aminoalkynes in the presence of 5 mol% Cp_2TiMe_2 complex. The reactions proceed at 100-110 °C to give 5- and 6-membered cyclic imines within 4-6 h. The cyclic imines are subsequently reduced with an organic reagent (zinc-modified sodium cyanoborohydride) to afford the cyclic amines in good to excellent yields (62-94%), however the reaction conditions were relatively harsh (Scheme 4.1).[5]



Scheme 4.1 (i) 5 mol% Cp_2TiMe_2, toluene, 110 °C, 6 h; (ii) sodium cyanoborohydride, zinc chloride in diethyl ether, tetrahydrofuran, 25 °C, 20 h.

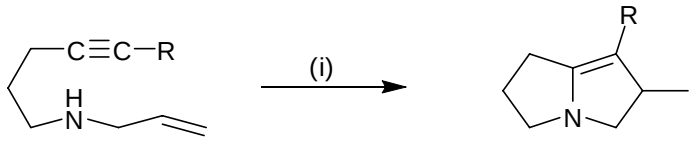
Advantages associated with the use of early transition metal complexes are that the metal precursors are relative inexpensive (compared to palladium, rhodium and iridium) and non-toxic (compared to mercury and thallium). A major disadvantage associated with early transition metal complexes is that they tend to be highly oxophilic, thus they are susceptible to decomposition by air and moisture and therefore have low functional group tolerance.[5]

Lanthanide and Actinide Catalysts

The activity of organolanthanide and organoactinide complexes as catalysts for hydroamination and activation of unsaturated organic compounds is believed to be due to high electrophilicity of the *f*-element centres, relatively large ionic radii, an absence of oxidative addition and reductive elimination mechanistic steps and high kinetic lability.[5]

Organolanthanide and organoactinide[11] complexes exhibit relatively high catalytic efficiency for intramolecular hydroamination reactions and tandem carbon-nitrogen and carbon-carbon bond forming reactions.[12] Organolanthanide complexes of the general type Cp^*_2LnR, (where $Cp^* = \eta^5\text{-}Me_5C_5$; R = H, $CH(TMS)_2$, $N(TMS)_2$, $\eta^3\text{-}C_3H_5$; Ln = lanthanum, niobium, samarium, yttrium, lutetium) catalysed the regiospecific cyclisation of terminal aminoolefin compounds to 5-, 6- and 7-membered nitrogen-containing heterocycles. The scope of reactions included primary and secondary amines as well as aromatic amino olefins.[13] Marks *et al*.[14] reported the catalytic hydroamination of a series of aminoalkynes with an organolanthanide complex of the general type $Cp^*_2LnCH(TMS)_2$. Under rigorously anaerobic reaction conditions, these complexes were shown to be highly efficient, with full conversion at room temperature and good turnover frequency (>7600).

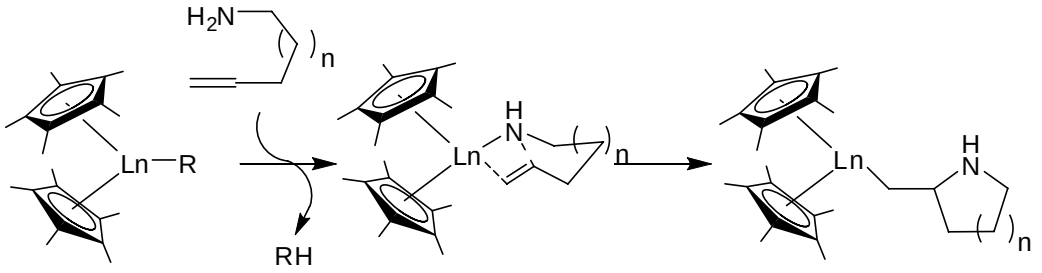
Further to this work, the intramolecular hydroamination of aminoallenes[15] was also successfully catalysed by a similar organolanthanide system, as was the tandem *intra-* and *inter*molecular carbon-nitrogen and carbon-carbon bond-forming reactions of aminoalkynes, aminoalkenynes (Scheme 4.2) and amidoalkynes which gave direct access to various nitrogen-containing heterocyles including pyrrolizidine, indolizidine, pyrrole and pyrazine.[5, 16]



Scheme 4.2 (i) $Cp^*_2SmCH(TMS)_2$ (5 mol%) (R = Ph, H).

The reaction mechanism for hydroamination catalysed by lanthanide complexes involves activation of the amine functionality by protonolysis to form a lanthanide-amido complex followed by insertion of the tethered olefin into the metal-nitrogen bond (Scheme 4.3).[17] The reaction mechanism was explored for reactivity trends including an influence based on ionic radius of the metal and

ancillary ligand effects.[13]



Scheme 4.3 Mechanism for organolanthanide catalysed hydroamination of amino olefins.

Roesky *et al.*[18] have reported the synthesis of Cp-free lanthanide complexes for the hydroamination of aminoalkynes. The complexes mono- and *bis*-[*N*-isopropyl-2-(isopropylamino)-troponiminato]yttrium amide incorporating one or two anionic nitrogen based bidentate ligands, $(Pr^{i}_{2}ATI)_{n}Y[(N(TMS)_2]_2$ (n = 1, 2) (Figure 4.2), proved to be active for the cyclisation of a terminal and internal alkyne (4-pentyn-1-amine (**21**) and 5-phenyl-4-pentyn-1-amine respectively) with both the reactions proceeding regiospecifically to completion.

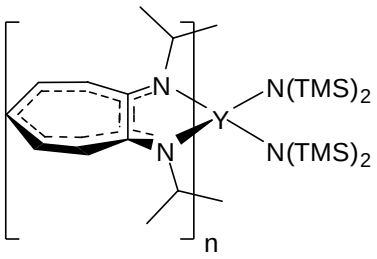


Figure 4.2 $(Pr^{i}_{2}ATI)_{n}Y[(N(TMS)_2]_2$ (n = 1, 2).

The reactivity observed for these complexes were significantly lower in comparison to the yttrium Cp^*_2 complexes with turnover frequency of less than 2 h^{-1} for the catalysts.[5]

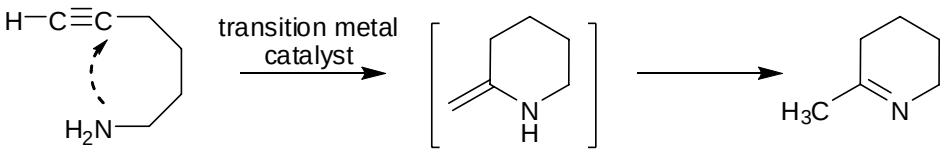
Advantages for using organolanthanides for the hydroamination of aminoalkynes include the high reactivity and the fact that both primary and secondary amines and internal and terminal alkynes are tolerated under the reaction conditions.

Unfortunately these complexes are highly air and moisture sensitive and this means that their synthesis is difficult and restricts their general use as catalysts.

Late Transition Metal Catalysts

In contrast to early transition metals and lanthanide complexes, late transition metal complexes have the advantage of having lower oxophilicity, so they are less susceptible to decomposition by air and moisture and are more compatible with substrates with oxygen-containing substituents. Thus late transition metals have been prepared and used more routinely in synthetic organic laboratories.[6]

Müller *et al*. investigated the application of late transition metal catalysts for the intramolecular hydroamination reactions. The cyclisation of 5-hexyn-1-amine (**81**) was tested with 1 mol% of the metal catalyst which generated the intermediate 2-methylene-piperidone (**82**). Subsequent tautomerism led to 6-methyl-2, 3, 4, 5-tetrahydropyridine (**83**) as the isolated product (Scheme 4.4).



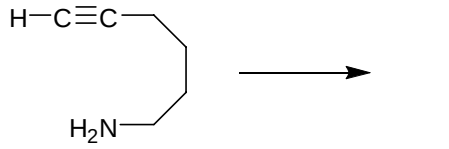
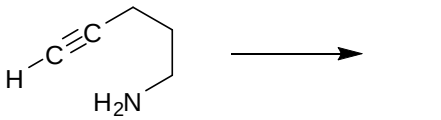
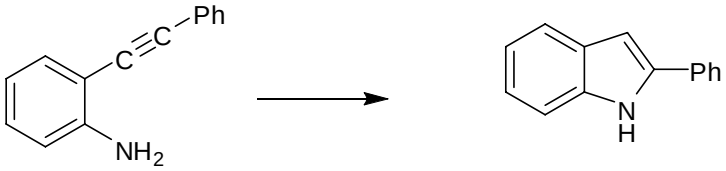
81 **82** **83**

Scheme 4.4

Potential catalyst complexes were assessed from the transition metal series of groups 9-12. The best yields for the cyclic product 6-methyl-2, 3, 4, 5-tetrahydropyridine (**83**) were achieved with copper, palladium and rhodium complexes and from this study a number of mechanistic observations were made. The valence state of the metals was shown to be important as only one oxidation state for each metal was catalytically active. All of the catalytically active complexes contained metals with either electronic configuration d^8 or d^{10}. It was also concluded that the mechanism of intramolecular hydroamination probably involved activation of the alkyne by the metal prior to nucleophilic

attack of the amine.[19, 20] However, a mechanism proceeding *via* an oxidative addition of the amine to the metal centre could not be excluded for ruthenium, rhodium and nickel where activity was only evident for those complexes in the lower oxidation state.

Table 4.1 The regioselective catalysed cyclisation of aminoalkynes with 1 mol% of $[Pd(triphos)](CF_3SO_3)_2$ in toluene, 111° C.

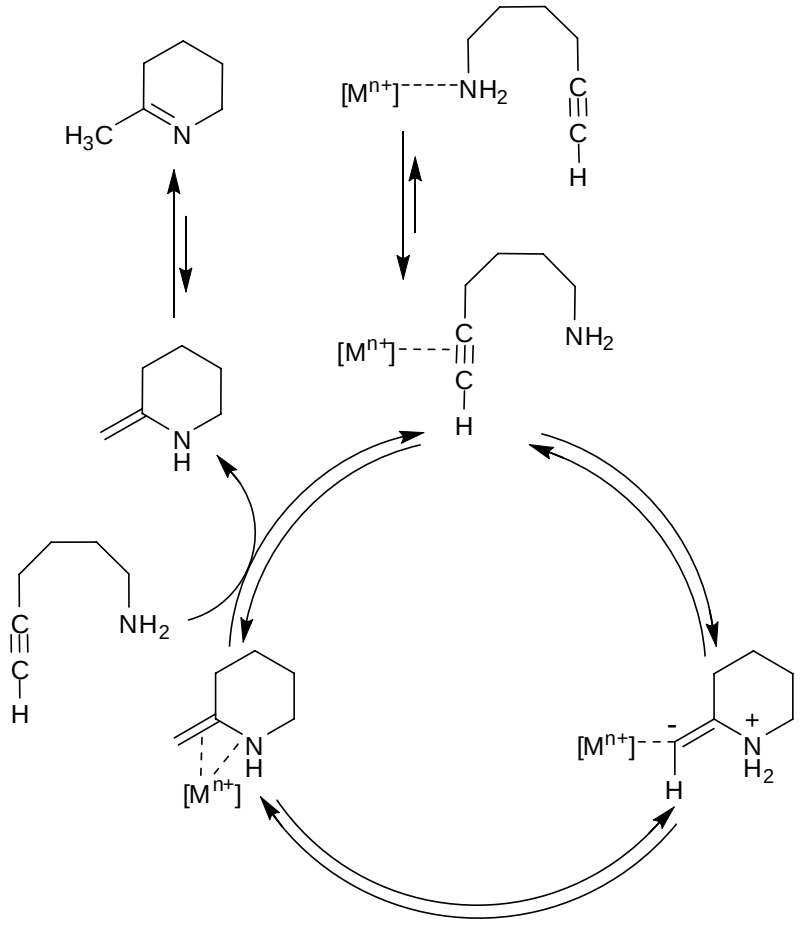
Cyclisation Reaction	* N_t (h^{-1})
	103
	≥1686
	117

***** Turnover number = moles of product produced per mole of catalyst used per hour.

Specific complexes $[Cu(CH_3CN)_4][PF_6]$, $[Zn(CF_3SO_3)_2]$ and $[Pd(triphos)](CF_3SO_3)_2$ (triphos = *bis*(diphenylphosphinoethyl)phenylphosphine) were chosen for further investigation of their catalytic properties with a number of representative substrates (Table 4.1). Optimisation of the reaction conditions revealed that the catalyst performance was influenced by the ligands associated with the metal centre, solvent, temperature and the choice of counterion.[21] Addition of acid to the $[Pd(triphos)](CF_3SO_3)_2$ complex was found to greatly increase the reaction rate.[22]

Müller *et al.*[21, 23] proposed a common mechanism for all late transition metal hydroamination reactions. Detailed mechanistic and kinetic investigations were carried out using $[Pd(triphos)](CF_3SO_3)_2$ and $[Zn(CF_3SO_3)_2]$ and from these

studies a mechanism was proposed (Scheme 4.5).



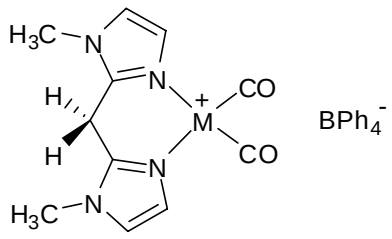
Scheme 4.5 Proposed mechanism for metal-catalysed cyclisation of 5-hexyn-1-amine (**81**) (M^{n+} = [Pd(triphos)]$(CF_3SO_3)_2$).

The first step in the proposed mechanism involves the coordination of the substrate to the metal *via* the amine group. The complex then isomerises so that the alkyne group becomes coordinated to the metal centre. Nucleophilic attack of the nitrogen lone pair on the coordinated alkyne gives a 2-ammonio alken-1-yl complex. Finally, protolytic cleavage of the metal-carbon bond leads to the release of the enamine which tautomerises to the more stable cyclic imine product.

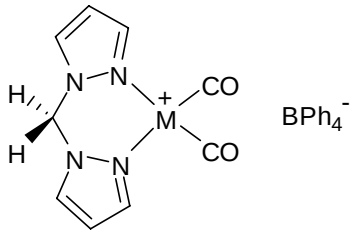
There are very few reports of rhodium and iridium complexes for the catalysis of

intramolecular hydroamination of aminoalkynes. However, in the study by Müller[20] for the cyclisation of 5-hexyn-1-amine (**81**) complexes of both rhodium(I) and iridium(I) were investigated. The rhodium complex [Rh(COD)(DIPAMP)][BF_4] (COD = η^4-1, 5-cyclooctadiene and DIPAMP = 1, 2-*bis*[(*o*-methyl-phenyl)(phenyl)phosphino]ethane) was found to effect the cyclisation in 80% conversion at 111 °C in toluene. However, the iridium complex [Ir(COD)(PCy_3)(py)][PF_6] (Cy = cyclohexyl and py = pyridine) was found to effect the same cyclisation in 42% conversion at 40 °C in dichloromethane. The rhodium(III) complex [Rh(COD)I_2Cl] was also tested and no conversion of **81** was observed.

Burling *et al.*[24] have investigated the rhodium(I) and iridium(I) cationic complexes with bidentate nitrogen donor ligands as catalysts for the intramolecular hydroamination of aliphatic and aromatic aminoalkynes. The four main catalysts utilised in these studies were of the type [M(bim)$(CO)_2$][BPh_4] (M = Rh(I) (**1**) and Ir(I) (**84**)) (bim = *bis*(*N*-methylimidazol-2-yl)methane) and [M(bpm)$(CO)_2$][BPh_4] (M = Rh(I) (**85**) and Ir(I) (**86**)) (bpm = *bis*(1-pyrazolyl)methane). These catalysts were investigated for the hydroamination of 4-pentyn-1-amine (**21**). [Ir(bpm)$(CO)_2$][BPh_4] was found to be the most active for this transformation (Table 4.2).



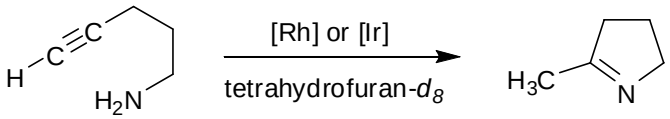
M = Rh(I) (**1**), Ir(I) (**84**)



M = Rh(I) (**85**), Ir(I) (**86**)

The rhodium(I) and iridium(I) complexes were tested as hydroamination catalysts for a series of different aminoalkynes with both terminal and internal alkyne bonds. 5-Membered heterocycles were formed in preference to 6-membered heterocycles which were possible but less facile, while the formation of

7-membered heterocycles was not possible.[25]



21 **22**

Table 4.2 Comparison of the rhodium(I) and iridium(I) (1.5 mol%) catalysed cyclisation of 4-pentyn-1-amine (**21**) to 2-methyl-1-pyrroline (**22**) in tetrahydrofuran-d_8 at 60 °C.

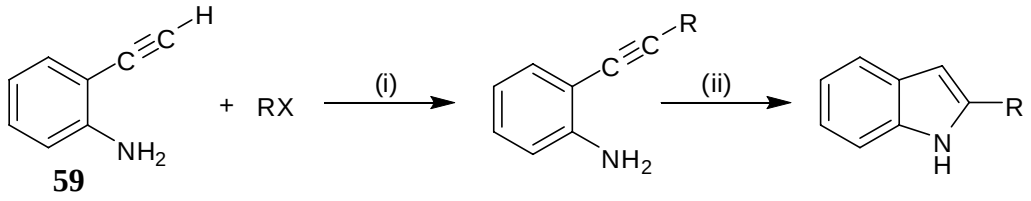
Complex	Time (h)	Conversion (%)	* N_t (h^{-1})
$[Rh(bim)(CO)_2][BPh_4]$ (**1**)	14	100	17
$[Ir(bim)(CO)_2][BPh_4]$ (**84**)	24	92	5
$[Rh(bpm)(CO)_2][BPh_4]$ (**85**)	12	90	20
$[Ir(bpm)(CO)_2][BPh_4]$ (**86**)	2.2	100	50

***** Turnover number = moles of product produced per mole of catalyst used per hour; typically calculated at time of 50% conversion.

It was also found that catalysis was less effective when the co-ligand was changed from carbon monoxide to triphenylphosphine, and when the counterion was changed from tetraphenylborate to tetrafluoroborate or hexafluorophosphate. The rate of catalysis was significantly increased when the reaction was conducted at reflux in tetrahydrofuran-d_8.[24, 25]

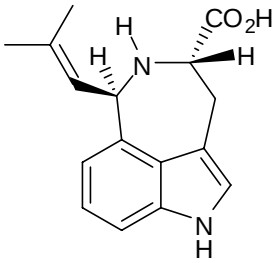
A considerable number of palladium complexes for hydroamination of aminoalkynes have been developed. Palladium is now the most utilised of the late transition metals for hydroamination.[5, 26-34] Cacchi *et al*. have contributed numerous reports for the synthesis of indoles by palladium-catalysed cyclisation of aromatic aminoalkynes to 2-substituted indoles.[35-39] A wide range of substituted alkynylaniline substrates were readily prepared through palladium-catalysed coupling reactions of aryl and vinyl triflates or halides with 2-ethynylaniline (**59**). A one-pot procedure for the conversion of **59** to 2-substituted indoles was developed, producing 2-alkynyl- or 2-(arylethynyl)aniline *in situ* followed by the palladium-catalysed cyclisation

(Scheme 4.6).



Scheme 4.6 (i) tetrakis(triphenylphosphine)palladium(0), copper(I) iodide, diethylamine, room temperature, 3-5 h, R = vinyl, aryl, heteroaryl and X = OTf, Br, I; (ii) palladium(II) chloride, acetonitrile, 70 °C, 2.5-9 h.

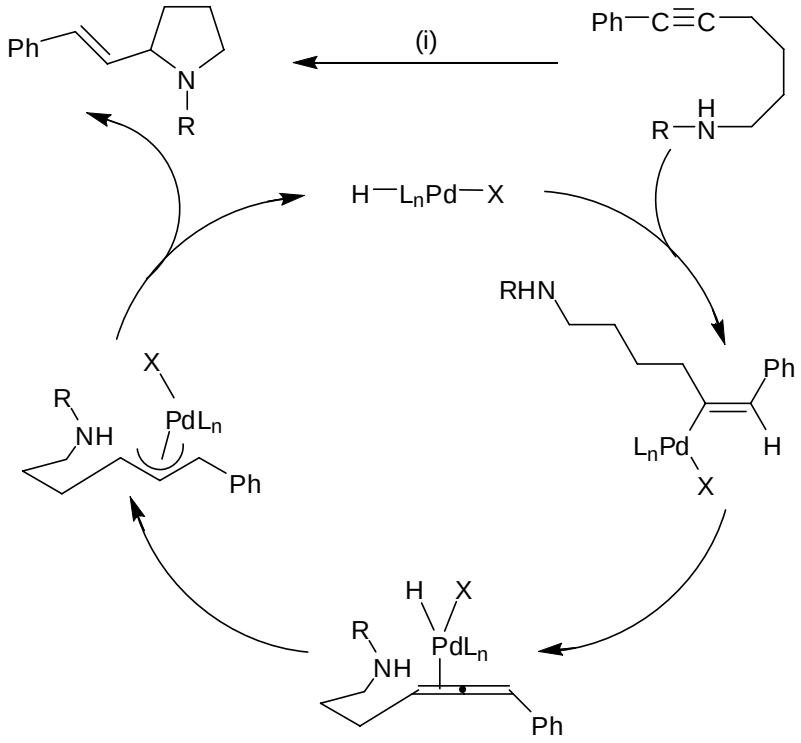
Aminoolefin substrates often react with palladium complexes to form stable olefin-amine-palladium complexes which inhibit the hydroamination reaction due to the strong coordination of the amine group. This limitation was overcome by converting the amines to their tosamide or benzamide derivatives prior to reaction with the catalyst.[40] The resulting tosylates were readily reduced and deprotected to the cyclic amines. This procedure was utilised in a key step for the total synthesis of an ergot alkaloid (±)-Claviciptic acid.[41]



Claviciptic acid

Yamamoto *et al.*[42] reported the synthesis of 5- and 6-membered nitrogen heterocycles using a combination of palladium(0) and benzoic acid as catalyst for the hydroamination of *N*-protected aminoalkynes (Scheme 4.7).

The presence of benzoic acid was essential for the reaction to occur, better yields were obtained for substrates bearing electon-donting groups on the aromatic ring.[5] A plausible catalytic cycle for this transformation is illustrated in Scheme 4.7.[6]

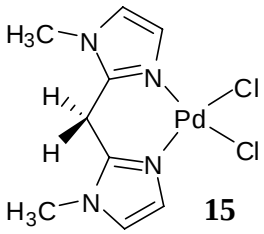


Scheme 4.7 (i) tetrakis(triphenylphosphine)palladium(0) 5 mol%, benzoic acid 10 mol%, dioxane, 100 °C (R = protecting group X = $PhCO_2$).[43]

The palladium-catalysed intramolecular reaction of alkynes has proved very versatile, with the synthesis of a range of nitrogen heterocycles reported, including lactams, oxazolidinones, imidazolidinones[44] and pyrroles.[45]

4.2 Structure of Target Metal Complexes

Based on the previous success of cationic rhodium and iridium complexes for homogeneously catalysed reactions, a series of analogous palladium complexes were targeted with some modification to the co-ligands and metal, however retaining the bidentate nitrogen donor ligand, bim (**2**). This work targeted complexes of the type $[Pd(bim)(L)_2]$ (where bim = *bis*(*N*-methylimidazol-2-yl)methane, L = co-ligand) for the metal-catalysed hydroamination reaction.



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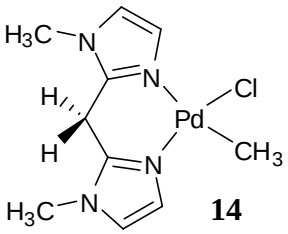

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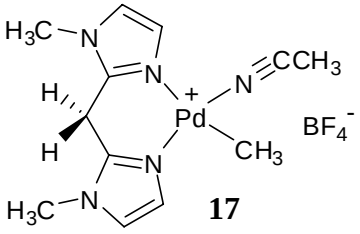

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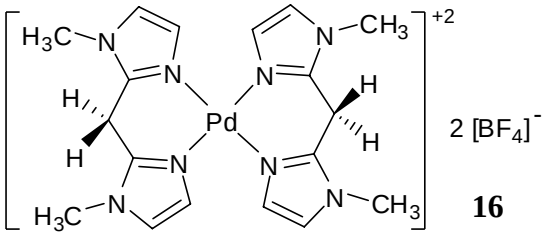


16

The nitrogen donor ligand selected was a neutral bidentate ligand containing two imidazole moieties. Metal complexes containing this ligand have been established as effective catalysts for a limited number of transformations. Bidentate imidazole ligands have been studied as part of metal (rhodium and iridium) complex systems for the particular purpose of acting as catalysts for hydroamination chemistry.

The target metal complexes in this work were neutral and cationic palladium(II) complexes, typically incorporating one bim ligand and two co-ligands.

4.2.1 Imidazole ligands

Poly(1-imidazolyl)alkanes are a class of heterocyclic nitrogen donor ligands. Imidazole (**87**) is a 5-membered nitrogen-containing heterocycle with nitrogen atoms at the 1 and 3 positions (Figure 4.3). In the case of imidazole, a single carbon atom (C2) separates the nitrogen atoms in the heterocyclic ring. It is through this carbon atom that the methylene bridge typically joins the two or three heterocyclic rings to form *bis*(imidazolyl)methane or *tris*(imidazolyl) ligands respectively. To prevent further coodination of the imidazole residue to a second metal in the formation of a complex, one nitrogen atom in each ring is typically protected by a methyl group (**88**).

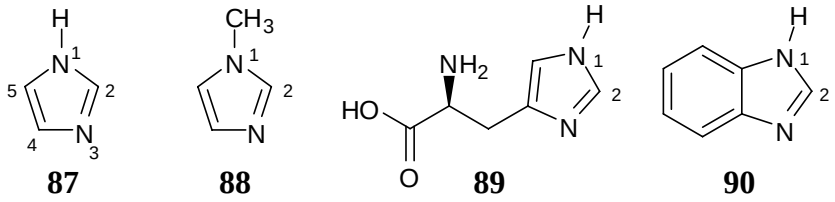


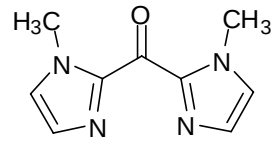
Figure 4.3 Atom numbering scheme for imidazole (**87**), *N*-methylimidazole (**88**), histidine (**89**) and benzimidazole (**90**).

Early studies of imidazole-based ligands focused on the role of imidazole as an analogue of the amino acid histidine (**89**). Imidazole (**87**) and benzimidazole (**90**) ligands have been used to model the binding sites of enzymes to provide insight into the nature of enzymatic catalytic cycles. For example, the zinc binding sites of carbonic anhydrase, alkaline phosphatase, carboxypeptidase and thermolysin have been modelled by using imidazole ligands.[46, 47]

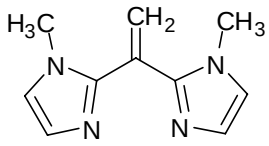
Canty and co-workers have contributed significantly to the chemistry of transition metal complexes containing *bis*- and *tris*(2-imidazolyl) ligands. Many bidentate and tridentate ligands were found to form neutral organometallic complexes with palladium[48], platinum[48], mercury[49] and ruthenium.[50]

A series of methyl(iodo)palladium(II) [PdIMe(N-N)] and dimethylpalladium(II)

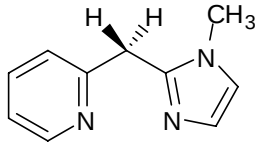
[$PdMe_2$(N-N)] complexes were formed where (N-N) were the *bis*(*N*-methylimidazolyl) ligands $(mim)_2C{=}O$ (bik = *bis*(*N*-methylimidazol-2-yl)ketone; **91**), $(mim)_2CH_2$ (bim; **2**), $(mim)_2C{=}CH_2$ (**92**), $(mim)_2CHCH_3$ (**93**) or mixed bidentate ligands, containing one imidazole and one pyridine residue: (py)(mim)C=O (**94**), (py)(mim)CH_2 (**95**) (Figure 4.4).[51] Methylpalladium(II) complexes containing tridentate ligands, including mixed ligands with pyridines and pyrazoles have also been developed.[52]



91



92



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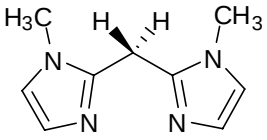

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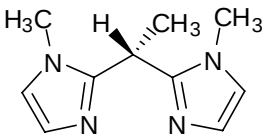

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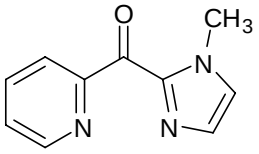
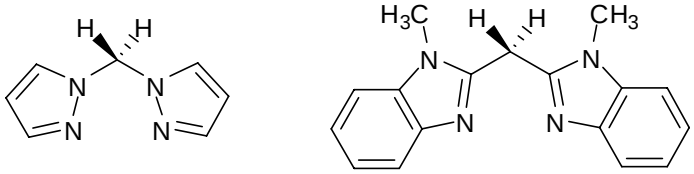


94

Figure 4.4

Palladium(II) and chromium(III) complexes have recently been synthesised with various substituted bidentate imidazole ligands and imidazole-based chelate ligands respectively. These complexes have been explored for catalytic activity in the Heck reaction, carbon monoxide/ ethylene co-polymerisation and oligomerisation of ethylene.[53, 54]

Several ruthenium(II) complexes of *bis*(imidazolyl) ligands and ruthenium(II) and osmium(II) complexes of *tris*(imidazolyl) ligands are known.[55, 56] Rhodium(I) and iridium(I) complexes incorporating bidentate heterocyclic nitrogen donor ligands bik (Scheme 4.4, **91**), bim (Scheme 4.4, **2**), *bis*(1-pyrazolyl)methane (bpm; (**96**) and *bis*(*N*-methylbenzimidazol-2-yl)methane (mbnzim; (**97**)) have been reported (Figure 4.5).[24, 57, 58]

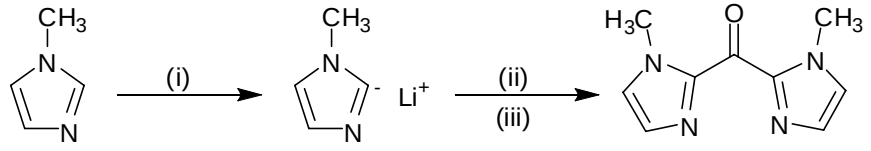


96 **97**

Figure 4.5

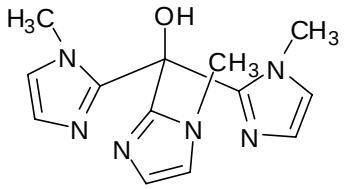
4.2.2 Synthesis of *Bis*(*N*-methylimidazol-2-yl)methane (bim; 2)

The general synthetic procedure was based on that reported in the literature.[25, 51, 59] Deprotonation of *N*-methylimidazole (**88**) at the C2 position of the imidazole ring with *n*-butyllithium at low temperature afforded the corresponding lithium salt (Scheme 4.8). Addition of diethyl carbonate at -78 °C gave the ketone bridged ligand **91** after quenching with solid carbon dioxide at -78 °C. Failure to quench the reaction at low temperature led to further addition of the imidazole to the ketone to form, amongst other products, the tridentate alcohol *tris*(*N*-methylimidazol-2-yl)methanol (**100**).



88 **91**

Scheme 4.8 (i) *n*-butyllithuim (1.6M), tetrahydrofuran, -78 °C; (ii) diethyl carbonate; (iii) carbon dioxide, -78 °C.



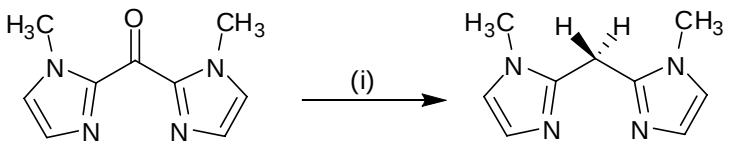
100

Isolation of compound **91** was achieved after continuous extraction overnight of the aqueous layer with chloroform. Recrystallisation of the crude product from

dichloromethane/ hexane afforded *bis*(*N*-methylimidazole)ketone (**91**) as a creamy/ white crystalline solid which exhibited identical spectroscopic properties to those reported previously.[51]

Preparation of *bis*(*N*-methylimidazol-2-yl)methane (**2**) was based on the methods reported by Byers and Canty,[51] Elgafi *et al*.[55] and Burling *et al*.[25] which employed a Wolff-Kishner reduction using hydrazine and base in a sealed bomb reactor.

Ligand **91** was reduced to the methylene-bridged ligand (**2**) using a large excess of hydrazine monohydrate and sodium hydroxide. The reagents were placed in a stainless steel bomb and sealed. The reaction vessel was heated in an oil bath at 150 °C for 24 h (Scheme 4.9). The crude residue in the vessel was worked up and recrystallised to give *bis*(*N*-methylimidazol-2-yl)methane (**2**) as a creamy coloured solid in 62% yield, the product exhibiting identical spectroscopic properties to those reported previously.[51]



91 **2**

Scheme 4.9 (i) hydrazine monohydrate, sodium hydroxide, 24 h, 150 °C.

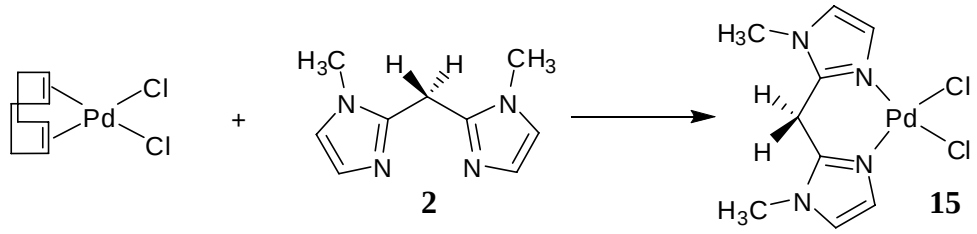
4.3 Synthesis of Palladium(II) Complexes with a Nitrogen Donor Ligand

Previously reported palladium complexes and two new palladium complexes were synthesised and characterised during the course of this work. The palladium complexes consisted of both neutral and cationic analogues.

The target palladium complexes in this work were four coordinate complexes incorporating the bim (**2**) nitrogen donor ligand and two co-ligands. Complexes were of the form [Pd(bim)L_2] and [Pd(bim)L L'] (where L and L' = methyl, chloride, acetonitrile). A direct method to the target complexes enabled the use of the common palladium precursors dichloro(η^4-1, 5-cyclooctadiene)palladium(II) ([Pd(COD)Cl_2]) and (η^4-1, 5-cyclooctadiene)chloromethylpalladium(II) ([Pd(COD)(Cl)(CH_3)]). [Pd(COD)Cl_2] was prepared as previously reported by Drew and Doyle[60] by the addition of COD to a solution of palladium(II) chloride in concentrated hydrochloric acid to afford [Pd(COD)Cl_2] as a fine yellow powder in good yield. [Pd(COD)(Cl)(CH_3)] was prepared according to Rülke *et al.*[61] whereby tetramethyltin was added to a suspension of [Pd(COD)Cl_2] in dichloromethane at room temperature and stirred for seven days to afford [Pd(COD)(Cl)(CH_3)] as a white solid also in good yield.

4.3.1 [Pd(bim)Cl_2] (15)

The neutral complex [Pd(bim)Cl_2] (**15**) was prepared by the addition of bim (**2**) (1 equivalent) as a methanol solution to a methanol solution of [Pd(COD)Cl_2] under an atmosphere of nitrogen at room temperature and the resulting reaction mixture was stirred overnight (Scheme 4.10). After work up, [Pd(bim)Cl_2] (**15**) was obtained in high yield (85%). The COD ligand from the palladium precursor was selectively displaced by the nitrogen donor ligand to produce the target four-coordinate complex. Complex **15** was significantly more stable in air and solution than the corresponding rhodium(I) complex (**1**).



Scheme 4.10

Coordination of bim (**2**) to the palladium metal centre was evident by the downfield shift of the resonances in the ^{1}H NMR spectrum, particularly of the imidazole H4 and H5 protons compared to the free ligand. Complex **15** was also characterised by $^{13}C\{^{1}H\}$ NMR, where all the chemical shifts were consistent with the structure proposed. The composition of the compound was confirmed by microanalysis, high resolution and positive electrospray mass spectrometry.

4.3.2 X-ray Crystal Structure of [Pd(bim)Cl$_2$] (15)

An orange prismatic crystal, suitable for X-ray crystallographic analysis, was isolated from a solution of **15** in dimethyl-d_6 sulfoxide. The asymmetric unit contains one palladium(II) atom, one bim (**2**) ligand, two chloride anions and a dimethyl sulfoxide solvent molecule. ORTEP plots of the crystal structure with the atom numbering system are given in Figure 4.6. Selected bond lengths and angles are listed in Table 4.3. Crystallographic data is presented in Appendix 1.

The geometry is essentially square planar about the palladium centre comprising of one chelating bim (**2**) ligand and two chloride co-ligands. The slight deviation from the ideal square planar geometry, results from the small restraint placed on the bim (**2**) ligand by the flexible methylene bridge. This is shown by the placement of the methylene carbon atom C(4) 0.244 Å from the plane containing Cl(1)-Cl(2)-N(1)-N(2) atoms in the crystal structure.

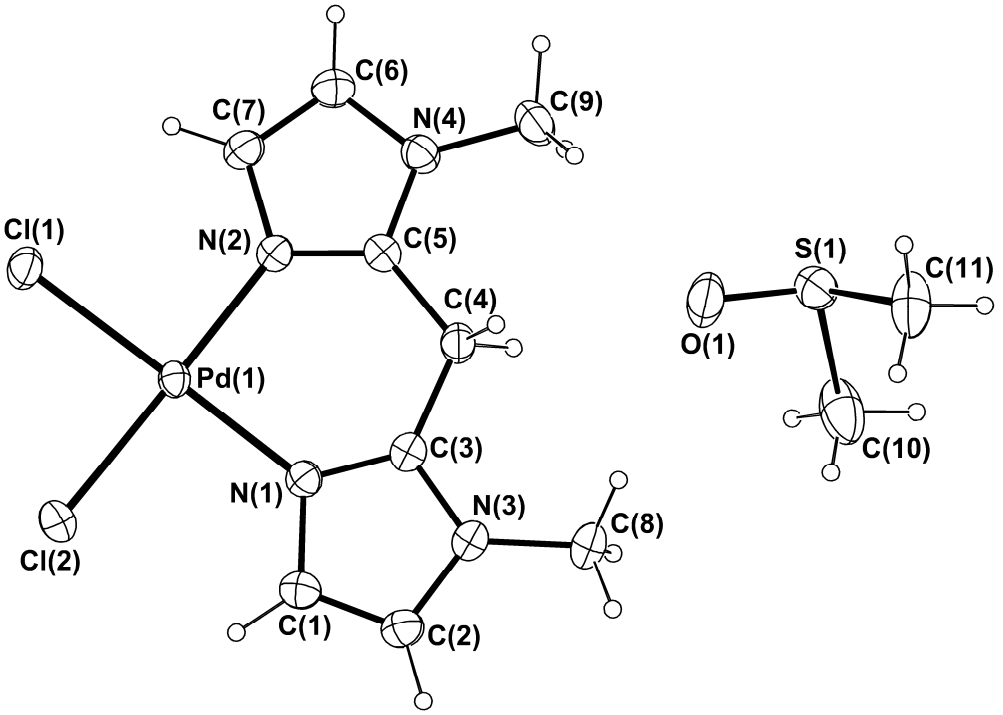


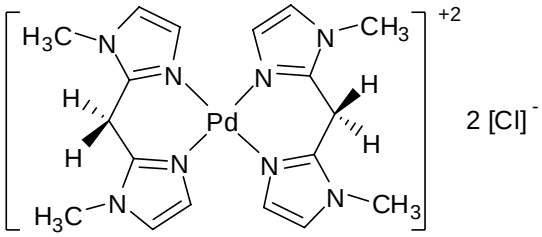
Figure 4.6 ORTEP plot and crystal structure numbering of [Pd(bim)Cl_2] (**15**) and the dimethyl sulfoxide solvate.

Table 4.3 Selected bond distances and bond angles of [Pd(bim)Cl_2] (**15**)			
[Pd(bim)Cl_2] (15)			
Atoms	**Bond Distance (Å)**	**Atoms**	**Bond Angles (°)**
Pd(1)-N(2)	2.0255(13)	N(2)-Pd(1)-N(1)	89.74(5)
Pd(1)-N(1)	2.0284(13)	N(1)-Pd(1)-Cl(2)	91.09(4)
Pd(1)-Cl(2)	2.3011(5)	N(2)-Pd(1)-Cl(1)	91.43(4)
Pd(1)-Cl(1)	2.3042(4)	Cl(2)-Pd(1)-Cl(1)	87.786(15)

4.3.3 [Pd(bim)$_2$][Cl]$_2$ (98)

An alternative synthesis for [Pd(bim)Cl_2] (**15**) was attempted using the same synthetic method as described above but using dichloromethane in place of methanol. Under these conditions however, a mixture of [Pd(bim)Cl_2] (**15**) and [Pd(bim)$_2$][Cl]$_2$ (**98**) was obtained and the composition of **98** was confirmed by

NMR spectroscopy and high resolution mass spectrometry. The mixture of complexes **15** and **98** was also examined by DOSY (Figure 4.7).



98

Complex **98** was isolated as a solid by counterion exchange. Sodium tetrafluoroborate was added to a solution of **98** in methanol to precipitate $[Pd(bim)_2][BF_4]_2$ (**17**) as an off-white solid in low yield (8.7%). The ^{1}H NMR spectrum and the positive electrospray mass spectrum which showed the presence of the $(M\text{-}BF_4)^+$ ion are consistent with the formulation $[Pd(bim)_2][BF_4]_2$ (**17**). The composition of **17** was confirmed by high resolution mass spectrometry. Complex **17** was insoluble in most organic solvents and attempts to precipitate a crystalline material failed.

4.3.3.1 DOSY

DOSY (*d*iffusion-*o*rdered *s*pectroscop*y*) is an NMR technique which permits the measurement of the rate of diffusion of species in solution.[62-65] This method offers insight into a range of physical molecular properties including size and shape. Prior to the purification and separation of complexes **15** and **98**, an NMR DOSY experiment was undertaken on a mixture consisting of **15** and **98** dissolved in dimethyl-d_6 sulfoxide.

The relative difference in the diffusion of **15** and **98** was evident in the 2D representation of the DOSY spectrum (Figure 4.7). The rate of diffusion of the molecules is represented along the y-axis (on a logarithmic scale) whereas the normal ^{1}H NMR spectrum of the complexes is along the x-axis (in ppm).

The diffusion coefficient of complex **15** was measured at 3.3×10^{-10} m^2s^{-1} (dimethyl-d_6 sulfoxide, 300 K) whereas**,** the diffusion coefficient for complex **98** was measured at 2.9×10^{-10} m^2s^{-1} (dimethyl-d_6 sulfoxide, 300 K) from the F1 projection of the 2D spectrum. These results indicate that the mono-substituted bim complex (**15**) diffuses faster in solution than the *bis*-substituted bim complex (**98**) and in principle one could calculate various secondary molecular parameters such as the effective molecular volume from the diffusion coefficients.

This experiment adds weight to the assignment of **98** as the larger species in solution and is consistent with its assignment as a species with two bidentate ligands.

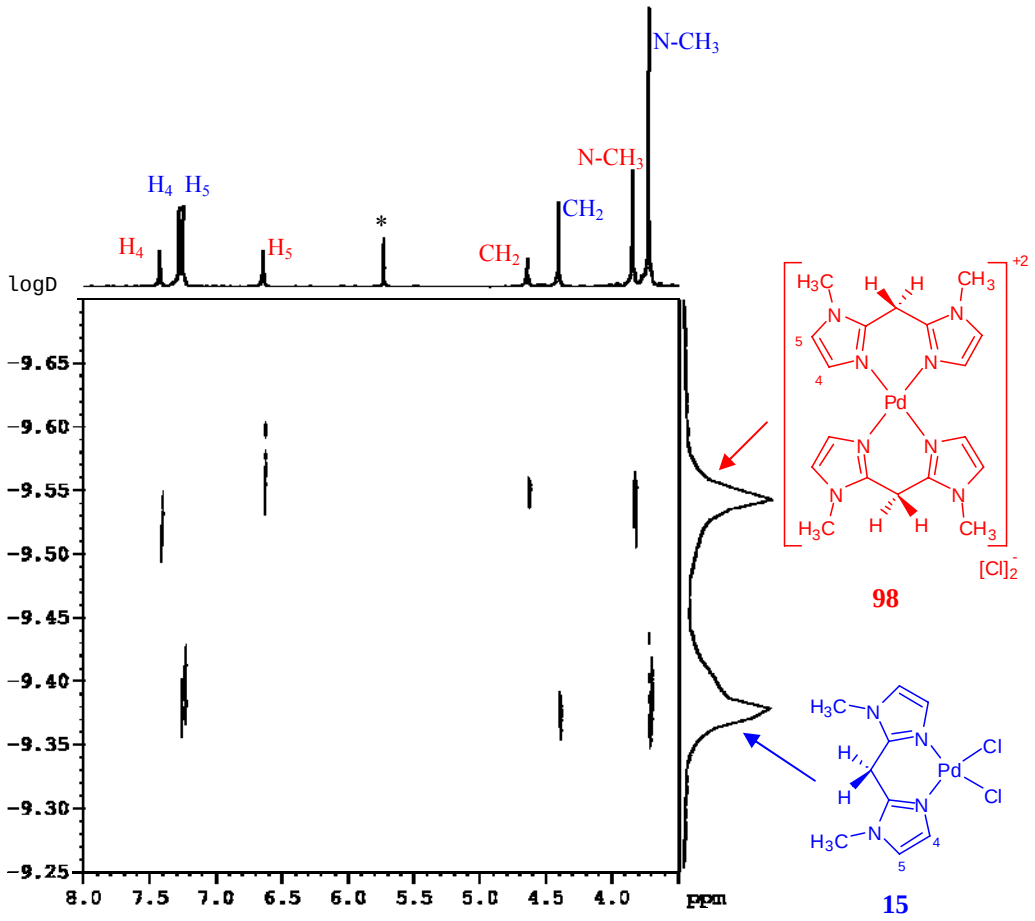
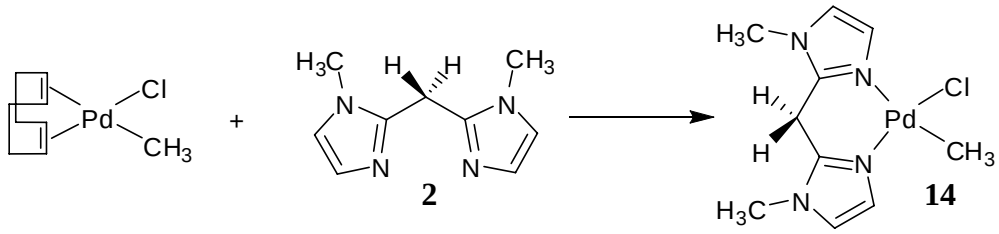


Figure 4.7 DOSY spectrum (400 MHz, dimethyl-d_6 sulfoxide, 300 K) of [Pd(bim)Cl_2] (**15**) and [Pd(bim)$_2$][Cl]$_2$ (**98**) as a mixture (* denotes the solvent residual, dichloromethane).

4.3.4 [Pd(bim)(Cl)(CH_3)] (14)

The complexes reported so far have been in the form of [Pd(bim)L_2] in this section the synthesis of complexes in the form of [Pd(bim)L L'] are reported.

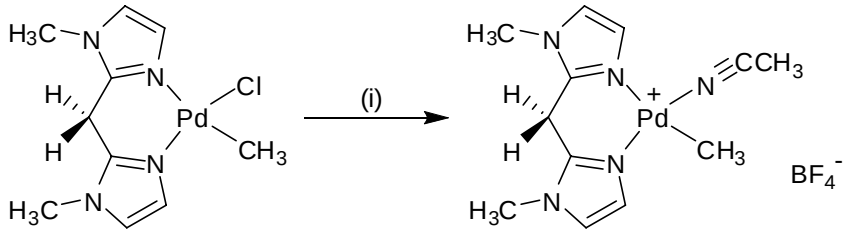
The synthesis of the neutral complex [Pd(bim)(Cl)(CH_3)] (**14**) followed the method previously reported by Cavell and co-workers from the reaction of one equivalent of bim (**2**) with one equivalent of [Pd(COD)(Cl)(CH_3)] in dichloromethane (Scheme 4.11).[53] The resulting precipitate was collected to give **14** in 71% yield as a white solid. The spectroscopic properties of **14** were identical to those reported previously.



Scheme 4.11

4.3.5 [Pd(bim)(CH_3)($NCCH_3$)][BF_4] (16)

[Pd(bim)(CH_3)($NCCH_3$)][BF_4] (**16**) was prepared by treating [Pd(bim)(Cl)(CH_3)] (**14**) with silver tetrafluoroborate in acetonitrile: dichloromethane (1:1) (Scheme 4.12) following the literature procedure.[53] Selection of anion was based on the stability of the complex since stability was found to decrease in the order tetrafluoroborate > $B(Ar^F)_4^-$ (Ar^F = 3, 5-$C_6H_3(CF_3)_2$ > tetraphenylborate ions. Complex **16** was isolated as its tetrafluoroborate salt in 70% yield. The spectroscopic properties of **16** were identical to those reported in the literature.[53]



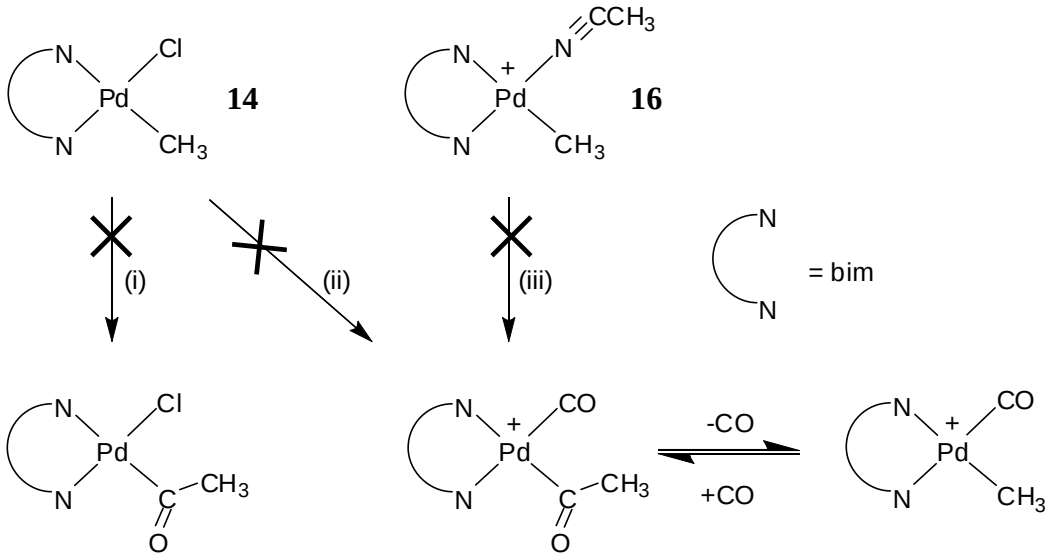
14 **16**

Scheme 4.12 (i) silver tetrafluoroborate, acetonitrile: dichloromethane (1:1), room temperature, 1 h.

4.3.5.1 Attempted Synthesis of $[Pd(bim)(CH_3)CO]^+$

The incorporation of a carbon monoxide co-ligand into a palladium complex was examined for the purpose of constructing an analogue of the rhodium(I) complex (**1**) to make a direct comparison of the catalytic activity of the two species.

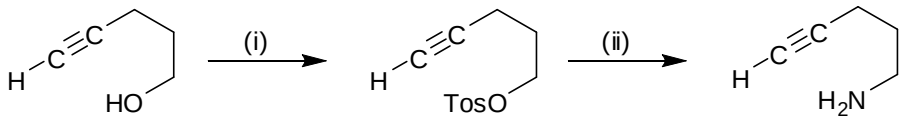
Attempts to synthesise a palladium complex with a carbon monoxide co-ligand followed the two basic approaches reported by Carfagna *et al.*[66] and Guan[67] respectively starting with complexes $[Pd(bim)(Cl)(CH_3)]$ (**14**) and $[Pd(bim)(CH_3)(NCCH_3)][BF_4]$ (**16**). Complexes **14** or **16** were dissolved in dichloromethane previously saturated with carbon monoxide and then suspended at -40 °C under a carbon monoxide atmosphere. NMR-scale experiments were performed to determine whether the carbon monoxide molecule was interacting with complexes **14** or **16** in solution. All three reactions undertaken (Scheme 4.13, (i), (ii) and (iii)) displayed no evidence for any coordinated carbonyl resonances in the ^{13}C NMR spectra. The product mixtures were complex and showed no evidence for the expected product or starting material.



Scheme 4.13 (i) dichloromethane, carbon monoxide, -20 °C; (ii) dichloromethane, $B(Ar^F)_4^-$ or silver tetrafluoroborate, carbon monoxide, -40 °C; (iii) dichloromethane, carbon monoxide, -40 °C.

4.4 Palladium Catalysed Cyclisation of 4-Pentyn-1-amine (21) to 2-Methyl-1-Pyrroline (22)

The potential of $[Pd(bim)Cl_2]$ (**15**), $[Pd(bim)(Cl)(CH_3)]$ (**14**), $[Pd(bim)(CH_3)(NCCH_3)][BF_4]$ (**16**), $[Pd(bim)_2][BF_4]_2$ (**17**), $[Pd(COD)Cl_2]$ (**18**), $[Pd(COD)(Cl)(CH_3)]$ (**19**) and $[Pd(COD)Cl]_2[BF_4]_2$ (**20**) as catalysts for the intramolecular hydroamination of 4-pentyn-1-amine (**21**) was investigated. Substrate **21** was chosen as a simple example for intramolecular hydroamination, representing the cyclisation of a terminal alkyne. Based on the results of this initial study, the most reactive palladium bim complex was then selected and investigated further to establish the scope of possible hydroamination reactions.



21

Scheme 4.14 (i) tosyl chloride, potassium hydroxide (ii) ammonia (liquid).

The synthesis of 4-pentyn-1-amine (**21**) was achieved by treating 4-pentyn-1-ol with tosyl chloride to form the tosylate, followed by nucleophilic substitution of the tosylate in liquid ammonia (Scheme 4.14).[68] 4-Pentyl-1-ol was reacted with a slight excess of tosyl chloride in the presence of potassium hydroxide and after workup 4-pentynyl tosylate was obtained as a pale yellow oil in good yield (90%). 4-Pentynyl tosylate was treated with a large excess of liquid ammonia in a pressure tube. This procedure resulted in **21** as a colourless oil in good purity and in 30% yield. The product is very volatile and the low yield reflects loss of some product during the purification procedure.

4.4.1 General Procedure for the Metal-Catalysed Cyclisation of 4-Pentyn-1-amine (21)

All palladium complexes prepared were reacted with 4-pentyn-1-amine (**21**) under identical conditions, and their rates of conversion compared to that of rhodium(I) catalyst (**1**), where a reactivity profile has already been established.[57] The rhodium catalyst (**1**) was also tested in the solvent mixture used for the palladium complexes (methanol-d_3 and methanol) for direct comparison.

The standard catalytic reaction conditions employed for the cyclisation of **21** were as follows: 4-pentyn-1-amine (**21**) was added to approximately 1.5 mol% of the metal complex in methanol-d_3 (0.1 mL) and methanol (0.4 mL) in an NMR tube. The reactions were performed under an atmosphere of nitrogen. The reaction mixture was then heated at 60 °C in the NMR spectrometer. In some cases, the metal complexes were only partially soluble in the solvent prior to heating. Complexes commonly dissolved during the reaction or upon addition of **21** to the complex in solution at room temperature.

The conversion of starting material to product was determined by integration of the product resonances relative to the substrate resonances in the ^{1}H NMR spectrum (Figure 4.8). 100% conversion was taken to be the time where no remaining substrate peaks (<1%) were evident in the ^{1}H NMR spectrum. The turnover rate (N_t (h^{-1})), typically calculated at the point of 50% conversion of the substrate to product, is defined as the number of moles of product/ mole of catalyst/ hour. This number provides a measure on which to gauge the reactivity of each complex.

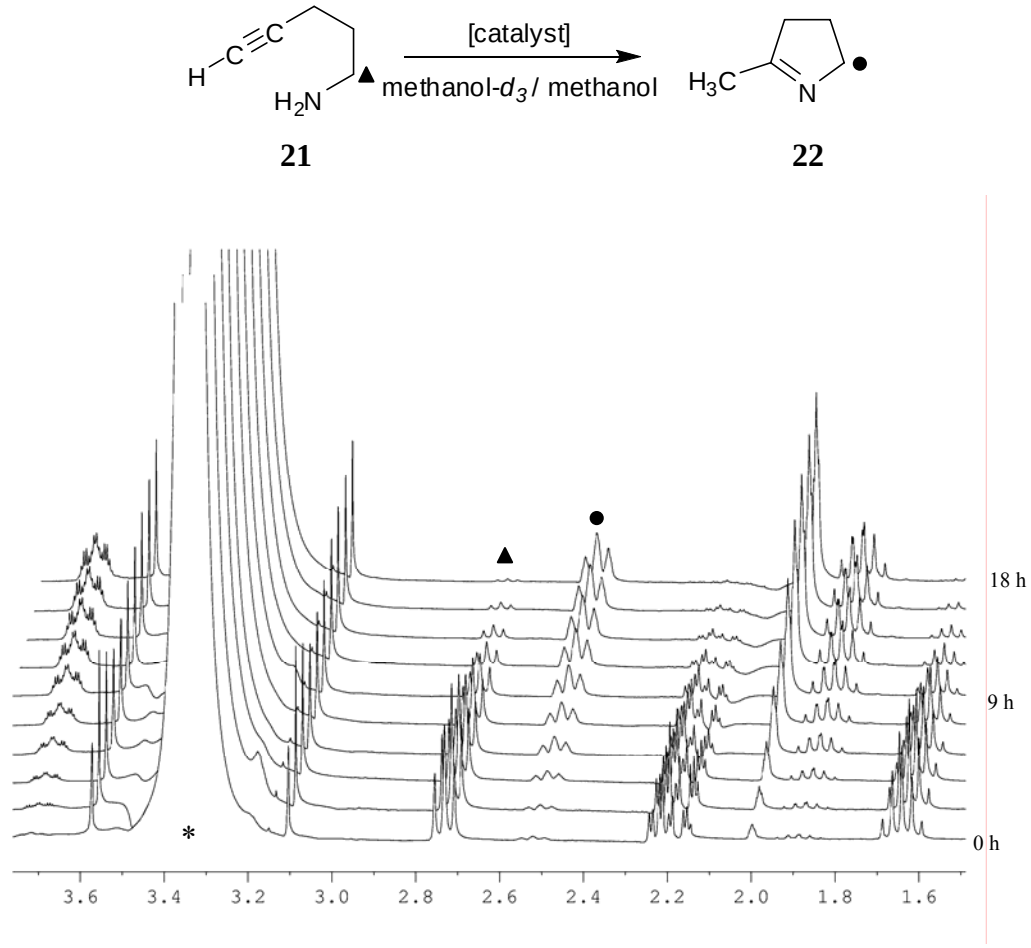
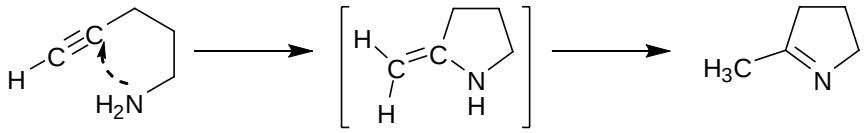


Figure 4.8 Selected portion of ^{1}H NMR spectra following the progress of the reaction, indicating the substrate (▲) and product (●) resonance typically integrated to calculate the percentage conversion (* denotes solvent, methanol).

Methanol was selected as the reaction solvent as it gave 100% conversion to product after 24 h (significantly lower conversions were observed in tetrahydrofuran, dimethyl sulfoxide and acetonitrile). Partially deuteriated methanol-d_3 was used in preference to methanol-d_4 since deuterium exchange with protons on the cyclised products was observed by ^{1}H NMR when methanol-d_4 was used as a solvent. Acetone was not an appropriate solvent for the reaction due to the competing condensation (imine formation) of the aliphatic amine with the

solvent.

All metal complexes tested catalytically cyclised the substrate regioselectively to form the 5-membered heterocycle 2-methyl-1-pyrroline (**22**), with varying degrees of reactivity. Ring-closure occurred by *exo* addition of N-H to the acetylene, initially forming a cyclic enamine intermediate (**99**) which rapidly tautomerised to the more stable imine product (Scheme 4.15). No 6-membered heterocyclic products resulting from the alternative *endo*-cyclisation pathway were observed.



21 **99** **22**

Scheme 4.15

4.5 Catalysis by Palladium(II) Complexes

The palladium complexes [Pd(bim)Cl_2] (**15**), [Pd(bim)(Cl)(CH_3)] (**14**), [Pd(bim)(CH_3)($NCCH_3$)][BF_4] (**16**), [Pd(bim)$_2$][BF_4]$_2$ (**17**), [Pd(COD)Cl_2] (**18**), [Pd(COD)(Cl)(CH_3)] (**19**) and [Pd(COD)Cl]$_2$[BF_4]$_2$ (**20**) (Figure 4.9) were tested as catalysts for the hydroamination reaction using 4-pentyn-1-amine (**21**) as a substrate. Hydroamination kinetic data is presented in Appendix 2.

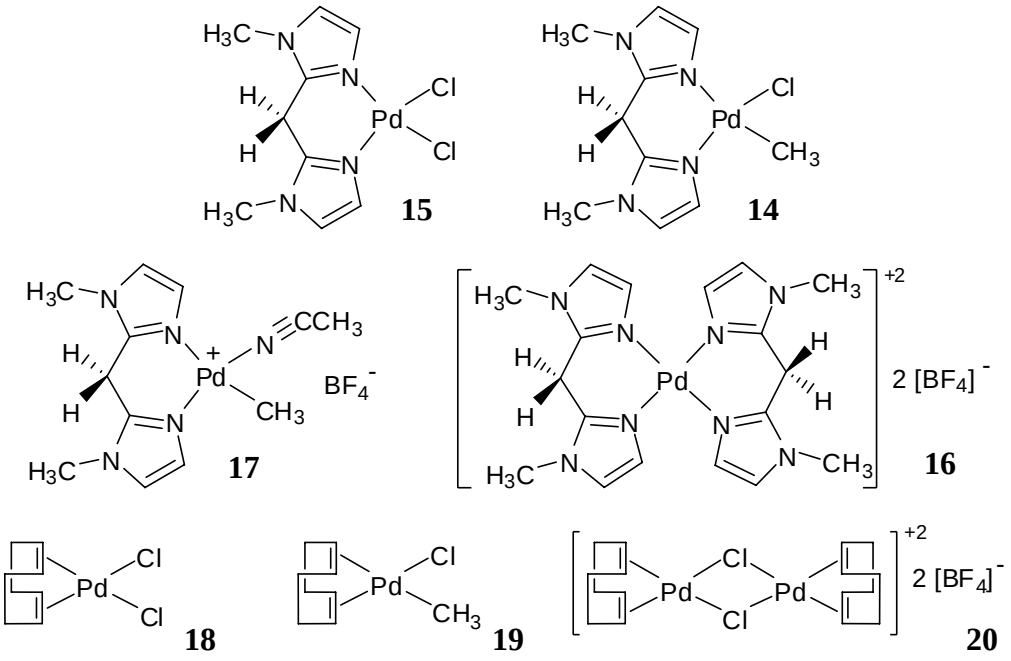
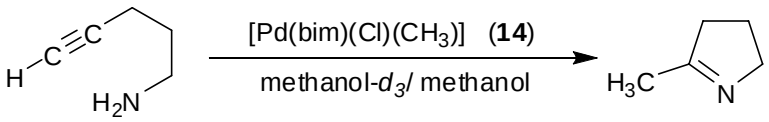


Figure 4.9 The palladium(II) complexes utilised as catalysts for the cyclisation of 4-pentyn-1-amine (**21**) to 2-methyl-1-pyrroline (**22**). The neutral palladium complexes (**15** and **14**) contain different co-ligands; cationic palladium complex (**17** and **16**) were stabilised by tetrafluoroborate counterions. COD donor ligands with different co-ligands were also investigated as catalysts (**18**, **19** and **20**).

4.5.1 Cyclisation Catalysed by [Pd(bim)(Cl)(CH_3)] (14)

4-Pentyn-1-amine (**21**) was added to a suspension of [Pd(bim)(Cl)(CH_3)] (**14**) in methanol-d_3 at -78 °C (Scheme 4.16). The mixture was warmed to room temperature resulting in a clear colourless solution. The mixture was immediately

heated to 60 °C within the probe of an NMR spectrometer and ^{1}H NMR spectra were recorded at regular intervals to monitor conversion of the substrate to the cyclic product. Reacting 1.5 mol% of [Pd(bim)(Cl)(CH_3)] (**14**) with 4-pentyn-1-amine (**21**) produced complete conversion of the substrate to 2-methyl-1-pyrroline (**22**) in 18 h.



21 **22**

Scheme 4.16

Interaction of the substrate with the complex was immediate, as indicated by the complex dissolving in solution upon contact with the substrate. The reaction profile in Figure 4.10 illustrates the percentage of substrate converted to product with time. With 1.5 mol% of catalyst at 60 °C, the graph demonstrates how the reaction proceeds rapidly in the first instance, with almost 50% conversion to product after 1.1 h, corresponding to 31 turnovers per hour. The reaction soon slows, probably as a result of the loss of active catalytic species.

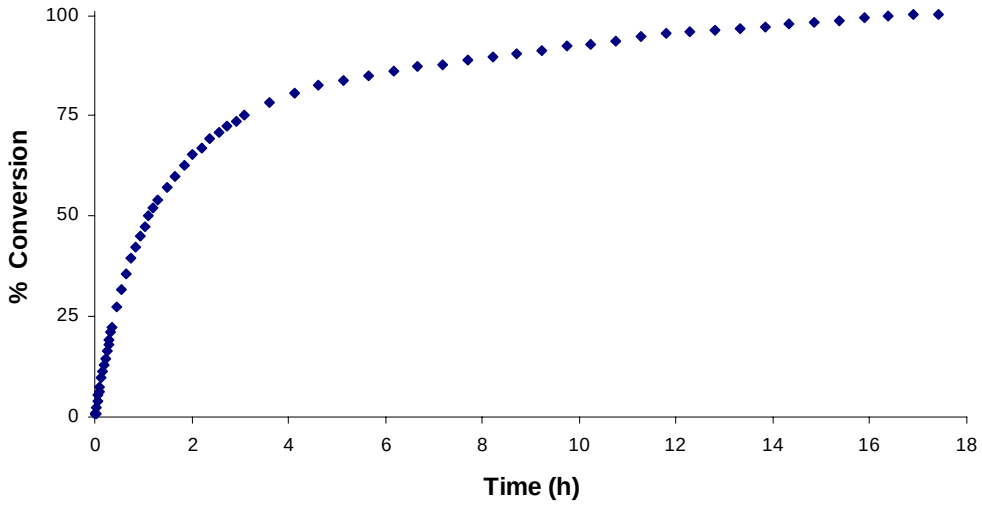


Figure 4.10 Reaction profile of the [Pd(bim)(Cl)(CH_3)] (**14**) catalysed cyclisation of 4-pentyn-1-amine (**21**) to 2-methyl-1-pyrroline (**22**) with 1.5 mol% of catalyst at 60 °C in methanol-d_3.

The lifetime of the catalyst was tested by adding a second aliquot of the substrate to the reaction mixture containing the catalyst and 2-methyl-1-pyrroline (**22**) and monitoring the continued progress by ^{1}H NMR spectroscopy (Figure 4.11). The decrease in catalytic turnover (9 h^{-1}) as the concentration of the product increases is possibly due to the decomposition of the complex in solution or by inhibition of the active species by the presence of an increasing amount of product. The product, 2-methyl-1-pyrroline (**22**) may act as a nitrogen donor ligand itself and may actively compete with the substrate for binding sites at the metal centre.[24]

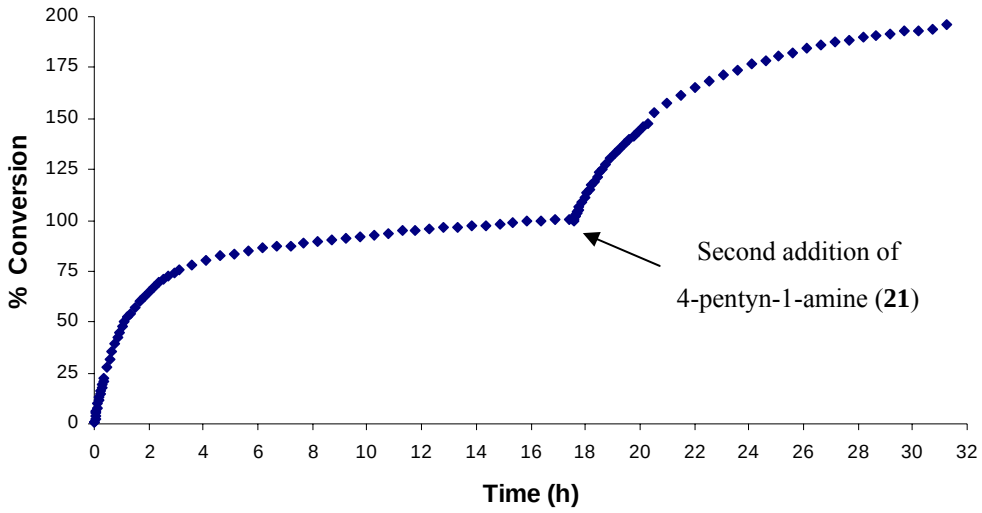


Figure 4.11 Reaction profile of the [Pd(bim)(Cl)(CH_3)] (**14**) (1.5 mol%, methanol-d_3, 60 °C) catalysed cyclisation of 4-pentyn-1-amine (**21**) with the addition of a second aliquot of substrate to the reaction mixture at approximately 18 h.

4.5.2 Cyclisation Catalysed by [Pd(bim)Cl_2] (15), [Pd(bim)(CH_3)($NCCH_3$)][BF_4] (16) and [Pd(bim)$_2$][BF_4]$_2$ (17)

Reactions of the complexes [Pd(bim)Cl_2] (**15**), [Pd(bim)(CH_3)($NCCH_3$)][BF_4] (**16**) and [Pd(bim)$_2$][BF_4]$_2$ (**17**) with 4-pentyn-1-amine (**21**) resulted in the successful cyclisation of the substrate regioselectively to 2-methyl-1-pyrroline (**22**) in all cases. The rates of reaction, represented by the turnover numbers and the conversion times were not significantly different for any of the complexes (**15**,

16 and **17**) in comparison to complex **14** (Table 4.4). The overall reactivity of each catalyst was moderately lower, although similar exponential reaction profiles were produced for each complex (Figure 4.12). Each of the three complexes demonstrate an initial period of relatively rapid cyclisation which slowed considerably after 30 min, the effect was most evident in the reaction catalysed by $[Pd(bim)(CH_3)(NCCH_3)][BF_4]$ (**16**).

The reaction of $[Pd(bim)Cl_2]$ (**15**) and $[Pd(bim)_2][BF_4]_2$ (**17**) with 4-pentyn-1-amine (**21**) afforded 2-methyl-1-pyrroline (**22**) as the single product with 83% and 76% conversion after 18 h respectively, corresponding to 16 and 6 turnovers per hour respectively. Full conversion to product was achieved within 24 h. Slightly lower conversion and turnover rate ($4\ h^{-1}$) was produced in the reaction catalysed by $[Pd(bim)(CH_3)(NCCH_3)][BF_4]$ (**16**). Initially, the reaction catalysed by **16** was rapid, reaching 25% conversion within 17 min, however the rate of the reaction was dramatically reduced as the reaction progressed with only 58% conversion after 18 h (Figure 4.12). A decrease in activity associated with complex **16** was probably due to stronger catalytic inhibition by the increased presence of product, 2-methyl-1-pyrroline (**22**). As the pyrroline product of the cyclised reaction contains a nitrogen atom with a lone pair of electrons, the product could possibly behave as a nitrogen donor ligand competing with the substrate for binding sites at the metal centre. Alternatively, 2-methyl-1-pyrroline (**22**) may form a stable adduct with the metal complex and therefore reduce the amount of active catalyst available to continue the reaction.[24]

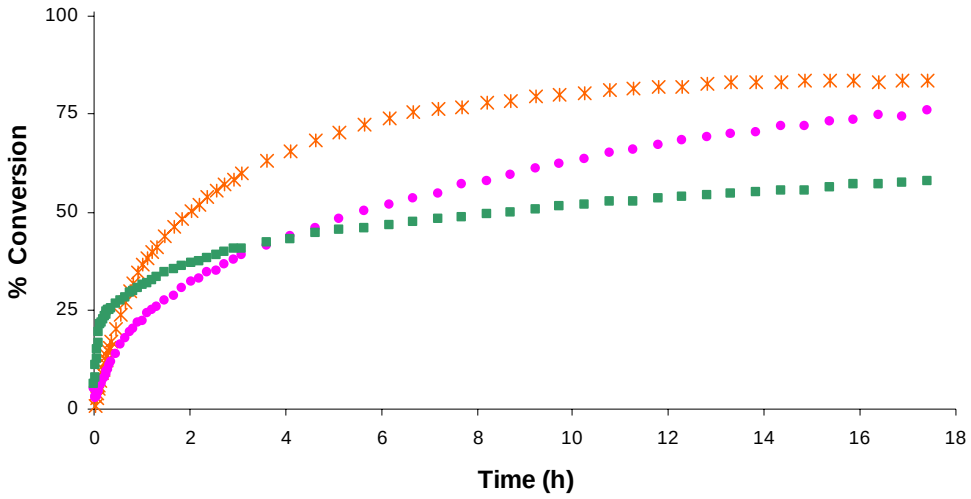


Figure 4.12 Reaction profile of the cyclisation of 4-pentyn-1-amine (**21**) to 2-methyl-1-pyrroline (**22**) catalysed by [Pd(bim)Cl_2] (**15**) (*), [Pd(bim)(CH_3)($NCCH_3$)][BF4] (**16**) (■) and [Pd(bim)$_2$][BF_4]$_2$ (**17**) (•).

4.5.3 Cyclisation Catalysed by [Rh(bim)$(CO)_2$][BPh_4] (1)

The influence of solvent on the reactivity of the rhodium(I) complex (**1**) was investigated with tetrahydrofuran-d_8 and methanol-d_3/ methanol. Reaction of the rhodium(I) complex (**1**) under different solvent conditions with 4-pentyn-1-amine resulted in the successful cyclisation of the substrate in both cases. The rate of reaction, represented by the turnover number and conversion after 18 h (Table 4.4) was significantly different under different solvent conditions. The overall reactivity of each reaction was moderately low and similar exponential reaction profiles were produced for each reaction (Figure 4.13).

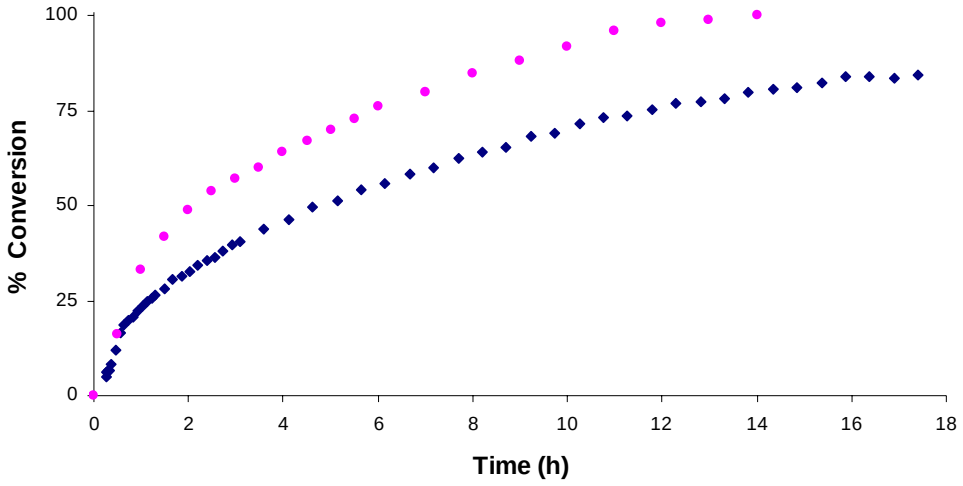


Figure 4.13 Reaction profile of the cyclisation of 4-pentyn-1-amine (**21**) to 2-methyl-1-pyrroline (**22**) catalysed by rhodium(I) complex (**1**) at 60 °C in tetrahydrofuran-d_8[57] (●) and at 60 °C in methanol-d_3 and methanol (◆).

The reaction of the rhodium(I) complex (**1**) in tetrahydrofuran-d_8 with 4-pentyn-1-amine (**21**) afforded 2-methyl-1-pyrroline (**22**) as the single product with 100% conversion in 14 h, corresponding to 17 turnovers per hour.[57] The reaction of **1** in methanol-d_3 and methanol also afforded 2-methyl-1-pyrroline (**22**) as the single product but only produced 84% conversion after 18 h and 100% conversion after 24 h, corresponding to 7 turnovers per hour. It should be noted that **1**, in methanol-d_3 and methanol, was initially partially soluble in the reaction solvent. The lack of solubility could have contributed to an initial barrier or induction period, however the complex was fully dissolved after heating with the substrate.

4.5.4 Cyclisation Catalysed by $[Pd(COD)Cl_2]$ (18), $[Pd(COD)(Cl)(CH_3)]$ (19) and $[Pd(COD)Cl]_2[BF_4]_2$ (20)

The palladium COD complexes $[Pd(COD)Cl_2]$ (**18**), $[Pd(COD)(Cl)(CH_3)]$ (**19**) and $[Pd(COD)Cl]_2[BF_4]_2$ (**20**) (Section 4.5) were utilised to develop a standard procedure for the hydroamination of 4-pentyn-1-amine (**21**). The COD complexes were initially tested in order to better understand the catalytic procedure required prior to the use of the palladium bim complexes. The rates of reaction for each catalyst are presented in Table 4.4, with turnover numbers and percentage conversions at specified times. All of the palladium COD complexes were catalytically active and even more efficient than the corresponding palladium bim analogues. The palladium COD complexes produced an exponential rate curve with an initially rapid rate of reaction, which later slowed as the concentration of product increased under standard reaction conditions (1.2-1.5 mol% complex, tetrahydrofuran-d_8, 60 °C).

The reaction of both $[Pd(COD)Cl_2]$ (**18**) and $[Pd(COD)Cl]_2[BF_4]_2$ (**19**) with 4-pentyn-1-amine (**21**) resulted in complete conversion to the cyclic pyrroline product in approximately 9 h. The catalysed reaction using $[Pd(COD)Cl]_2[BF_4]_2$ (**20**) was even more rapid reaching 98% conversion within 3 h, corresponding to 425 turnovers per hour, a superior result when compared to the other rhodium and palladium bim analogues. The improved catalytic activity of the COD complexes over the bim complexes could be due to the greater lability of the COD ligand giving more rapid access to the active catalytic species.

Eaborn *et al.*[69] identified the rapid formation of $[Pd(2\text{-}R\text{-}COT)Cl]_2$ (COT = 1, 3, 5, 7-cyclooctatetraene, R = MeO, $MeCO_2$ or HO) when **20** was treated with methanol, ethanoic acid or water. This type of ligand-based reaction could play an active role in labilising the COD ligand and providing more ready access for the substrate to a vacant palladium coordination site. The chloride-bridge dimer probably provides even better access to a vacant coordination site on palladium.

4.6 Summary of the Synthesis of Palladium Complexes and the Cyclisation of 4-Pentyn-1-amine

Table 4.4 Yields of 2-methyl-1-pyrroline (**22**) obtained from rhodium(I) (**1**) and palladium(II) complexes (**14**-**20**) catalysing the cyclisation of 4-pentyn-1-amine (**21**) in methanol-d_3 and methanol at 60 °C.

Complex	Mol% of Catalyst	Time (h)	% Conversion	* N_t (h^{-1})
$[Rh(bim)(CO)_2][BPh_4]$ (**1**)	1.5	14	100	17[a]
	1.5	18	84	7
$[Pd(bim)(Cl)(CH_3)]$ (**14**)	1.5	18	100	31
$[Pd(bim)Cl_2]$ (**15**)	1.5	18	83	16
		24	100	
$[Pd(bim)(CH_3)(NCCH_3)][BF_4]$ (**16**)	1.4	18	58	4
$[Pd(bim)_2][BF_4]_2$ (**17**)	1.4	18	76	6
		24	100	
$[Pd(COD)Cl_2]$ (**18**)	1.5	9	96	32
$[Pd(COD)(Cl)(CH_3)]$ (**19**)	1.5	9	95	52
$[Pd(COD)Cl]_2[BF_4]_2$ (**20**)	1.3	3	98	425[b]

***** Turnover number = moles of product produced per mole of catalyst used per hour; typically calculated at time of 50% conversion.

[a] Reaction in tetrahydrofuran-d_8.[57]

[b] Reaction in tetrahydrofuran-d_8 and methanol.

Palladium(II) four-coordinate cationic and neutral complexes were readily prepared. The complexes synthesised and characterised included two new palladium complexes $[Pd(bim)Cl_2]$ (**15**) and $[Pd(bim)_2][BF_4]_2$ (**17**) as well as five known palladium complexes $[Pd(bim)(Cl)(CH_3)]$ (**14**), $[Pd(bim)(CH_3)(NCCH_3)][BF_4]$ (**16**). $[Pd(COD)Cl_2]$ (**18**), $[Pd(COD)(Cl)(CH_3)]$ (**19**) and $[Pd(COD)Cl]_2[BF_4]_2$ (**20**). All the palladium complexes investigated were catalytically active for the cyclisation of 4-pentyn-1-amine (**21**) to

2-methyl-1-pyrroline (**22**). The rates of reaction for each neutral and cationic palladium(II) catalyst are presented in Table 4.4 with turnover numbers and percentage conversion at specified times.

When comparing to $[Rh(bim)(CO)_2][BPh_4]$ (**1**) (both entries in Table 4.4), modifications to the metal centre and co-ligands in complexes **15, 16** and **17** did not produce any significant effect on the rate of reaction. However, complex **14** showed a marginal improvement.

On comparing neutral complexes **14** and **19** (with co-ligands L = Cl, CH_3) with complexes **15** and **18** (with co-ligands L = Cl), the methyl ligand appears to cause an improvement in the reaction rate.

Introduction of the COD ligand in complexes **18** and **19** also produced a noticeable improvement over **1** and the palladium bim complexes. In the course of this work, the best catalyst for the cyclisation of 4-pentyn-1-amine (**21**) to 2-methyl-1-pyrroline (**22**) was $[Pd(COD)Cl]_2[BF_4]_2$ (**20**), reaching 98% conversion after only 3 h under standard reaction conditions, corresponding to a turnover rate of 425 moles of product per mole of catalyst per hour.

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Chapter 5

Summary, Conclusions and Suggestions for Further Work

5.1 Summary and Conclusions

The principal aims of this work were:

(i) To more fully examine the potential of the cationic rhodium(I) complex $[Rh(bim)(CO)_2][BPh_4]$ (**1**) as a catalyst for the intramolecular hydroamination of aminoalkynes;

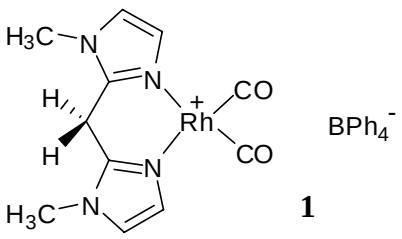
(ii) To examine metal-catalysed intramolecular hydroamination as a more general route to a range of heterocyclic compounds. This meant establishing synthetic approaches to suitably elaborate aminoalkyne precursors which could then be cyclised under appropriate conditions to heterocyclic products;

(iii) To examine the ability of compounds containing the $-NH_2$ group as part of an amide functional group to undergo intramolecular hydroamination;

(iv) To expand the scope of compounds known to be catalysts for alkyne hydroamination to suitable palladium(II) complexes;

All of these aims were addressed and to summarise the overall outcomes of this work are:

i) The rhodium(I) complex (**1**) ($[Rh(bim)(CO)_2][BPh_4]$) successfully fulfilled its potential as a catalyst for the hydroamination of more complex amino- and amidoalkynes substrates. This complex has demonstrated its capacity to intramolecularly cyclise a range of different aminoalkyne substrates.



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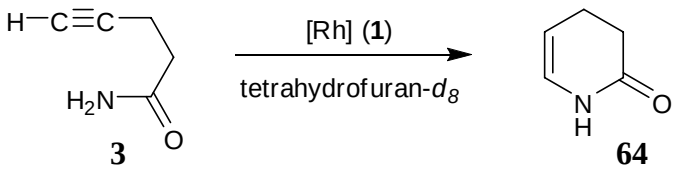
ii) In the course of this work, synthetic routes to a range of substrates containing both the $-NH_2$ and $-C\equiv C-$ functional groups were established. These substrates included aliphatic compounds 4-pentyn-1-amide (**3**) and 5-hexyn-1-amide (**4**) as well as more elaborate aromatic substrates 1, 4-diamino-2, 5-diethynylbenzene (**5**), 1, 4-diamino-2, 5-*bis*(phenylethynyl)benzene (**6**), 2, 3-diamino-1, 4-diethynylbenzene (**7**), 2, 3-diamino-1, 4-*bis*(phenylethynyl)benzene (**8**), 1, 5-*bis*(acetamido)-2, 4-diethynylbenzene (**9**), 1, 5-*bis*(acetamido)-2, 4-*bis*(trimethylsilylethynyl)benzene (**12**), *N*-(acetyl)-2-ethynylbenzylamine (**10**), *N*-(acetyl)-2-(trimethylsilylethynyl)benzylamine (**13**) and *N*-(acetyl)-2-(phenylethynyl)benzylamine (**11**). All of the compounds were synthesised, purified and characterised.

iii) A standard protocol was established for studying intramolecular hydroamination quantitatively. The procedure involved following the catalytic reactions directly by NMR spectroscopy to monitor product formation and the consumption of the starting material.

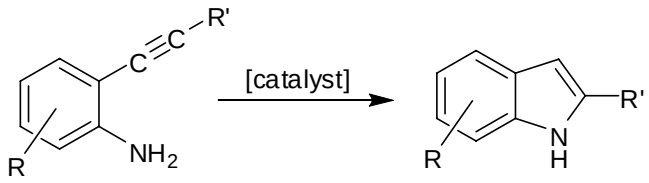
iv) The rhodium(I) complex (**1**) ($[Rh(bim)(CO)_2][BPh_4]$) regioselectively cyclised 4-pentyn-1-amide **3** to produce exclusively the 6-membered ring 3, 4-dihydro-2-pyridone (**64**).



3 **64**

Examples of aromatic amides 1, 5-*bis*(acetamido)-2, 4-diethynylbenzene (**9**) and 1, 5-*bis*(acetamido)-2, 4-*bis*(trimethylsilylethynyl)benzene (**12**) were also catalytically cyclised to 1, 7-diacetyl-pyrrolo[3, 2-*f*]indole (**76**). Not only does this further demonstrate that the $-NH_2$ embedded in an amide functional group readily undergoes the catalytic hydroamination reaction but also that it is possible

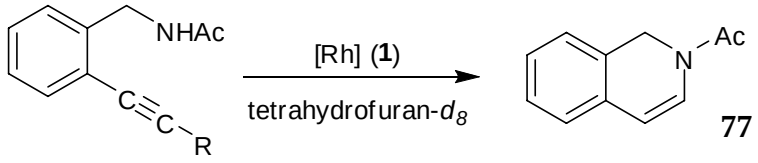
to access *N*-substituted indoles by the intramolecular hydroamination approach.



The most rapid reaction recorded for the hydroamination of an aromatic substrate was the cyclisation of 1, 4-diamino-2, 5-*bis*(phenylethynyl)benzene (**6**) to 1, 5-dihydro-2, 6-diphenyl-pyrrolo[2, 3-*f*]indole (**73**). The reaction was complete in less than 40 minutes and the product was crystallographically characterised.

v) The intramolecular hydroamination reaction of all the aromatic amines studied, including those with terminal and internal acetylenes, was successful with preferential formation of the 5-membered heterocyclic rings in all cases. This approach - the internal cyclisation of 2-alkynyl anilines - provides an excellent general route to the indole skeleton. In general, the required 2-alkynyl anilines can be accessed *via* a Sonogoshira coupling of the appropriate 2-halo-aniline with a terminal acetylene.

vi) In the course of this work, 2-ethynylbenzylamines were also tested as potential precursors to the isoquinoline skeleton. In particularly, substrates *N*-(acetyl)-2-ethynylbenzylamine (**10**) and *N*-(acetyl)-2-(trimethylsilylethynyl)benzylamine (**13**) both catalytically cyclised to *N*-(acetyl)-1, 2-dihydroisoquinoline (**77**).



R = H (**10**), $Si(CH_3)_3$ (**13**)

vii) Synthetic routes to palladium(II) four coordinate, square-planar, cationic and neutral complexes containing the bidentate nitrogen donor ligand, bim (**2**), were established. The complexes $[Pd(bim)Cl_2]$ (**15**), $[Pd(bim)_2][BF_4]_2$ (**17**), $[Pd(bim)(Cl)(CH_3)]$ (**14**), $[Pd(bim)(CH_3)(NCCH_3)][BF_4]$ (**16**) were synthesised and characterised. The use of common palladium precursors $[Pd(COD)Cl_2]$ (**18**) and $[Pd(COD)(Cl)(CH_3)]$ (**19**) enabled a good direct synthetic route to the target palladium bim complexes.

viii) One previously unknown palladium complex $[Pd(bim)Cl_2]$ (**15**) was crystallographically characterised. Complex **15** has essentially square planar geometry at the palladium centre.

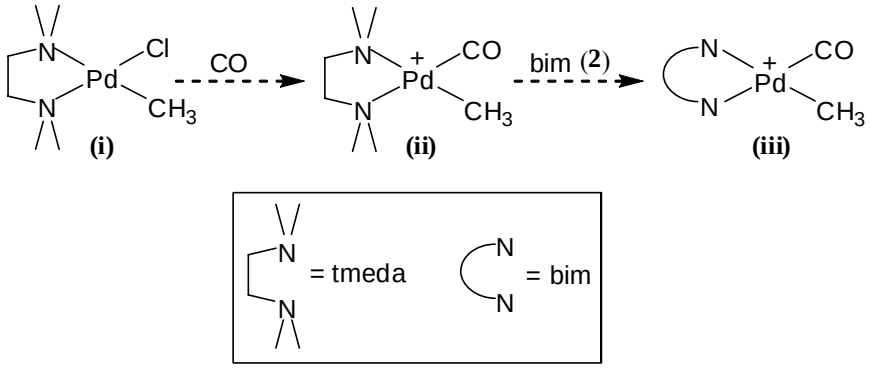
ix) The rate of reaction, and selectivity of the reaction, for the intramolecular hydroamination of 4-pentyn-1-amine (**21**) was not significantly affected by modifications to the metal and co-ligands when comparing $[Rh(bim)(CO)_2][BPh_4]$ (**1**) to complexes $[Pd(bim)Cl_2]$ (**15**), $[Pd(bim)(Cl)(CH_3)]$ (**14**), $[Pd(bim)(CH_3)(NCCH_3)][BF_4]$ (**16**) and $[Pd(bim)_2][BF_4]_2$ (**17**). All of the palladium COD complexes ($[Pd(COD)Cl_2]$ (**18**), $[Pd(COD)(Cl)(CH_3)]$ (**19**) and $[Pd(COD)Cl]_2[BF_4]_2$ (**20**)) were catalytically active and more efficient then the palladium bim analogues. In the course of this work, $[Pd(COD)Cl]_2[BF_4]_2$ (**20**) recorded the highest turnover number of 425 h^{-1} for the conversion of 4-pentyn-1-amine (**21**) to 2-methyl-1-pyrroline (**22**).

5.2 Suggestions for Further Work

The work in this thesis clearly established the reactivity of the palladium complexes towards catalysed hydroamination reactions, however there are still a number of areas where further work would more conclusively establish reaction trends and lead to potential improvements in catalytic activity.

i) In the course of this work, it was not possible to establish routes to access the palladium(II) complexes of the type (iii) (Scheme 5.1). From our previous

work on rhodium(I) complexes, cationic complexes with carbon monoxide ligands provide good catalytic activity for hydroamination. A palladium complex of the type $[Pd(bim)(CH_3)(CO)]^+$ could be accessed by the following sequence (Scheme 5.1).

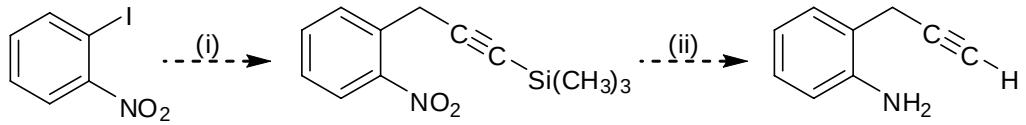


Scheme 0.1

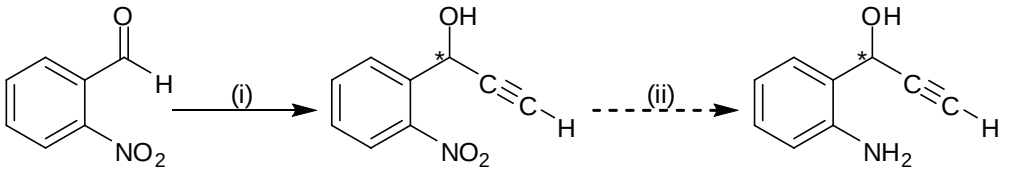
Complex (**i**) is a known compound and was prepared by Boersma *et al.*[1*] Complex (**i**) could undergo a reaction with carbon monoxide following similar procedures reported by Carfagna *et al.*[2] and Guan[3] to form the carbonyl complex. Finally ligand exchange from tmeda (*N, N, N', N'*-tetramethylethanediamine) to bim (**2**) ligand could give the desired product (**iii**).

ii) The catalysed formation of molecules containing the quinoline nucleus warrants a more complete investigation. The success achieved in cyclising *N*-(acetyl)-2-ethynylbenzylamine (**10**) to *N*-(acetyl)-1, 2-dihydroisoquinoline (**77**) demonstrates great potential for expanding the scope of the intramolecular hydroamination reaction to more readily access the quinoline and isoquinoline skeletons. For isoquinolines, access to the appropriate propargyl anilines needs further development. Schemes 5.2 and 5.3 illustrate potential reaction pathways for the target 2-(prop-2-ynyl)benzamine substrates.

[*] References begin on page 135.



Scheme 0.2 (i) magnesium, 3-bromo-1-(trimethylsilyl)-1-propyne; (ii) TBAF, iron power, acetic acid, reflux.



Scheme 0.3 (i) ethynylmagnesium bromide, cerium chloride[4]; (ii) iron power, acetic acid, reflux.

Both reaction sequences utilise a Grignard reagent to attach the propynyl group to the aromatic ring followed by reduction of the nitro group.[4, 5]

iii) In the course of this work, the transformation of an aryl-bromide to an aryl-alkynyl functional group was carried out using the Sonogashira coupling reaction (Chapter 2, Scheme 2.10 (v)). Unfortunately, in compounds **44**, **45**, **54** and **55** the aromatic bromides failed to couple to the acetylene groups. However, a lithium/bromide exchange followed by a transmetallation with copper then palladium, may be an alternative method that could be utilised to achieve the desired products.[6]

iv) The work described in this thesis has clearly demonstrated the potential to utilise the intramolecular hydroamination reaction to assemble a number of different heterocyclic skeletons. There has yet to be a more systematic study of the functional group tolerance of the catalysts employed for the reactions. Already in a number of examples in this work, product inhibition was apparent and this probably arises because the product contains potential nitrogen donors which competitively limit the catalyst available for the desired reaction. There are

many functional groups which need to be assessed to establish the robustness and tolerance that the catalysts have for a range of common functional groups which could be commonly encountered in substrates (esters, alcohols, carbonyls, nitriles).

v) It is apparent that considerable improvement in catalyst performance was encountered when the palladium complexes had a COD ligand. The positive influence of COD as a co-ligand on iridium[7] has also been noted in terms of hydroamination catalyst efficiency. There is clearly scope to both tune and improve the catalyst efficiency by exploring a wider range of co-ligands particularly building on the lead that COD complexes appear to provide better catalysts.

5.3 References

1. deGraaf, W.; Boersma, J.; Smeets, W. J. J.; Spek, A. L.; vanKotent, G. *Organometallics* **1989**, *8*, 3907.

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5. Jung, M. E.; Hagenah, J. A. *J. Org. Chem.* **1989**, *52*, 1889.

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7. Vuong, K. Q. *Metal Complex Catalysed C-X (X = S, O and N) Bond Formation*. Ph.D. Thesis, University of New South Wales, Sydney, **2005**.

Chapter 6

Experimental

6.1 General Procedures

All manipulations of metal complexes and air sensitive reagents were carried out using standard Schlenk techniques,[1*] or in a nitrogen-filled glovebox.

The following reagents were purchased from Aldrich Chemical Company Inc. and used as received: *N*-methylimidazole, *n*-butyllithium, hydrazine monohydrate, sodium tetrafluoroborate, 1, 5-cyclooctadiene, sodium hexafluorophosphate, silver tetrafluoroborate, triethyloxonium tetrafluoroborate, methyl lithium (LiBr salt, 1.0M), chromium(VI) oxide, 3-butyn-1-ol, 4-pentyn-1-ol, 5-hexyn-1-ol, 2-butynoic acid, sodium amide, morpho-CDI, 2, 5-dibromoaniline, copper(II) acetate, triphenylphosphine, (trimethylsilyl)acetylene, tetrabutylammonium fluoride (1M in tetrahydrofuran), tetrakis(triphenylphosphine)palladium(0) ($[Pd(PPh_3)_4]$), *bis*(triphenylphosphine)palladium(II) chloride ($[PdCl_2(PPh_3)_2]$), 1, 3, 5-tribromobenzene, iron powder, potassium nitrate, fuming sulfuric acid (20% oleum), 1, 4-dibromobenzene, 1, 2-phenylenediamine, sodium borohydride, potassium fluoride, 2-bromobenzylamine hydrochloride, and copper(I) iodide. Phenylacetylene, thionyl chloride, were purchased from Aldrich and were distilled prior to use. The metal halide salts rhodium(III) chloride hydrate, palladium(II) chloride were purchased from Precious Metals Online and used as received.

Di-μ-chloro-tetracarbonyldirhodium ($[Rh(CO)_2Cl]_2$) (**63**),[2] dichloro(η^4-1, 5-cyclooctadiene)palladium(II) ($[Pd(COD)Cl_2]$) (**18**),[3] (η^4-1, 5-cyclooctadiene)chloromethylpalladium(II) ($[Pd(COD)(Cl)(CH_3)]$) (**19**),[4] 2, 5-dibromo-4-aminoaniline,[5] fuming nitric acid,[6] were prepared by literature methods and gave identical spectroscopic details to the published data. Pentyn-1-amine (**21**) was prepared by the Organic Synthesis Centre, at the University of Sydney following the literature procedures by Jackie Morgan.[7]

* References begin on page 192.

For the purposes of air sensitive manipulations and in the preparation of metal complexes, solvents were dried and distilled under nitrogen using standard procedures[8] and stored under nitrogen in glass ampoules, each fitted with a Youngs© Teflon valve prior to use. Tetrahydrofuran and hexane were pre-dried over sodium wire, then distilled from benzophenone over sodium wire under an inert atmosphere prior to use. Methanol was dried over, and distilled from magnesium turnings under nitrogen. Acetonitrile, dichloromethane, diisopropylamine and triethylamine, were dried over, and distilled from calcium hydride under nitrogen. Acetone was dried over, and distilled from, calcium sulfate under nitrogen.

The bulk compressed gases nitrogen (>99.5%) and carbon monoxide (>99.5%) were obtained from British Oxygen Company (BOC Gases) and used as supplied.

Infrared spectra were obtained using a Shimadzu 8400 Series FTIR spectrometer or an Avatar 370 FTIR spectrometer as KBr discs. The following abbreviations are for convenience in reporting the intensities of IR absorbance: s - strong; m - medium; w - weak. Microanalyses were carried out at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. Electron impact mass spectra (EI) were recorded on a Finnigan Polaris Q mass spectrometer at the University of Sydney. Low resolution solid phase mass spectra were recorded on a VG Quattro Triple Quadrupole mass spectrometer at the University of New South Wales. For electron impact ionisation (EI) an electron energy of 70 eV was used. Electrospray mass spectra (ESI) were recorded on a Finnigan LCQ mass spectrometer at the University of Sydney. Data is quoted in the form x(y) where x is the mass/ charge ratio and y is the percentage abundance relative to the base peak. High resolution mass spectra (HRMS) were recorded on a VG Autospec-oa-TOF mass spectrometer at the University of Wollongong and on a Finnigan MAT 900 XL mass spectrometer at the University of Queensland. In reporting mass spectral data, M is defined as the molecular weight of the compound of interest.

Melting points were determined using a Gallenkamp melting point apparatus and

are uncorrected.

Safety Note: The polynitroarenes described in this thesis are potentially explosive and nitroarenes are known to be potential carcinogens. These compounds should be handled with appropriate caution and only in small quantities.

6.2 NMR Spectroscopy

Air sensitive NMR samples were either prepared in a nitrogen-filled glove-box or on a high vacuum line by vacuum transfer of solvent into an NMR tube fitted with a concentric Teflon valve. Deuterated solvents for NMR purposes were obtained from Cambridge Isotopes. Chloroform-*d* and dimethyl-d_6 sulfoxide were used as supplied. Tetrahydrofuran-d_8, methanol-d_3, methanol-d_4, acetonitrile-d_3, acetone-d_6 and chloroform-*d* for the use with air sensitive compounds, were degassed using three consecutive freeze-pump-thaw cycles and vacuum distilled from suitable drying agents immediately prior to use.

^{1}H NMR spectra were recorded using Bruker Avance 200 (200.13 MHz), Bruker Avance 300 (300.13 MHz), Bruker DPX300 (300.17 MHz) or Bruker DRX400 (400.13 MHz) spectrometers. Spectra were recorded at approximately 300 K for characterisation purposes unless otherwise stated. ^{1}H NMR chemical shifts were referenced to internal solvent references. Chemical shifts (δ) are quoted in ppm. Uncertainties in chemical shifts are typically ±0.01 ppm for ^{1}H. Coupling constants (*J*) are given in Hz and have an uncertainty of ±0.05 Hz for ^{1}H-^{1}H couplings. The following abbreviations are for the convenience in reporting the multiplicity of NMR resonances: s - singlet; d - doublet; t - triplet; q - quartet; p - pentet; app. - apparent; sep. - septet; m - multiplet; bs - broad singlet.

^{13}C{^{1}H} NMR spectra were recorded using Bruker Avance 200 (50.3 MHz), Bruker Avance 300 (75.5 MHz), Bruker DPX300 (75.5 MHz) or Bruker DRX400 (100.6 MHz) spectrometers at 300 K with complete proton decoupling. ^{13}C NMR chemical shifts were referenced to internal solvent references. Chemical shifts (δ)

are quoted in ppm. Uncertainties in chemical shifts are typically ±0.05 ppm for ^{13}C.

The following two-dimensional NMR techniques were routinely used for the assignment of organic and organometallic compounds: COSY (*c*orrelation *s*pectroscop*y*), DOSY (*d*iffusion-*o*rdered *s*pectroscop*y*), NOESY (*n*uclear *o*verhauser *e*ffect *s*pectroscop*y*), HSQC (*h*eteronuclear *s*ingle *q*uantum *c*oherence), and HMBC (*h*eteronuclear *m*ultiple *b*ond *c*oherence).

NMR data was processed using standard Bruker software (xwinnmr).

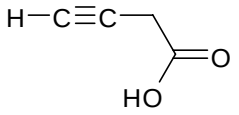
Analytical thin layer chromatography (TLC) was performed using 0.2 mm thick, aluminium backed, precoated silica gel plates (Merck Silicagel 60 F_{254}). Compounds were visualised by ultra-violet fluorescence or by staining with a potassium permanganate stain.

Silica column chromatography was performed using Merck Silicagel 60 (230-400 mesh ASTM), under a positive pressure of nitrogen, with the indicated solvents. Solvent compositions were *v/v* as specified. All solvents were purified by distillation prior to use.

6.3 Synthesis of Aliphatic Substrates

6.3.1 3-Butynoic Acid (23)

The synthesis of 3-butynoic acid (**23**) was undertaken by a method based on the procedure reported by Heilbron *et al*.[9]

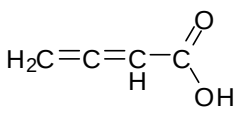


Chromium(VI) oxide (69.7 g, 0.697 mol) in sulfuric acid (4.5M, 450 mL) was added dropwise to a cooled solution of 3-butyn-1-ol (15.1 g, 0.215 mol) in acetone (450 mL) over 2 h and the temperature was maintained between 5-10 °C. The mixture was stirred for a further 1.5 h at 5-10 °C after addition was complete. The blue/ green solution was concentrated under vacuum to remove the acetone, then brine (250 mL) was added and the mixture was extracted with diethyl ether (5 × 100 mL, 5 × 50 mL). The ether extracts were combined, dried over magnesium sulfate and then concentrated under reduced pressure. The oily residue was distilled (kugelrohr) then recrystallised from hexane to yield 3-butynoic acid (**23**) as white plates (2.3 g, 12 %), m.p. 83-84 °C (lit.[9] 82-83.5 °C).[10]

^{1}H NMR (200 MHz, chloroform-*d*): δ 9.78 (bs, 1H, O**H**), 3.37 (d, $^{4}J_{H2\text{-}H4}$ = 2.8 Hz, 2H, **H2**), 2.24 (t, $^{4}J_{H4\text{-}H2}$ = 2.8 Hz, 1H, **H4**) ppm.
^{13}C{^{1}H} NMR (75 MHz, chloroform-*d*): δ 174.3 (**C1**), 74.9 (**C3**), 72.5 (**C4**), 25.7 (**C2**) ppm.
m/z (ESI^{-}, methanol): 83 ((M-H)$^{-}$, 100%).

6.3.2 The Attempted Synthesis of 3-Butynoic Acid (23)

The synthesis of 3-butynoic acid was attempted using the procedure described by Brandsma and Verkruijsse.[11]



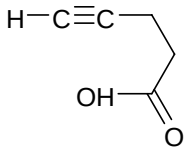
A suspension of 2-butynoic acid (0.60 g, 7.1 mmol) in tetrahydrofuran (4 mL) was added over a few minutes to an efficiently stirred solution of sodamide (1.3 g,

33 mmol). The reaction mixture was cooled to -78 °C and ammonia (30 mL was condensed into the reaction mixture). After an additional 30 min at -78 °C, ammonium chloride (3.0 g, 56 mmol) was added slowly with vigorous stirring and the mixture was allowed to come to room temperature under nitrogen. Crushed ice was added to the resulting solid to give a solution which was acidified with hydrochloric acid (5M) with swirling to give a pH of 3. The solution was saturated with ammonium chloride, then extracted with diethyl ether (10 × 25 mL). The ether extracts were combined and dried over magnesium sulfate and concentrated under reduced pressure to give buta-2, 3-dienoic acid (**24**) as a yellow oil (0.10 g, 18 %).

^{1}H NMR (200 MHz, chloroform-*d*): δ 5.53 (t, $^{4}J_{H2\text{-}H4}$ = 6.5, 1H, **H2**), 5.15 (d, $^{4}J_{H4\text{-}H2}$ = 6.5, 2H, **H4**), ppm.
^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 216.3 (**C3**), 168.9, (**C1**), 88.0 (**C2**), 79.2(**C4**) ppm.

6.3.3 4-Pentynoic Acid (26)

The synthesis of 4-pentynoic acid was undertaken by a method based on the procedure described by Holland and Gilman.[12]



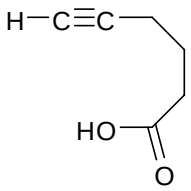
A solution of 4-pentyn-1-ol (5.17 g, 61.5 mmol) in acetone (50 mL) was added dropwise to a cooled solution of chromium(VI) oxide (10 g, 0.10 mol) in sulfuric acid (5M, 125 mL) over 2 h and the temperature was maintained between 5-10 °C. The mixture was stirred for a further 1.5 h at 5-10 °C after addition was complete. The blue/ green solution was concentrated under vacuum, water (80 mL) was added and the mixture was extracted with diethyl ether (2 × 50 mL, 5 × 20 mL). The ether extracts were combined, dried over magnesium sulfate and then concentrated under reduced pressure. The oily residue was dissolved in diethyl ether (20 mL) and extracted with sodium hydroxide (3M, 2 × 50 mL). The basic solution was cooled, acidified with hydrochloric acid (3M) and extracted

with diethyl ether (6 × 100 mL, 4 × 50 mL). The combined ether extracts were dried over magnesium sulfate and the solvent removed. The residue was recrystallised from diethyl ether/ hexane to give 4-pentynoic acid (**26**) as pale yellow crystals (0.8 g, 15%) m.p. 49-50 °C (lit.[12] 54.5-56.5 °C).[13]

^{1}H NMR (400 MHz, chloroform-*d*): δ 2.60 (m, 2H, **H2**), 2.50 (m, 2H, **H3**), 1.98 (t, $^{4}J_{H3\text{-}H5}$ = 2.6 Hz, 1H, **H5**) ppm.
^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 177.0 (**C1**), 82.0 (**C4**), 69.2 (**C5**), 33.0 (**C2**), 14.1 (**C3**) ppm.
m/z (ES^{-}, methanol): 97 ((M-H)$^{-}$, 100%), 115 (42), 195 (73), 213 (30).

6.3.4 5-Hexynoic Acid (27)

The synthesis of 5-hexynoic acid was undertaken using the procedure described by Holland *et al*. and Eglinton *et al*.[12, 14]



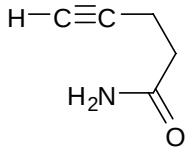
A solution of 5-hexyn-1-ol (15 g, 0.15 mol) in acetone (150 mL) was added dropwise to a cooled solution of chromium(VI) oxide (30 g, 0.30 mol) in sulfuric acid (5M, 375 mL) over 7 h and the temperature was maintained between 5-10 °C. The mixture was stirred for a further 1.5 h at 5-10 °C after addition was complete. The blue/ green solution was concentrated under vacuum and the mixture extracted with diethyl ether (2 × 50 mL, 8 × 25 mL). The ether extracts were combined and dried over magnesium sulfate then concentrated under reduced pressure. The residue was dissolved in diethyl ether (50 mL) and extracted with sodium hydroxide (3M, 2 × 20 mL, 2 × 10 mL). The basic solution was cooled and acidified with hydrochloric acid (3M) and extracted with diethyl ether (4 × 50 mL, 8 × 25 mL). The combined ether extracts were dried over magnesium sulfate, the solvent removed and the residue distilled to give 5-hexynoic acid (**27**) as a colourless oil (5.3 g, 32%).

^{1}H NMR (200 MHz, chloroform-*d*): δ 9.97 (bs, 1H, COO**H**), 2.49 (t,

$^{3}J_{H2\text{-}H3}$ = 7.3 Hz, 2H, **H2**), 2.26 (td, $^{3}J_{H3\text{-}H4}$ = 7.3 Hz, $^{4}J_{H4\text{-}H6}$ = 2.6 Hz, 2H, **H4**), 1.91 (t, $^{4}J_{H4\text{-}H6}$ = 2.6 Hz, 1H, **H6**), 1.85 (app. sep, $^{3}J_{H2\text{-}H3}$ = 7.3 Hz, $^{3}J_{H3\text{-}H4}$ = 7.3 Hz, 2H, **H3**) ppm.

$^{13}C\{^{1}H\}$ NMR (100 MHz, chloroform-*d*): δ 179.8 (**C1**), 83.1 (**C5**), 69.4 (**C6**), 32.8 (**C2**), 23.3 (**C3**), 17.7 (**C4**) ppm.

6.3.5 4-Pentyn-1-amide (3)



A solution of 4-pentynoic acid (**26**) (94.5 mg, 1.00 mmol) in chloroform (2 mL, anhydrous) was stirred for 30 min in a stoppered glass Ace pressure tube and morpho-CDI (0.45 g, 1.0 mmol) was added. After addition was complete, the resulting mixture was stirred at room temperature for 18 h. After this time, a pale yellow precipitation was evident. The reaction mixture was cooled to -78 °C and then ammonia (1 mL, excess) was condensed into the reaction mixture. The pressure tube was immediately stoppered and the mixture stirred at room temperature for 18 h. The tube was cooled to -78 °C, the lid was removed and the excess ammonia and solvent were allowed to evaporate in a stream of nitrogen at room temperature. The resulting residue was extracted with ethyl acetate (5 × 20 mL). The ethyl acetate extracts were combined and the solvent removed to give a yellow oily residue. The residue was purified by column chromatography (hexane: ethyl acetate, 1:3) (TLC, hexane: ethyl acetate, 1:3, R_f = 0.28, potassium permanganate indicator), and recrystallised from ethyl acetate to give 4-pentyn-1-amide (**3**) as a colourless crystalline solid (44.5 mg, 47%), m.p. 110-111 °C (lit.[15] 112-113 °C).

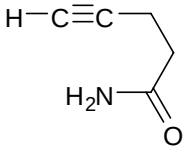
^{1}H NMR (400 MHz, tetrahydrofuran-d_8): δ 6.76 (br, 1H, N**H**), 6.57 (br 1H, N**H**), 2.41 (m, 2H, **H2**), 2.33 (m, 2H, **H3**), 2.22 (t, $^{4}J_{H3\text{-}H5}$ = 2.6 Hz, 1H, **H5**) ppm.

$^{13}C\{^{1}H\}$ NMR (100 MHz, tetrahydrofuran-d_8): δ 172.2 (**C1**), 84.0 (**C4**), 69.4 (**C5**), 35.1 (**C2**), 15.0 (**C3**) ppm.

m/z (ESI^{+}, methanol): 98 (M^{+}, 31%), 195 (50), 217 (35), 240 (20), 336 (100).

6.3.6 Synthesis of 4-Pentyn-1-amide (3) *via* Acid Chloride Intermediate

The synthesis of 4-pentyn-1-amide was also undertaken by a method based on the procedure described by Jacobi *et al*.[15]

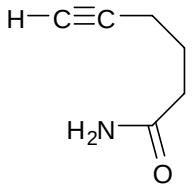


A solution of 4-pentynoic acid (1.0 g, 10 mmol) in dry benzene (10 mL) was treated with thionyl chloride (1 mL, excess). The reaction mixture was stirred for 4 h at room temperature and then refluxed for 1 h. At the end of this period, the excess thionyl chloride and benzene were removed under reduced pressure and the residue was taken up with tetrahydrofuran (5 mL, anhydrous) and cooled to -78 °C, and dry ammonia (10 mL, excess) was condensed into the reaction mixture. The reaction mixture was allowed to stir for an additional 8 h. The tetrahydrofuran was then removed under reduced pressure and the residue was treated with brine (5 mL) and the mixture was extracted with ethyl acetate (5 × 10 mL). The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure to yield 4-pentyn-1-amide (**26**) as a pale yellow solid (70 mg, 7%) m.p. 101-103 °C (lit.[15] 112-113 °C)

^{1}H NMR (300 MHz, chloroform-*d*): δ 5.60 (bs, 2H, N**H**), 2.52 (m, 2H, **H2**), 2.45 (m, 2H, **H3**), 2.01 (t, $^{4}J_{H3\text{-}H5}$ = 2.5 Hz, 1H, **H5**) ppm.
^{13}C{^{1}H} NMR (75 MHz, tetrahydrofuran-d_8): δ 173.6 (**C1**), 84.1 (**C4**), 69.6 (**C5**), 35.3 (**C2**), 15.1 (**C3**) ppm.

6.3.7 Synthesis of 5-Hexyn-1-amide (4)

A solution of 5-hexynoic acid (**27**) (2.0 g, 18 mmol) in chloroform (10 mL, anhydrous) was stirred for 30 min in a stoppered glass Ace pressure tube, and morpho-CDI (2.0 g, 4.7 mmol) was added. After the addition was complete, the resulting mixture was stirred at room temperature for 18 h. After this time, a white precipitate was evident. The reaction mixture was cooled to -78 °C and dry ammonia (4 mL, excess) was condensed into the reaction mixture. The pressure



tube was immediately stoppered and the mixture stirred at room temperature for 18 h. The tube was cooled to -78 °C, the lid removed and the excess ammonia and solvent was evaporated in a stream of nitrogen at room temperature. The resulting residue was extracted with ethyl acetate (5 × 20 mL). The ethyl acetate extracts were combined and the solvent removed to give a yellow oily residue. The residue was purified by column chromatography (hexane: ethyl acetate, 1:3) (TLC, hexane: ethyl acetate, 1:3, $R_f = 0.15$, potassium permanganate indicator), to give 5-hexyn-1-amide (**4**) as a white solid (0.93 g, 47%) m.p. 75-75 °C.

^{1}H NMR (400 MHz, tetrahydrofuran-d_8, 330 K): δ 6.58 (bs, 1H, N**H**), 6.35 (bs, 1H, N**H**), 2.22 (t, $^3J_{H2\text{-}H3} = 7.2$ Hz, 2H, **H2**), 2.19 (td, $^3J_{H4\text{-}H3} = 7.2$ Hz, $^4J_{H4\text{-}H6} = 2.6$ Hz, 2H, **H4**), 2.14 (t, $^4J_{H6\text{-}H4} = 2.6$ Hz, 1H, **H6**), 1.80 (app. sep, $^3J_{H2\text{-}H3} = 7.2$ Hz, 2H, **H3**) ppm.

^{13}C{^{1}H} NMR (100 MHz, tetrahydrofuran-d_8): δ 174.8 (**C1**), 84.4 (**C5**), 69.8 (**C6**), 34.7 (**C2**), 18.5 (**C3**), 15.1 (**C4**) ppm.

m/z (EI): 112 ($(M+H)^+$, 55%), 110 (35).

High resolution mass spectrum: calculated for C_6H_9NO (M^+) 111.0684, found 111.0684.

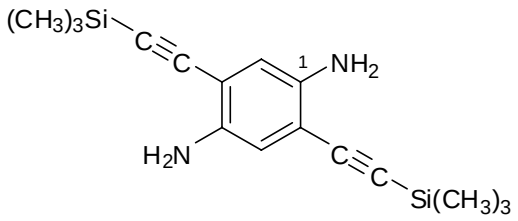
Anal. Found: C, 64.60; H, 8.18; N, 12.85. C_6H_9NO requires C, 64.84; H, 8.16; N, 12.60%.

ν (KBr): 3184s (N-H), 2115w (C≡C), 1661s, 1634s (C=O), 1426s, 1301s, 1228, 668s cm^{-1}.

6.4 Synthesis of the Aromatic Substrates

6.4.1 1, 4-Diamino-2, 5-*bis*(trimethylsilylethynyl)benzene (29)

The synthesis of 1, 4-diamino-2, 5-*bis* (trimethylsilylethynyl)benzene (**29**) was undertaken by a modification of the method reported by Moroni *et al*.[5]



Palladium(II) chloride (104 mg, 0.500 mmol), copper(II) acetate (110 mg, 0.80 mmol), triphenylphosphine (482 mg, 1.84 mmol) and 2, 5-dibromo-4-aminoaniline[5] (1.00 g, 3.76 mmol) were mixed under nitrogen with dry and degassed triethylamine (176 mL). (Trimethylsilyl)acetylene (2.6 mL, 38 mmol) was added and the reaction mixture was stirred and heated at 85 °C under nitrogen for 8 h. The mixture was cooled to room temperature and then filtered to remove the insoluble salts and the triethylamine was removed under reduced pressure. The solid residue was dissolved in dichloromethane and then purified by column chromatography (hexane: dichloromethane, 1:2) (TLC, (hexane: dichloromethane, 1:2, $R_f = 0.4$) to give 1, 4-diamino-2, 5-*bis*(trimethylsilylethynyl)benzene (**29**) as a yellow crystalline solid (0.67 g, 60%), m.p. 141-143 °C.

^{1}H NMR (400 MHz, chloroform-*d*): δ 6.69 (s, 2H, **H3** and **H6**), 3.78 (bs, 4H, N**H**$_2$), 0.22 (s, 18H, C**H**$_3$) ppm.

^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 140.1 (**C1** and **C4**), 117.8 (**C3** and **C6**), 110.6 (**C2** and **C5**), 101.5 (**C**≡C), 101.2 (C≡**C**), 1.1 (CCSi(**C**H$_3$)$_3$) ppm.

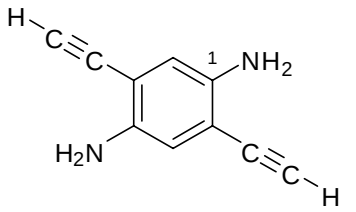
m/z (EI): 300 (M^+, 100%), 73 (24).

High resolution mass spectrum: calculated for $C_{16}H_{24}N_2Si_2$ (M^+) 300.1468, found 300.1478.

ν (KBr): 3424m, 3321m (N-H), 3030w (aromatic C-H), 2143s (C≡C), 1614m, 1494s 1429m, 1246s, 880s, 866s, 844s, 758s, 626m cm^{-1}.

6.4.2 1, 4-Diamino-2, 5-diethynylbenzene (5)

The synthesis of 1, 4-diamino-2, 5-diethynylbenzene (**5**) was undertaken by a method based on the procedure reported by Moroni *et al*.[5]

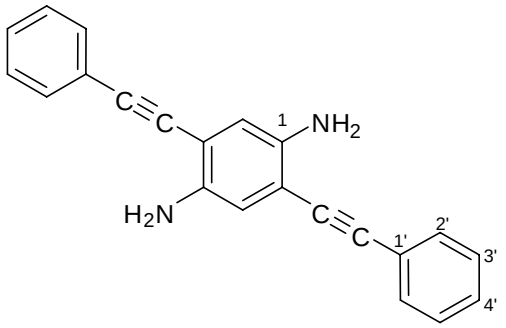


Tetrabutylammonium fluoride (1M in tetrahydrofuran, 4.5 mL) was added to 1, 4-diamino-2, 5-*bis*(trimethylsilylethynyl)benzene (**29**) (0.67 g, 2.2 mmol) in tetrahydrofuran (25 mL). After stirring for 5 min at room temperature, the tetrahydrofuran was removed under reduced pressure and the residue was purified by column chromatography (hexane: dichloromethane, 1:4) (TLC, hexane: dichloromethane, 1:4, $R_f = 0.14$) to give 1, 4-diamino-2, 5-diethynylbenzene (**5**) as a bright yellow powder which easily oxidized to a dark coppery powder on standing (0.21 g, 60%), m.p. 184-185 ºC (dec).

^{1}H NMR (400 MHz, chloroform-*d*): δ 6.73 (s, 2H, **H3** and **H6**), 3.82 (bs, 4H, N**H**$_2$), 3.39 (s, 2H, C≡C**H**), ppm.
^{13}C{^{1}H} NMR (100 MHz, tetrahydrofuran-d_8): δ 141.7 (**C1** and **C4**), 118.1 (**C3** and **C6**), 109.8 (**C2** and **C5**), 84.0 (**C**≡CH), 81.8 (C≡**C**H) ppm.
m/z (EI): 156 (M^+, 100%), 155 (46), 129 (45), 75 (15).
High resolution mass spectrum: calculated for $C_{10}H_8N_2$ (M^+) 156.0693, found 156.0687.
ν (KBr): 3430w, 3396w (N-H), 2100w (C≡C-H), 1499s, 1428s cm^{-1}.

6.4.3 1, 4-Diamino-2, 5-*bis*(phenylethynyl)benzene (6)

The synthesis of 1, 4-diamino-2,5-*bis*(phenylethynyl) benzene (**6**) was undertaken by modification of the method reported by Moroni *et al*.[5]

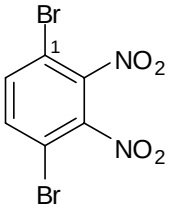


Palladium(II) chloride (99 mg, 0.56 mmol), copper(II) acetate (107 mg, 0.880 mmol), triphenylphosphine (466 mg, 1.78 mmol) and 2, 5-dibromo-4 aminoaniline[5] (1.51 g, 5.68 mmol) were mixed under nitrogen with dry and degassed triethylamine (175 mL). Phenylacetylene (2.6 mL, 11.4 mmol) was added and the reaction mixture was stirred and heated at 85 ºC under nitrogen for 8 h. At room temperature, the mixture was filtered to remove the insoluble salts and triethylamine was removed *in vacuo*. The oily residue was dissolved in dichloromethane and purified by column chromatography (hexane: dichloromethane, 1:1) (TLC, hexane: dichloromethane, 1:1, $R_f = 0.1$) to give 1, 4-diamino-2, 5-*bis*(phenylethynyl)benzene (**6**) as an orange powder (0.24 g, 13%), m.p. 179-181 ºC.

^{1}H NMR (400 MHz, tetrahydrofuran-d_8): δ 7.52 (m, 4H, *o*-**H**), 7.31 (m, 6H, *m*-**H** and *p*-**H**), 6.70 (s, 2H, **H3** and **H6**), 4.35 (bs, 4H, N**H**$_2$) ppm.
^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 140.0 (**C1** and **C4**), 131.7 (**C2'**), 129.2 (**C4'**), 128.6 (**C3'**), 123.2 (**C1'**), 118.0 (**C3** and **C6**), 110.8 (**C2** and **C5**), 96.0 (**C**≡C), 86.0 (C≡**C**) ppm.
m/z (EI): 308 (M^+, 100%).
High resolution mass spectrum: calculated for $C_{22}H_{16}N_2$ (M^+) 308.1312, found 308.1313.
ν (KBr): 3389w (N-H), 3289w, 3190w (aromatic C-H), 2198w (C≡C), 1261m, 754s, 690s cm^{-1}.

6.4.4 1, 4-Dibromo-2, 3-dinitrobenzene (35)

1, 4-Dibromo-2, 3-dinitrobenzene (**35**) was undertaken by a method based on a literature procedure.[16-19]

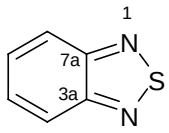


1, 4-Dibromobenzene (30.7 g, 130 mmol) was added to a stirred mixture of concentrated sulfuric acid (150 mL) and concentrated nitric acid (150 mL). The mixture was refluxed for 3 h. The reaction mixture was then stirred in an excess of crushed ice. The solid precipitate formed was collected by filtration and washed with water until the filtrate was neutral. The crude solid was recrystallised from hot glacial acetic acid which was allowed to stand in a cool place overnight. Two crops were collected to give 1, 4-dibromo-2, 3-dinitrobenzene (**35**) as a bright yellow crystalline solid (2.7 g, 6.5%), m.p. 151-154 °C (lit.[18] 159-160 °C).

^{1}H NMR (200 MHz, chloroform-*d*): δ 7.75 (s, 2H, **H5** and **H6**) ppm.
^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 144.9 (**C2** and **C3**), 137.0 (**C5** and **C6**), 114.5 (**C1** and **C4**) ppm.
m/z (EI): 326 (M^{+}, 71%), 250 (39), 199 (100).

6.4.5 2, 1, 3-Benzothiadiazole (37)

The synthesis of 2, 1, 3-benzothiadiazole (**37**) was undertaken by a method based on the procedure reported by Khaletskii *et al*.[20]



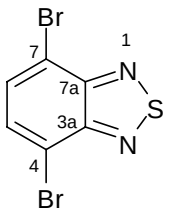
1, 2-Phenylenediamine (5.42 g, 50.0 mmol), triethylamine (30 mL) and benzene (150 mL) were stirred vigorously under nitrogen with dropwise addition of thionyl chloride (9.5 mL) in benzene (30 mL). The reaction was exothermic and the temperature of the reaction mixture increased to 40-50 °C as the reaction progressed. After the addition was complete, the reaction was heated at reflux for 15 min. The mixture was filtered, the solid residue was washed with benzene then discarded. The filtrate was evaporated *in vacuo* to give a black residue. The residue was recrystallised from hexane to give 2, 1, 3-benzothiadiazole (**37**) as

yellow needles (3.7 g, 54%), m.p. 43-45 °C (lit.[20] 44 °C).

^{1}H NMR (200 MHz, chloroform-*d*): δ 7.99 (m, 2H, **H4** and **H7**), 7.56 (m, 2H, **H5** and **H6**) ppm.
^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 154.9 (**C3a** and **C7a**), 129.4 (**C5** and **C6**), 121.7 (**C4** and **C7**) ppm.

6.4.6 4, 7-Dibromo-2, 1, 3-benzothiadiazole (38)

The synthesis of 4, 7-dibromo-2, 1, 3-benzothiadiazole (**38**) was undertaken by a method based on a literature procedure.[21, 22]

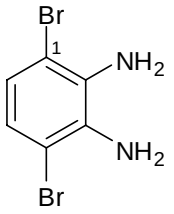


2, 1, 3-Benzothiadiazole (**37**) (10.1 g, 74.5 mmol) in hydrobromic acid (47%, 60 mL) was refluxed with stirring while bromine (13 mL, 0.25 mol) was added dropwise over a period of 30 min. Towards the end of the addition, the mixture became a suspension, hydrobromic acid (47%, 30 mL) was added to facilitate stirring and the mixture was refluxed for an additional 2.5 h after completion of the bromine addition. The mixture was filtered while still hot, then cooled and filtered again. The solid precipitate collected was washed with water until the filtrate was neutral. Recrystallisation from acetone gave 4, 7-dibromo-2, 1, 3-benzothiadiazole (**38**) as yellow needles (21 g, 98%), m.p. 182-184 °C (lit.[21] 184-185 °C).

^{1}H NMR (200 MHz, chloroform-*d*): δ 7.73 (s, 2H, **H5** and **H6**) ppm.
^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 153.1 (**C3a** and **C7a**), 132.5 (**C5** and **C6**), 114.0 (**C4** and **C7**) ppm.
m/z (EI): 294 (M^{+}, 100%), 213 (26), 134 (24).

6.4.7 2, 3-Diamino-1, 4-dibromobenzene (34)

The synthesis of 2, 3-diamino-1, 4-dibromobenzene (**34**) was undertaken by a method based on the procedure reported by Edelmann.[22]

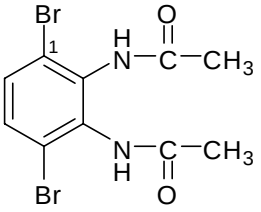


Sodium borohydride (1.30 g, 34.4 mmol) was added portionwise to a suspension of 4, 7-dibromo-2, 1, 3-benzothiadiazole (**38**) (0.559 g, 1.90 mmol) in ethanol (20 mL) at 0 °C. The reaction mixture was allowed to slowly return to room temperature and the mixture was stirred for 20 h at room temperature. The solvent was removed *in vacuo*, water (20 mL) was added and the mixture was extracted with diethyl ether (3 × 50 mL). The ether extracts were combined, washed with brine and then dried over magnesium sulfate. The solvent was removed to give 2, 3-diamino-1, 4-dibromobenzene (**34**) as a creamy solid (0.34 g, 68%), m.p. 92-94 °C (lit.[22] 94-95 °C).

^{1}H NMR (400 MHz, chloroform-*d*): δ 6.84 (s, 2H, **H5** and **H6**), 3.90 (bs, 4H, N**H**$_2$) ppm.
^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 133.8 (**C2** and **C3**), 123.4 (**C5** and **C6**), 109.8 (**C1** and **C4**) ppm.
m/z (EI): 266 (M^+, 100%), 185 (20), 105 (13).

6.4.8 2, 3-*Bis*(acetamido)-1, 4-dibromobenzene (39)

The synthesis of 2, 3-*bis*(acetamido)-1, 4-dibromobenzene (**39**) was undertaken by a method based on the procedure reported by Ward.[23]



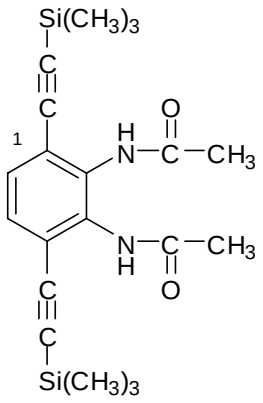
Acetic anhydride (25 mL) was added to a solution of 2, 3-diamino-1, 4-dibromobenzene (**34**) (1.68 g, 6.31 mmol) in dichloromethane (50 mL). The reaction mixture was stirred and refluxed for 72 h and the reaction was monitored by TLC (TLC, hexane: ethyl acetate, 1:1). The solvent was removed *in vacuo*. The residue was recrystallised from absolute ethanol to give 2, 3-*bis*(acetamido)-1, 4-dibromobenzene (**39**) as a creamy solid (0.68 g, 31%),

m.p. 284-286 ºC.

^{1}H NMR (200 MHz, dimethyl-d_6 sulfoxide): δ 9.53 (bs, 2H, N**H**), 7.54 (s, 2H, **H5** and **H6**), 2.01 (s, 6H, C**H**$_3$) ppm.
^{13}C{^{1}H} NMR (100 MHz, dimethyl-d_6 sulfoxide): δ 168.2 (**C**=O), 136.3 (**C2** and **C3**), 131.7 (**C5** and **C6**), 122.1 (**C1** and **C4**), 22.6 (**C**H$_3$) ppm.
m/z (EI): 351 ((M+H)$^+$, 3%), 308 (45), 266 (100), 229 (40).
High resolution mass spectrum: calculated for $C_{10}H_{10}Br_2N_2NaO_2$ $(M+Na)^+$ 372.8986, found 372.8980.
Anal. Found: C, 34.53; H, 3.00; N, 7.87. $C_{10}H_{10}Br_2N_2O_2$ requires C, 34.32; H, 2.88; N, 8.00%.
ν (KBr): 3249s (CONH), 3095w, 3025w (aromatic C-H) cm^{-1}.

6.4.9 2, 3-*Bis*(acetamido)-1, 4-*bis*(trimethylsilylethynyl)benzene (40)

The synthesis of 2, 3-*bis*(acetamido)-1, 4-*bis*(trimethylsilylethynyl)benzene (**40**) was undertaken by a method based on the procedure reported by Moroni *et al*.[5]



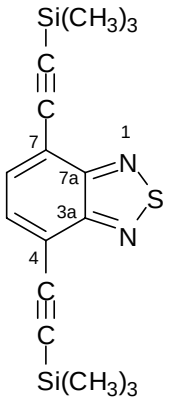
Palladium(II) chloride (3.40 mg, 19.0 μmol), copper(II) acetate (5.50 mg, 33.0 μmol), triphenylphosphine (482 mg, 1.84 mmol) and 2, 3-*bis*(acetamido)-1, 4-dibromobenzene (**39**) (51.1 mg, 0.147 mmol) were mixed under nitrogen with dry and degassed triethylamine (25 mL). (Trimethylsilyl)acetylene (0.10 mL, 0.51 mmol) was added and the reaction mixture was stirred and heated at 85 ºC under nitrogen for 24 h. At room temperature, the mixture was filtered to remove the insoluble salts and triethylamine was removed under reduced pressure. The solid residue was dissolved in ethyl acetate and adsorbed onto silica and then purified by column chromatography (hexane: ethyl acetate, 1:1) (TLC, hexane: ethyl acetate, 1:1, R_f = 0.2) to give 2, 3-*bis*(acetamido)-1, 4-*bis*(trimethylsilylethynyl)benzene (**40**)

as a peachy/ creamy solid (6.1 mg, 11%).

^{1}H NMR (200 MHz, chloroform-*d*): δ 7.87 (bs, 2H, N**H**), 7.33 (s, 2H, **H5** and **H6**), 2.18 (s, 6H, COC**H**$_3$), 0.25 (s, 18H, Si(C**H**$_3$)$_3$) ppm.
^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 168.7 (**C**=O), 133.9 (**C2** and **C3**), 130.3 (**C5** and **C6**), 121.4 (**C1** and **C4**), 102.9 (**C**≡C), 100.8 (C≡**C**), 23.8 (CO**C**H$_3$), 0.0 (Si(C**H$_3$**)$_3$) ppm.
m/z (ESI$^+$, methanol): 791 ((2M+Na)$^+$, 100%), 385 (28).
High resolution mass spectrum: calculated for $C_{20}H_{29}N_2O_2Si_2$ (M+H)$^+$ 385.1768, found 385.1761.

6.4.10 4, 7-*Bis*(trimethylsilylethynyl)-2, 1, 3-benzothiadiazole (41)

The synthesis of 4, 7-*bis*(trimethylsilylethynyl)-2, 1, 3-benzothiadiazole (**41**) was undertaken by a method based on the procedure reported by Khan *et al.*[24]



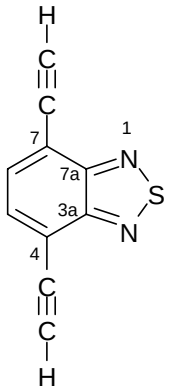
Palladium(II) chloride (11.1 mg, 62.4 μmol), copper(II) acetate (27.9 mg, 0.154 mmol), triphenylphosphine (44.7 mg, 0.170 mmol) and 4, 7-dibromo-2, 1, 3-benzothiadiazole (**38**) (1.50 g, 5.11 mmol) were mixed under nitrogen with dry and degassed diisopropylamine/ tetrahydrofuran (50 mL, 1:4 *v/v*). The solution was stirred for 30 min at room temperature and then (trimethylsilyl)acetylene (1.6 mL, 11 mmol) was added at room temperature to the vigorously stirred solution. The reaction mixture was refluxed under nitrogen for 2 h and the reaction was monitored by TLC (TLC, hexane: dichloromethane, 1:2). After being cooled to room temperature, the mixture was filtered to remove the insoluble salts and the solvent was removed *in vacuo*. The solid residue was dissolved in dichloromethane and adsorbed onto silica and purified by column chromatography (hexane: dichloromethane, 1:2) (TLC, hexane: dichloromethane, 1:2, R_f = 0.71) to give 4, 7-*bis*(trimethylsilylethynyl)-2, 1, 3-benzothiadiazole (**41**) as a yellow/

brown solid (1.3 g, 79%), m.p. 90-92 ºC.

^{1}H NMR (400 MHz, chloroform-*d*): δ 7.69 (s, 2H, **H5** and **H6**), 0.33 (s, 18H, Si(C**H**$_3$)$_3$) ppm.
^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 154.4 (**C3a** and **C7a**), 133.3 (**C5** and **C6**), 117.4 (**C4** and **C7**), 103.8 (**C**≡C), 100.1 (C≡**C**), 0.0 (Si(C**H$_3$**)$_3$) ppm.
m/z (EI): 331 ((M+3H)$^+$, 100%), 328 (53).

6.4.11 4, 7-*Bis*(ethynyl)-2, 1, 3-benzothiadiazole (42)

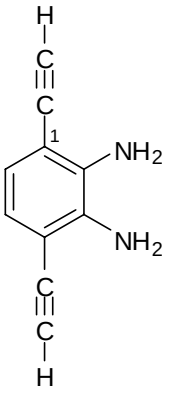
The synthesis of 4, 7-*bis*(ethynyl)-2, 1, 3-benzothiadiazole (**42**) was undertaken by a method based on the procedure reported by Arcadi *et al*.[25]



4, 7-*Bis*(trimethylsilylethynyl)-2,1,3-benzothiadiazole (**41**) (7.66 g, 23.3 mmol) was dissolved in methanol (300 mL). Potassium fluoride (4.06 g, 70.0 mmol) was added and the reaction mixture stirred for 2 h at room temperature. The solvent was removed *in vacuo*, water (200 mL) was added, and the mixture was extracted with diethyl ether (4 × 100 mL). The combined organic layers were washed with water (2 × 50 mL) and brine (50 mL), and then dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate, 9:1) (TLC, hexane: ethyl acetate, 9:1, R_f = 0.3) to give 4, 7-*bis*(ethynyl)-2, 1, 3-benzothiadiazole (**42**) as an orange solid which easily oxidized to a dark brown solid on standing (0.53 g, 12%), m.p. >300 ºC.

^{1}H NMR (400 MHz, chloroform-*d*): δ 7.75 (s, 2H, **H5** and **H6**), 3.68 (s, 2H, C≡C-**H**) ppm.
^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 154.5 (**C3a** and **C7a**), 133.4 (**C5** and **C6**), 116.9 (**C4** and **C7**), 85.5 (C≡**C**-H), 79.0 (**C**≡C-H) ppm.
m/z (EI): 184 (M$^+$, 100%).

6.4.12 2, 3-Diamino-1, 4-diethynylbenzene (7)



Sodium borohydride (0.983 g, 26.0 mmol) was added portionwise to a suspension of 4, 7-*bis*(ethynyl)-2, 1, 3-benzothiadiazole (**42**) (0.502 g, 1.53 mmol), palladium(II) chloride (0.027 g, 0.153 mmol, 10 mol%), copper(II) acetate (0.028 g, 0.153 mmol, 10 mol%) in ethanol (40 mL) at 0 °C. The reaction mixture was allowed to return slowly to room temperature and the mixture was stirred for 65 h at room temperature. The solvent was removed *in vacuo*, water (100 mL) was added and the mixture was extracted with diethyl ether (3 × 50 mL). The ether extracts were combined and washed with brine then dried over magnesium sulfate. The solvent was removed to give a dark red oil which was purified by column chromatography (hexane: ethyl acetate, 7:3) (TLC, hexane: ethyl acetate, 7:3, $R_f = 0.4$) to give 2, 3-diamino-1, 4-diethynylbenzene (**7**) as a dark red solid (0.10 g, 43%).

^{1}H NMR (400 MHz, tetrahydrofuran-d_8): δ 6.77 (s, 2H, **H5** and **H6**), 4.72 (bs, 4H, N**H**$_2$), 3.98 (s, 2H, C≡C-**H**) ppm.

^{13}C{^{1}H} NMR (100 MHz, tetrahydrofuran-d_8): δ 138.6 (**C2** and **C3**), 121.9 (**C5** and **C6**), 108.3 (**C1** and **C4**), 84.7 (C≡**C**-H), 82.5 (**C**≡C-H) ppm.

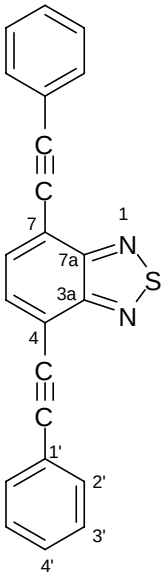
m/z (EI): 157 ((M+H)$^+$, 21%), 156 (100), 155 (33).

High resolution mass spectrum: calculated for $C_{10}H_8N_2$ (M^+) 156.0687, found 156.0688.

ν (KBr): 3417m, 3336m (N-H), 2093w (C≡C) cm^{-1}

6.4.13 4, 7-*Bis*(phenylethynyl)-2, 1, 3-benzothiadiazole (43)

The synthesis of 4, 7-*bis*(phenylethynyl)-2, 1, 3-benzothiadiazole (**43**) was undertaken by a method based on the procedure reported by Dupont *et al*.[26]



Palladium(II) chloride (11.1 mg, 62.4 μmol), copper(II) acetate (29.2 mg, 0.161 mmol), triphenylphosphine (52.0 mg, 0.170 mmol) and 4, 7-dibromo-2, 1, 3-benzothiadiazole (**38**) (51 g, 5.1 mmol) were mixed under nitrogen with dry and degassed diisopropylamine/ tetrahydrofuran (50 mL, 1:4 *v/v*). The solution was stirred for 30 min at room temperature and phenylacetylene (1.2 mL, 11 mmol) was added at room temperature to the vigorously stirred solution. The reaction mixture was heated at reflux under nitrogen for 2 h and the reaction was monitored by TLC (TLC, hexane: dichloromethane, 1:2). After being cooled to room temperature, the mixture was filtered to remove the insoluble salts and the solvent was removed *in vacuo*. The solid residue was dissolved in dichloromethane and adsorbed onto silica and purified by column chromatography (hexane: dichloromethane, 1:2) (TLC, hexane: dichloromethane, 1:2, $R_f = 0.71$) to give 4, 7-*bis*(phenylethynyl)-2, 1, 3-benzothiadiazole (**43**) as a yellow/ brown solid (2.2 g, 89%).

^{1}H NMR (400 MHz, chloroform-*d*): δ 7.78 (s, 2H, **H5** and **H6**), 7.67 (m, 4H, **Ph**), 7.39 (m, 6H, **Ph**) ppm.

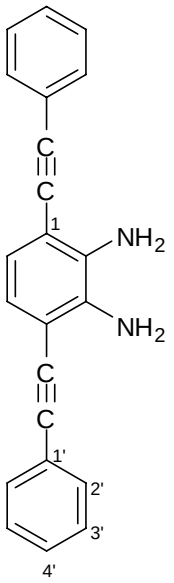
^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 154.5 (**C3a** and **C7a**), 132.6 (**C5** and **C6**), 132.1 (**C2'**), 129.2 (**C4'**), 128.6 (**C3'**), 122.6 (**C1'**) 117.3 (**C4** and **C7**), 97.6 (C≡**C**), 85.4 (**C**≡C) ppm.

m/z (EI): 336 (M^+, 100%).

High resolution mass spectrum: calculated for $C_{22}H_{12}N_2S$ (M^+) 336.0721, found 336.0720.

ν (KBr): 3047w (aromatic C-H), 2216w (C≡C), 1597w, 1562w, 1499s, 1481w (C=N) cm^{-1}.

6.4.14 2, 3-Diamino-1,4-*bis*(phenylethynyl)benzene (8)



Sodium borohydride (2.57 g, 68.0 mmol) was added portionwise to a suspension of 4, 7-*bis*(phenylethynyl)-2, 1, 3-benzothiadiazole (**43**) (1.34 g, 4.00 mmol), palladium(II) chloride (0.071 g, 0.400 mmol, 10 mol%), copper(II) acetate (0.073 g, 0.400 mmol, 10 mol%) in ethanol (125 mL) at 0 °C. The reaction mixture was allowed to slowly return to room temperature and the mixture was stirred for 24 h at room temperature. The reaction was monitored by TLC (TLC, hexane: dichloromethane, 1:1, $R_f = 0.21$). The solvent was removed *in vacuo*, water (200 mL) was added and the mixture was extracted with diethyl ether (3 × 150 mL). The ether extracts were combined and washed with brine then dried over magnesium sulfate. The solvent was removed to give 2, 3-diamino-1, 4-*bis*(phenylethynyl)benzene (**8**) as a brown solid (1.1 g, 92%).

^{1}H NMR (400 MHz, chloroform-*d*): δ 7.56-7.54 (m, 4H, **Ph**), 7.40-7.33 (m, 6H, **Ph**), 6.93 (s, 2H, **H5** and **H6**), 4.04 (bs, 4H, N**H$_2$**) ppm.

^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 136.2 (**C2** and **C3**), 132.6 (**C2'**) 131.6 (**C4'**), 128.6 (**C3'**), 123.3 (**C1'**), 122.3 (**C5** and **C6**), 109.8 (**C1** and **C4**), 95.8 (C≡**C**), 86.2 (**C**≡C) ppm.

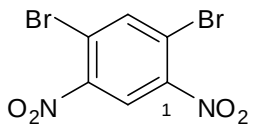
m/z (EI): 309 ((M+H)$^+$, 27%) 308 (100).

High resolution mass spectrum: calculated for $C_{22}H_{16}N_2$ (M^+) 308.1313, found 308.1311.

ν (KBr): 3427m, 3394m (N-H), 2198w (C≡C) cm^{-1}.

6.4.15 1, 5-Dibromo-2, 4-dinitrobenzene (44)

1, 5-Dibromo-2, 4-dinitrobenzene (**44**) was prepared by a method based on the procedure reported by Dacons.[27]



1, 3-Dibromobenzene (5.70 g, 24.2 mmol) was added slowly to a stirred mixture of concentrated sulfuric acid (5.3 mL) and fuming nitric acid[6] (5.3 mL) cooled in an ice bath. The rate of addition was such as to maintain a temperature of 10-20 °C and the temperature was then maintained between 35-40 °C for 40 min after the addition was complete. The reaction mixture was then stirred with an excess of crushed ice. A solid precipitate formed and was collected by filtration and washed with water until the filtrate was neutral. The crude solid was stirred in a mixture of absolute ethanol (90 mL) and acetone (20 mL) then filtered and cooled in the fridge overnight. Two crops of crystals were collected and washed with cold ethanol to give 1, 5-dibromo-2, 4-dinitrobenzene (**44**) as a bright yellow crystalline solid (5.2 g, 66%) m.p. 117-120 °C (lit.[27] 117 °C)

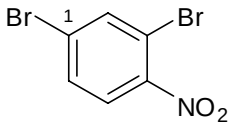
^{1}H NMR (200 MHz, chloroform-*d*): δ 8.44 (s, 1H, **H3**), 8.21 (s, 1H, **H6**) ppm.
^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 148.3 (**C2** and **C4**), 141.5 (**C6**), 123.0 (**C1** and **C5**), 120.0 **(C3**) ppm.
m/z (EI): 326 (M^{+}, 69%), 234 (40), 324 (28), 74 (100).

6.4.16 The Attempted Synthesis of 1, 5-Dibromo-2, 4-dinitrobenzene (44)

The synthesis of 1, 5-dibromo-2, 4-dinitrobenzene (**44**) was attempted by a method based on the procedure reported by Dacons.[27]

1, 3-Dibromobenzene (0.76 g, 3.2 mmol) was added slowly to a stirred mixture of concentrated sulfuric acid (5 mL) and nitric acid (5 mL, 75%) was cooled in an ice bath. The rate of addition was such as to maintain a temperature of 10-20 °C and the temperature was then maintained between 35-40 °C for 40 min after the addition was complete. The reaction mixture was stirred in an excess of crushed

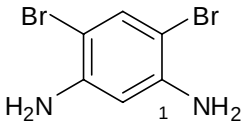
ice. A solid precipitation formed and was collected by filtration and washed with water until the filtrate was neutral to give 1, 3-dibromo-4-nitrobenzene (**47**) as a yellow solid (0.65 g, 73%).



^{1}H NMR (400 MHz, chloroform-*d*): δ 7.89 (d, $^{3}J_{H5\text{-}H6}$ = 8.6 Hz, 1H, **H5**), 7.73 (d, $^{4}J_{H2\text{-}H6}$ = 1.9 Hz, 1H, **H2**), 7.57 (dd, $^{4}J_{H6\text{-}H2}$ = 1.9 Hz, $^{3}J_{H6\text{-}H5}$ = 8.6 Hz, 1H, **H6**) ppm.
^{13}C{^{1}H} NMR (75 MHz, chloroform-*d*): δ 141.5 (**C4**), 137.7 (**C2**), 131.6 (**C6**), 127.5 (**C1**), 126.9(**C5**), 115.8 (**C3**) ppm.

6.4.17 1, 5-Diamino-2, 4-dibromobenzene (45)

The synthesis of 1, 5-diamino-2, 4-dibromobenzene (**45**) was undertaken using the method reported by Dumont and Slegers.[28]



Iron powder (21 g, 0.38 mol) and acetic acid (21 mL) were added, in turn, to a stirred solution of 1, 5-dibromo-2, 4-dinitrobenzene (**44**) (7.6 g, 23 mmol) in ethanol (75 mL). The colour of the reaction mixture turned to black. The mixture was refluxed for 5.5 h then cooled to give a grey precipitate. The reaction mixture was monitored by TLC to establish completion (TLC, hexane: ethyl acetate, 4:1, R_f = 0.26). The mixture was filtered through Celite and washed with ethanol (1 L). Sodium hydroxide solution (25%) was added to the filtrate until pH 12 was achieved. The basic solution was filtered through Celite and the solvent was removed to give a brown residue. The residue was extracted with diethyl ether (12 × 50 mL, 15 × 100 mL). The ether extracts were combined, dried over magnesium sulfate and removed *in vacuo* to give 1, 5-diamino-2, 4-dibromobenzene (**45**) as an orange flaky solid (4.2 g, 69%), m.p 133-135 °C.

^{1}H NMR (50 MHz, dimethyl-d_6 sulfoxide): δ 7.22 (s, 1H, **H3**), 6.24 (s, 1H, **H6**), 5.09 (bs, 4H, N**H**$_2$) ppm.

$^{13}C\{^{1}H\}$ NMR (75 MHz, dimethyl-d_6 sulfoxide): δ 145.6 (**C1** and **C5**), 133.6 (**C3**), 100.6 (**C6**), 94.9 (**C2** and **C4**) ppm.

m/z (EI): 266 (M^+, 100%), 264 (55), 185 (29), 106 (16), 105 (12)

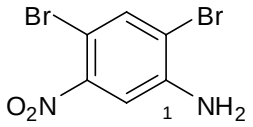
Anal. Found: C, 27.53; H, 1.82; N, 10.58. $C_6H_6Br_2N_2$ requires C, 27.10; H, 2.27; N,10.53%.

ν (KBr): 3408s, 3326s (N-H), 3189w (C-H aromatic), 1620s, 1486s, 1415s, 1264s, 657s cm^{-1}.

6.4.18 The Attempted Synthesis of 1, 5-Diamino-2, 4-dibromobenzene (45)

The synthesis of 1, 5-diamino-2, 4-dibromobenzene (**45**) was attempted by a method based on the procedure reported by Dumont and Slegers.[28]

Iron powder (8.4 g, 0.15 mol) and acetic acid (16 mL) were added to a stirred solution of 1, 5-dibromo-2, 4-dinitrobenzene (**44**) (6.2 g, 19 mmol) in ethanol (70 mL). The colour of the reaction mixture turned to black. The mixture was refluxed for 2 h and then cooled. The mixture was filtered through Celite and washed with ethanol (500 mL). Sodium hydroxide solution (25%) was added to the filtrate until pH 12 was achieved. The basic solution was filtered through Celite and the solvent was removed *in vacuo* to give 1-amino-2, 4-dibromo-5-nitrobenzene (**48**) (TLC, hexane: ethyl acetate, 4:1, $R_f = 0.46$) as an orange solid (5.4 g, 96%).



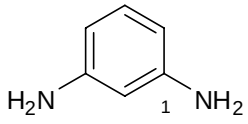
^{1}H NMR (200 MHz, chloroform-*d*): δ 7.74 (s, 1H, **H3**), 7.25 (s, 1H, **H6**), 4.42 (bs, 2H, N**H**) ppm.

$^{13}C\{^{1}H\}$ NMR (75 MHz, chloroform-*d*): δ 149.1 (**C5**), 144.5 (**C1**), 137.7 (**C3**), 133.4 (**C4**), 111.2 (**C6**), 100.8 (**C2**) ppm.

6.4.19 The Attempted Synthesis of 1, 5-Diamino-2, 4-dibromobenzene (45)

The synthesis of 1, 5-diamino-2, 4-dibromobenzene (**45**) was attempted using the method bases on the procedure reported by Moroni *et al*.[5]

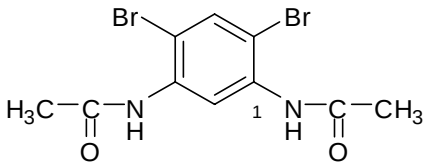
Tin powder (0.7 g, 5.6 mmol) was added to a solution of 1, 5-dibromo-2, 4-dinitrobenzene (**44**) (0.3 g, 1.0 mmol) in ethanol (10 mL) and concentrated hydrochloric acid (1 mL). The mixture was stirred for 6 h and then concentrated under vacuum. Water (5 mL) and diethyl ether (25 mL) were added and the mixture was filtered through Celite to remove the tin salts. The filtrate was neutralized with potassium carbonate and then extracted with diethyl ether (4 × 40 mL). The ether extracts were combined, and dried on magnesium sulfate and concentrated to give 1, 3-diaminobenzene (**49**) as a brown oil (25 mg, 23%).



^{1}H NMR (200 MHz, chloroform-*d*): δ 6.92 (t, $^{3}J_{H5\text{-}H4}$ = 7.9 Hz, 1H, **H5**), 6.10 (dd, $^{3}J_{H4\text{-}H5}$ = 7.9 Hz, $^{4}J_{H4\text{-}H2}$ = 2.0 Hz, 2H, **H4**), 6.02 (t, $^{4}J_{H2\text{-}H4}$ = 2.0 Hz, 1H, **H2**), 3.46 (bs, 4H, N**H**) ppm.
^{13}C{^{1}H} NMR (75 MHz, chloroform-*d*): δ 147.6 (**C1** and **C3**), 130.3 (**C5**) 106.2 (**C4** and **C6**), 102.1 (**C2**) ppm.

6.4.20 1, 5-*Bis*(acetamido)-2, 4-dibromobenzene (50)

The synthesis of 1, 5-*bis*(acetamido)-2, 4-dibromobenzene (**50**) was undertaken by a method based on the procedure reported by Ward.[23]



Acetic anhydride (0.3 mL) was added to a solution of 1, 5-diamino-2, 4-dibromobenzene (**45**) (52 mg, 0.20 mmol) in dichloromethane (2 mL), and the reaction was stirred at room temperature for 2 h. The solvent was removed *in vacuo*. The residue was recrystallised from ethanol to give 1, 5-*bis*(acetamido)-2, 4-dibromobenzene (**50**) as a white powder (41 mg, 61%).

^{1}H NMR (200 MHz, dimethyl-d_6 sulfoxide): δ 9.52 (bs, 2H, N**H**), 7.94 (s, 1H, **H3**), 7.88 (s, 1H, **H6**), 2.07 (s, 6H, C**H**$_3$) ppm.

^{13}C{^{1}H} NMR (75 MHz, dimethyl-d_6 sulfoxide): δ 168.7 (**C**=O), 136.1 (**C1** and **C5**), 135.0 (**C3**), 124.3 (**C6**), 114.2 (**C2** and **C4**), 23.3 (**C**H$_3$) ppm.

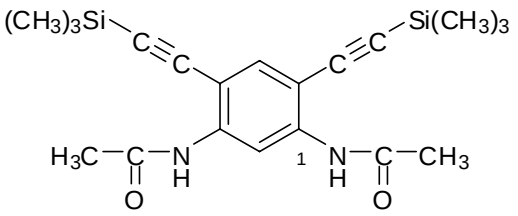
m/z (EI): 350 (M^+, 3%), 271 (100), 269 (93), 266 (28), 229 (60), 227 (53), 189 (50).

High resolution mass spectrum: calculated for $C_{10}H_{10}Br_2N_2O_2$ $(M)^+$ 347.9109, found 347.9111.

Anal. Found: C, 34.19; H, 2.74; N, 7.88. $C_{10}H_{10}Br_2N_2O_2$ requires C, 34.32; H, 2.88; N, 8.00%.

ν (KBr): 3224 s(N-H), 3087w, 3008w (C-H aromatic), 1666s (C-O), 1573s,1518s, 1382s, 1060s, 678s cm^{-1}.

6.4.21 1, 5-*Bis*(acetamido)-2, 4-*bis*(trimethylsilylethynyl)benzene (12)



Palladium(II) chloride (111 mg, 0.626 mmol), copper(II) acetate (128 mg, 1.04 mmol), triphenylphosphine (482 mg, 1.84 mmol) and 1, 5-*bis*(acetamido)-2, 4-dibromobenzene (**50**) (2.0 g, 5.7 mmol) were mixed under nitrogen with dry and degassed triethylamine (180 mL). (Trimethylsilyl)acetylene (2.6 mL, 18 mmol) was added and the reaction mixture was stirred and heated at 85 °C under nitrogen for 8 h. After being cooled to room temperature, the mixture was filtered to remove the insoluble salts and the triethylamine was removed under reduced pressure. The solid residue was dissolved in ethyl acetate, adsorbed on column silica and purified by column chromatography (hexane: ethyl acetate, 1:1) (TLC, hexane: ethyl acetate, 1:1, R_f = 0.46) to give 1, 5-*bis*(acetamido)-2, 4-*bis*(trimethylsilylethynyl)benzene (**12**) as a light brown solid (1.1 g, 50%), m.p. 168-170 °C.

^{1}H NMR (200 MHz, chloroform-*d*): δ 9.34 (b, 1H, **H6**), 7.90 (bs, 2H, N**H**), 7.46 (s, 1H, **H3**), 2.17 (s, 6H, C**H**$_3$), 0.27 (s, 18H, Si(C**H**$_3$)$_3$) ppm.

$^{13}C\{^{1}H\}$ NMR (75 MHz, chloroform-*d*): δ 167.9 (**C**=O), 140.7 (**C1** and **C5**) 134.6 (**C3**) 109.7 (**C6**), 106.9 (**C2** and **C4**), 102.1 (**C**≡C), 99.4 (C≡**C**), 24.9 (**C**H_3), 0.4 (Si(**C**H_3)$_3$) ppm.

m/z (EI): 384 (M^+, 75%), 343 (100), 301 (40), 74 (18).

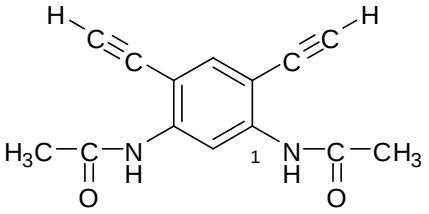
High resolution mass spectrum: calculated for $C_{20}H_{28}N_2Si_2$ $(M)^+$ 384.1689, found 384.1685.

Anal. Found: C, 63.00; H, 7.45; N, 7.17. $C_{20}H_{28}N_2Si_2$ requires C, 62.45; H, 7.34; N, 7.28%.

ν (KBr): 3293w (N-H), 2958w (C-H aromatic), 2155m (C≡C), 1671s (C=O), 1585s, 1412s, 1250s, 842s cm^{-1}.

6.4.22 1, 5-*Bis*(acetamido)-2, 4-diethynylbenzene (9)

The synthesis of 1, 5-*bis*(acetamido)-2, 4-diethynylbenzene (**9**) was undertaken by a method based on the procedure described by Arcadi *et al*.[25]



1, 5-*Bis*(acetamido)-2, 4-*bis*(trimethylsilylethynyl)benzene (**12**) (0.44 g, 1.2 mmol) was dissolved in methanol (40 mL), potassium fluoride (0.70 g, 12 mmol) added and the reaction mixture stirred for 1 h at room temperature. Water (30 mL) was added, and the reaction mixture was extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with water (2 × 25 mL) and brine (25 mL), then dried over magnesium sulfate. The solvent was removed *in vacuo* to give 1, 5-*bis*(acetamido)-2, 4-diethynylbenzene (**9**) as a creamy brown solid (107 mg, 39%), m.p. 300 °C (dec.).

^{1}H NMR (400 MHz, tetrahydrofuran-d_8): δ 9.08 (s, 1H, **H6**), 8.42 (bs, 2H, N**H**), 7.44 (s, 1H, **H3**), 3.92 (s, 2H, C≡C-**H**), 2.11 (s, 6H, C**H**$_3$) ppm.

$^{13}C\{^{1}H\}$ NMR (100 MHz, tetrahydrofuran-d_8): δ 168.2 (**C=O**), 142.1 (**C1** and **C5**), 136.6 (**C3**), 133.9 (**C6**), 108.1 (**C2** and **C4**), 84.8 (**C**≡C-H), 79.3 (C≡**C**-H), 24.2 (**C**H_3) ppm.

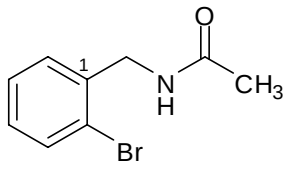
m/z (EI): 240 (M^+, 30%), 198 (77), 156 (100), 104 (26).

High resolution mass spectrum: calculated for $C_{14}H_{12}N_2O_2$ $(M)^+$ 240.0899, found 240.0897.

ν (KBr): 3392m (N-H), 3278s, 3206s (C≡**C-H**), 2097w (**C**≡**C-**H), 1699s, 1686s, 1664s (C=O), 1577s, 1529s, 1497s, 1417s cm^{-1}.

6.4.23 *N*-(Acetyl)-2-bromobenzylamine (51)

The synthesis of *N*-(acetyl)-2-bromobenzylamine (**51**) was undertaken by a method based on the procedure reported by DeVita *et al*.[29]



Triethylamine (2.2 mL, 50 mmol) was added to a suspension of 2-bromobenzylamine hydrochloride (4.90 g, 22.5 mmol) in dichloromethane (150 mL) under nitrogen. The resulting solution was stirred at 0 °C for 5 min and then treated with acetic anhydride (2.4 mL, 26 mmol). The reaction mixture was stirred at room temperature for 24 h then diluted with dichloromethane (150 mL). The solution was washed with water (2 × 100 mL), saturated aqueous ammonium chloride (100 mL), saturated aqueous sodium bicarbonate (4 × 100 mL) and brine (100 mL) then dried over magnesium sulfate. The solvent was removed to give *N*-(acetyl)-2-bromobenzylamine (**51**) as a white solid (4.7 g, 91%), m.p. 81-82.5 °C.

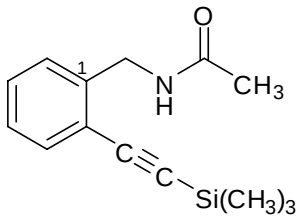
^{1}H NMR (200 MHz, chloroform-*d*): δ 7.53 (dd, $^3J_{H3\text{-}H4}$ = 7.8 Hz, $^4J_{H3\text{-}H5}$ = 1.2 Hz, 1H, **H3**), 7.36 (dd, $^3J_{H6\text{-}H5}$ = 7.5 Hz, $^4J_{H6\text{-}H4}$ = 1.6 Hz, 1H, **H6**), 7.26 (app. dt, 1H, **H5**), 7.13 (app. dt, 1H, **H4**), 6.16 (bs, 1H, N**H**), 4.48 (d, $^3J_{CH\text{-}NH}$ = 6.0 Hz, 2H, C$\mathbf{H}_2$), 2.00 (s, 3H, C$\mathbf{H_3}$) ppm.

^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 170.2 (**C**=O), 137.4 (**C1**), 132.8 (**C3**), 130.4 (**C5**), 129.2 (**C6**), 127.8 (**C4**), 123.8 (**C2**), 44.0 (**C**H_2), 23.3 (**C**H_3) ppm.

m/z (EI): 228 ($(M+H)^+$, 26%), 148 (100), 107 (50).

6.4.24 *N*-(Acetyl)-2-(trimethylsilylethynyl)benzylamine (13)

The synthesis of *N*-(acetyl)-2-(trimethylsilylethynyl)benzylamine (**13**) was undertaken by a method based on the procedure reported by Moroni *et al*.[5]

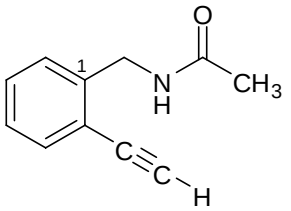


Palladium(II) chloride (0.280 g, 1.58 mmol), copper(II) acetate (0.464 g, 2.56 mmol), triphenylphosphine (1.57 g, 5.98 mmol) and *N*-(acetyl)-2-bromobenzylamine (**51**) (2.77 g, 12.2 mmol) were mixed under nitrogen with dry and degassed triethylamine (120 mL). (Trimethylsilyl)acetylene (3.4 mL, 24 mmol) was added and the reaction mixture was stirred and heated at 85 ºC under nitrogen for 8 h. At room temperature, the mixture was filtered to remove the insoluble salts and the triethylamine was removed under reduced pressure. The solid residue was dissolved in chloroform and adsorbed onto silica and then purified by column chromatography (hexane: ethyl acetate, 1:1) (TLC, hexane: ethyl acetate, 1:1, $R_f = 0.4$) to give *N*-(acetyl)-2-(trimethylsilylethynyl)benzylamine (**13**) as a brown solid (0.56 g, 18%).

^{1}H NMR (400 MHz, chloroform-*d*): δ 7.48 (dd, $^3J_{H3\text{-}H4} = 7.3$ Hz, $^4J_{H3\text{-}H5} = 1.2$ Hz, 1H, **H3**), 7.34 (m, 1H, **H6**), 7.30 (m, 1H, **H5**), 7.24 (m, 1H, **H4**), 6.10 (bs, 1H, N**H**), 4.56 (d, $^3J_{CH\text{-}NH} = 5.9$ Hz, 2H, C$\mathbf{H}_2$), 2.02 (s, 3H, C$\mathbf{H}_3$), 0.26 (s, 9H, Si(C$\mathbf{H}_3$)$_3$) ppm.
^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 169.9 (**C**=O), 140.5 (**C1**), 132.7 (**C3**), 129.1 (**C5**), 128.7 (**C6**), 127.5 (**C4**), 122.4 (**C2**), 103.0 (**C**≡C), 99.6 (C≡**C**), 42.6 (**C**H$_2$), 23.4 (**C**H$_3$), 0.1 (Si(**C**H$_3$)$_3$) ppm.
m/z (EI): 230 ((M-CH$_3$)$^+$, 16%), 203 (20), 202 (100), 186 (57), 130 (55), 115 (56).

6.4.25 *N*-(Acetyl)-2-ethynylbenzylamine (10)

The synthesis of *N*-(acetyl)-2-ethynylbenzylamine (**10**) was undertaken by a method based on the procedure reported by Moroni *et al*.[5]

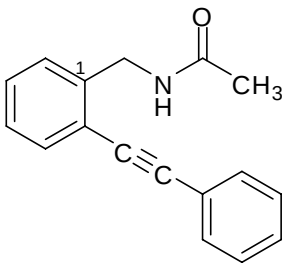


Tetrabutylammonium fluoride (1M in tetrahydrofuran, 1.4 mL) was added to *N*-(acetyl)-2-(trimethylsilylethynyl)benzylamine (**13**) (0.476 g, 1.94 mmol) in tetrahydrofuran (25 mL). After stirring for 1 hour at room temperature the tetrahydrofuran was removed under reduced pressure and the residue purified by column chromatography (hexane: ethyl acetate, 1:1) (TLC, hexane: ethyl acetate, 1:1, $R_f = 0.2$) to give *N*-(acetyl)-2-ethynylbenzylamine (**10**) as a yellow crystalline solid (0.17 g, 49%).

^{1}H NMR (400 MHz, tetrahydrofuran-d_8): δ 7.55-7.43 (bs, 1H, N**H**), 7.54 (dd, $^3J_{H3\text{-}H4}$ = 7.6 Hz, $^4J_{H3\text{-}H5}$ = 1.0 Hz, 1H, **H3**), 7.47
(dd, $^3J_{H6\text{-}H5}$ = 7.5 Hz, $^4J_{H6\text{-}H4}$ = 0.7 Hz, 1H, **H6**), 7.41 (m, 1H, **H5**), 7.30 (m, 1H, **H4**), 4.63 (d, $^3J_{CH\text{-}NH}$ = 5.8 Hz, 2H, C**H**$_2$), 3.92 (s, 1H, C≡C-**H**), 2.00 (s, 3H, C**H**$_3$) ppm.
^{13}C{^{1}H} NMR (100 MHz, tetrahydrofuran-d_8): δ 170.0 (**C**=O), 143.6 (**C1**), 133.9 (**C3**), 130.1 (**C5**), 129.2 (**C6**), 128.1 (**C4**), 122.8 (**C2**), 84.1 (**C**≡C-H), 82.7 (C≡**C**), 42.7 (**C**H$_2$), 23.2 (**C**H$_3$) ppm.
m/z (EI): 130 ((M-COCH$_3$)$^+$, 100%).

6.4.26 *N*-(Acetyl)-2-(phenylethynyl)benzylamine (11)

The synthesis of *N*-(acetyl)-2-(phenylethynyl)benzylamine (**11**) was undertaken by a method based on the procedure reported by Moroni *et al*.[5]



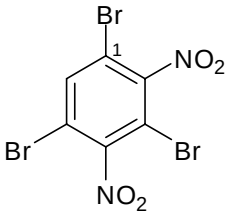
Palladium(II) chloride (11.5 mg, 0.650 mmol), copper(II) acetate (19.0 mg, 0.105 mmol), triphenylphosphine (64 mg, 0.240 mmol) and *N*-(acetyl)-2-bromobenzylamine (**51**) (0.114 g, 0.499 mmol) were mixed under

nitrogen with dry and degassed triethylamine (25 mL). Phenylacetylene (0.14 mL, 1.2 mmol) was added and the reaction mixture was stirred and heated at 85 ºC under nitrogen for 8 h. After being cooled to room temperature, the mixture was filtered to remove the insoluble salts and the triethylamine was removed under reduced pressure. The oily residue was adsorbed onto silica and then purified by column chromatography (hexane: ethyl acetate, 1:1) (TLC, hexane: ethyl acetate, 1:1, $R_f = 0.24$) to give *N*-(acetyl)-2-(phenylethynyl)benzylamine (**11**) as an orange solid (98 mg, 79%), m.p. 98 °C.

^{1}H NMR (400 MHz, chloroform-*d*): δ 7.55-7.52 (m, 3H, Ar-**H**), 7.38-7.23 (m, 6H, Ar-**H**), 6.42 (bs, 1H, N**H**), 4.64 (d, $^3J_{CH\text{-}NH}$ = 5.8 Hz, 2H, C**H**$_2$), 1.98 (s, 3H, C**H**$_3$) ppm.
^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 170.1 (**C**=O), 139.8 (**C1**), 132.3, 131.6, 128.7, 128.6, 128.5, 128.3, 127.4, 122.9, 122.3 (Ar-**C**), 94.3 (C≡**C**), 87.0 (**C**≡C), 42.4 (**C**H$_2$), 23.1 (**C**H$_3$) ppm.
m/z (EI): 248 ((M-H)$^+$, 7%), 207 (35), 206 (100).
High resolution mass spectrum: calculated for $C_{17}H_{15}NO$ (M^+) 249.1154, found 249.1156.

6.4.27 1, 3, 5-Tribromo-2, 4-dinitrobenzene (53)

The synthesis of 1, 3, 5-tribromo-2, 4-dinitrobenzene (**53**) was undertaken by a method based on the procedure described by Hill and Taylor.[30]



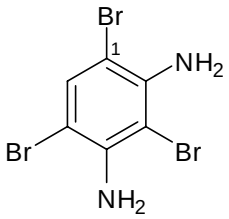
1, 3, 5-Tribromobenzene (5.07 g, 16.1 mmol) was added portionwise to a solution of concentrated sulfuric acid (6 mL) and fuming nitric acid[6] (17 mL) at room temperature. The rate of addition was such as to maintain a temperature below 60 ºC. The mixture was cooled after the addition was complete and then stirred in an excess of crushed ice. A solid precipitate formed and was collected by filtration and washed with water until the filtrate was neutral. The solid was

recrystallised from chloroform to give 1, 3, 5-tribromo-2, 4-dinitrobenzene (**53**) as a light brown solid (6.2 g, 95%), m.p. 189-191 ºC (lit.[30] 192 ºC).

^{1}H NMR (200 MHz, chloroform-*d*): δ 8.05 (s, 1H**, H6**) ppm.
^{13}C{^{1}H} NMR (50 MHz, chloroform-*d*): δ 151.4 (**C2** and **C4**), 137.4 (**C6**), 116.2 (**C1** and **C5**), 107.9 (**C3**) ppm.
m/z (EI): 404 (M^{+}, 31%), 374 (23), 265 (100), 152 (24).

6.4.28 2, 4-Diamino-1, 3, 5-tribromobenzene (55)

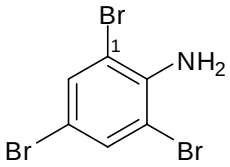
The synthesis of 2, 4-diamino-1, 3, 5-tribromobenzene (**55**) was undertaken by a method based on the procedure reported by Dumont and Slegers.[28]



Iron powder (2.64 g, 47.4 mmol) and acetic acid (15 mL) were added successively to a stirred solution of 1, 3, 5-tribromo-2, 4-dinitrobenzene (**53**) (1.13 g, 2.80 mmol) in ethanol (2.5 mL). The mixture was heated at reflux for 1 hour then cooled to give a brown precipitate. The reaction mixture was monitored by TLC (TLC, hexane: dichloromethane, 1:1, $R_f = 0.63$). The mixture was filtered off Celite and washed with ethanol (125 mL). Sodium hydroxide solution (25%) was added to the filtrate until pH 12 was achieved. The basic solution was filtered through Celite and the filtrate was reduced in volume to remove the ethanol. The resulting off-white suspension was diluted with water and extracted with diethyl ether (6 × 30 mL). The ether extracts were combined, dried over magnesium sulfate and the solvent was removed *in vacuo* to give 2, 4-diamino-1, 3, 5-tribromobenzene (**55**) as a white solid (0.66 g, 68%), m.p. 158-160 °C (lit.[31] 157-158.5 ºC).

^{1}H NMR (200 MHz, chloroform-*d*): δ 7.44 (s, 1H, **H6**) ppm.
^{13}C{^{1}H} NMR (50 MHz, chloroform-*d*): δ 141.8 (**C2** and **C4**), 133.4 (**C6**), 96.3 (**C1** and **C5**), 95.5 (**C3**) ppm.
m/z (EI): 344 (M^{+}, 100%), 261 (34), 184 (14), 105 (9).

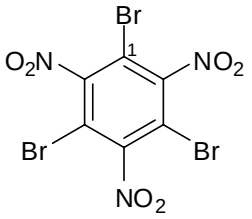
When the reaction mixture for the synthesis of compound **55** was refluxed for more than 16 h, 2, 4, 6-tribromoaniline (**56**) was also formed. Compound **56** was isolated by column chromatography (hexane: dichloromethane, 7:3) (TLC, hexane: dichloromethane, 7:3, $R_f = 0.54$) as a white solid (8.8 mg, 4.8%).[32]



^{1}H NMR (200 MHz, chloroform-*d*): δ 7.51 (s, 2H, **H4** and **H6**) ppm.
m/z (EI): 329 (M^+, 100%), 250 (29).

6.4.29 1, 3, 5-Tribromo-2, 4, 6-trinitrobenzene (52)

The synthesis of 1, 3, 5-tribromo-2, 4, 6-trinitrobenzene (**52**) was undertaken by a method based on the procedure reported by Hill and Taylor.[30]

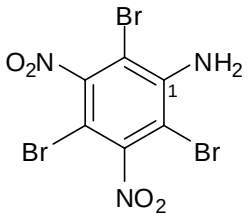


Potassium nitrate (3.40 g, 33.6 mmol) was added to fuming sulfuric acid (25 mL, 20% oleum) at 0 °C. The mixture was heated and 1, 3, 5-tribromo-2, 4,-dinitrobenzene (**53**) was added to the resulting mixture at 110 °C and then the temperature was raised further to 125 °C and stirred for 9 h at this temperature. After cooling to room temperature, the mixture was poured over crushed ice. The solid precipitate formed was collected by filtration and washed with water until the filtrate was neutral. The solid was recrystallised from ethyl acetate to give 1, 3, 5-tribromo-2, 4, 6-trinitrobenzene (**52**) as a yellow solid (0.22 g, 7%).

^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 152.9 (**C2, C4** and **C6**), 110.3 (**C1, C3** and **C5**) ppm.
m/z (EI): 449 (M^+, 39%), 419 (26), 310 (54), 232 (100).

6.4.30 2, 4, 6-Tribromo-3, 5-dinitroaniline (54)

The synthesis of 2, 4, 6-tribromo-3, 5-dinitroaniline (**54**) was undertaken using the method reported by Dumont and Slegers.[28]



Iron powder (210 mg, 3.76 mmol) and acetic acid (2.3 mL) were added, in turn, to a stirred solution of 1, 3, 5-tribromo-2, 4, 6-trinitrobenzene (**52**) (64.4 mg, 0.143 mmol) in ethanol (2.5 mL). The mixture was refluxed for 24 h and monitored by TLC (TLC, ethyl acetate: hexane, 1:4, $R_f = 0.58$). The mixture was filtered through Celite and washed with ethanol (25 mL). Sodium hydroxide solution (25%) was added to the filtrate until pH 12 was achieved. The basic solution was filtered through Celite and the filtrate was reduced in volume to remove the ethanol. The resulting suspension was diluted with water and extracted with diethyl ether (3 × 10 mL) to give 2, 4, 6-tribromo-3, 5-dinitroaniline **(54)** as a yellow solid (47 mg, 79%).

^{1}H NMR (400 MHz, chloroform-*d*): δ 4.75 (bs, 2H, **H1**) ppm.

^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 142.7 (**C3** and **C5**), 127.0 (**C1**), 99.4 (**C2** and **C6**), 93.7 (**C4**) ppm.

m/z (EI): 420 (M^+, 20%), 345 (30), 264 (21), 183 (14).

6.5 Metal-Catalysed Intramolecular Hydroamination Reactions

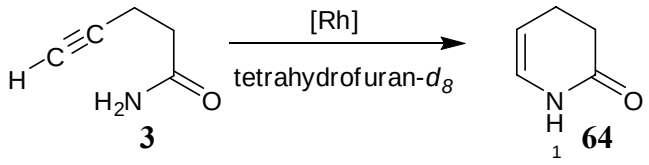
6.5.1 General Procedures for Catalytic Reactions

The rhodium(I) and the palladium(II) catalysed reactions were performed on small scale in NMR tubes fitted with concentric Teflon valves. The rhodium(I) complex catalysed reactions were also performed on larger scale in straight schlenk flasks (volume capacity 12 mL). The rhodium(I) catalyst was typically added to the substrate dissolved in an appropriate deuterated solvent. In the case of the palladium(II) complexes catalysed reactions, the substrate was added to the palladium(II) complex in a deuterated solvent, in a NMR tube at -78 °C. The catalytic reactions were performed at an elevated temperature by heating in an oil bath at 60 °C or heating within the NMR spectrometer at 60 °C, in the case of time course experiments. All reactions were performed under an atmosphere of nitrogen. The temperature within the magnet was calibrated using ethylene glycol.[33] Products were confirmed by comparison with spectral NMR data from the literature where possible or were isolated and characterised.

The conversion of starting material to product was determined by integration of the product resonances relative to the substrate resonances in the ^{1}H NMR spectrum. 100% conversion was taken to be the time where no remaining substrate peaks were evident. The turnover rate (N_t (h^{-1})) was calculated as the number of moles of product/ mole of catalyst/ hour and was usually calculated at the point of 50% conversion of substrate to product.

6.6 Cyclisation of Aliphatic Aminoalkynes

6.6.1 Cyclisation of 4-Pentyn-1-amide (3) to 3, 4-Dihydro-2-pyridone (64)



The rhodium(I) complex (**1**) catalysed cyclisation of 4-pentyn-1-amide (**3**) and led to the formation of a single product, 3, 4-dihydro-2-pyridone (**64**).

$[Rh(bim)(CO)_2][BPh_4]$ (**1**) (136 mg, 207 μmol) (10 mol%) was added to 4-pentyn-1-amide (**3**) (200 mg, 2.07 mmol) in tetrahydrofuran-d_8 (0.5 mL) in an NMR tube under an atmosphere of nitrogen. The mixture was heated at 60 °C and ^{1}H NMR spectra were recorded at regular intervals. The product **64** was formed after 40 h.

Once the reaction was complete, the NMR tube was opened to the atmosphere. The residue was poured into a mixture of hexane (2.5 mL) and ethyl acetate (7.5 mL) to give a solid brown precipitate. The supernatant liquid was isolated and the brown precipitate was washed with hexane: ethyl acetate (1:3) (4 × 20 mL). The solvent fractions were combined, reduced and purified by column chromatography, (hexane: ethyl acetate, 1:3) (TLC, hexane: ethyl acetate, 1:3, R_f = 0.36) to give 3, 4-dihydro-2-pyridone (**64**) as a yellow oil (16 mg, 11%).

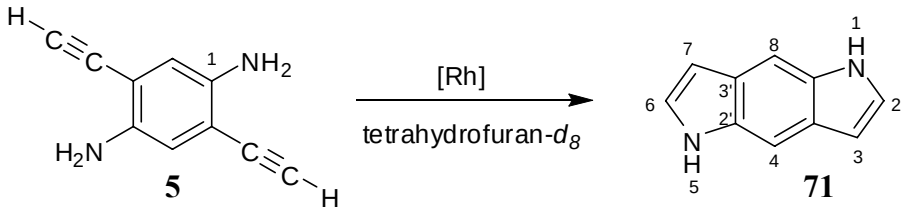
^{1}H NMR (400 MHz, chloroform-*d*): δ 7.90 (bs, 1H, N**H**), 6.04 (ddt, $^3J_{H6\text{-}H5}$= 7.6 Hz, $^3J_{H6\text{-}NH}$= 1.3 Hz, 1H, **H6**), 5.04 (dtd, $^3J_{H5\text{-}H6}$= 7.6 Hz, $^3J_{H5\text{-}H6}$= 4.3 Hz, 1H, **H5**), 2.46 (m, 2H, **H3**), 2.29 (m, 2H, **H4**) ppm.
^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 171.9 (**C2**), 125.1 (**C6**), 105.1 (**C5**), 30.5 (**C3**), 20.1 (**C4**) ppm.
m/z (EI): 97 (M^+, 48%).
m/z (ESI^+, methanol): 485 ($5M^+$, 46%), 418 (100), 316 (75), 217 (36), 152 (34), 120 (33), 98 (17).
High resolution mass spectrum: calculated for C_5H_7NO (M^+) 97.0528, found

97.0527.

ν (NaCl): 3258m (N-H),1679s, 1654s (C=O), 1367m, 1089m, 798m cm^{-1}.

6.7 Cyclisation of Aromatic Aminoalkynes

6.7.1 Cyclisation of 1, 4-Diamino-2, 5-*bis*(ethynyl)benzene (5) to 1, 5-Dihydro-pyrrolo[2, 3-*f*]indole (71)



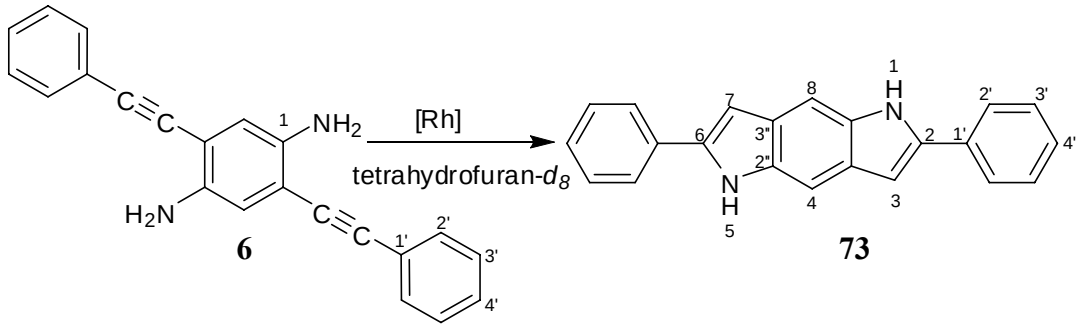
The rhodium(I) complex (**1**) catalysed cyclisation of 1, 4-diamino-2, 5-*bis*(ethynyl)benzene (**5**) and led to the formation of 1, 5-dihydro-pyrrolo[2, 3-*f*]indole (**71**) as the sole product. The assignment of the product was based on the ^{1}H NMR spectra with comparison to literature values by Berlin *et al*.[34]

$[Rh(bim)(CO)_2][BPh_4]$ (**1**) (25 mg, 38 μmol) (30 mol%) was added to 1, 4-diamino-2, 5-*bis*(ethynyl)benzene (**5**) (20 mg, 0.13 mmol) in tetrahydrofuran-d_8 (0.5 mL) in an NMR tube under an atmosphere of nitrogen. The mixture was heated at 60 °C and ^{1}H spectra were recorded at regular intervals. The product (**71**) was formed after 6.7 h.

Once the reaction was complete, the NMR tube was opened to the atmosphere. The residue was poured into acetone (10 mL) to give a solid black precipitate. The supernatant liquid was isolated and the black precipitate was washed with acetone (4 × 10 mL). The acetone fractions were combined, reduced, adsorbed onto silica and purified by column chromatography (hexane: ethyl acetate, 1:1) (TLC, hexane: ethyl acetate, 1:1, $R_f = 0.84$) to give 1, 5-dihydro-pyrrolo[2, 3-*f*]indole (**71**) as a light brown solid (7.7 mg, 20%).

^{1}H NMR (400 MHz, tetrahydrofuran-d_8): δ 9.61 (bs, 2H, N**H**), 7.41 (app. s, 2H, **H4** and **H8**), 7.12 (dd, $^{3}J_{H2\text{-}H3}$ = 3.2 Hz, $^{3}J_{H2\text{-}NH}$ = 2.5 Hz, 2H, **H2** and **H6**), 6.36 (ddd, $^{3}J_{H3\text{-}H2}$ = 3.2 Hz, $^{4}J_{H3\text{-}NH}$ = 2.0 Hz, $^{4}J_{H3\text{-}H4}$ = 0.6 Hz, 2H, **H3** and **H7**) ppm.
^{13}C{^{1}H} NMR (100 MHz, tetrahydrofuran-d_8): δ 134.4 (**C3'**), 127.0 (**C2'**), 125.9 (**C2** and **C6**), 101.0 (**C4** and **C8**), 100.4 (**C3** and **C7**) ppm.

6.7.2 Cyclisation of 1, 4-Diamino-2, 5-*bis*(phenylethynyl)benzene (6) to 2, 6-Diphenyl-1, 5-dihydro-pyrrolo[2, 3-*f*]indole (73)



The rhodium(I) complex (**1**) catalysed cyclisation of 1, 4-diamino-2, 5-*bis*(phenylethynyl)benzene (**6**) and led to the formation of 2, 6-diphenyl-1, 5-dihydro-pyrrolo[2, 3-*f*]indole (**73**) as the sole product. The assignment of the product was based on comparison to literature values by Geise *et al*.[35]

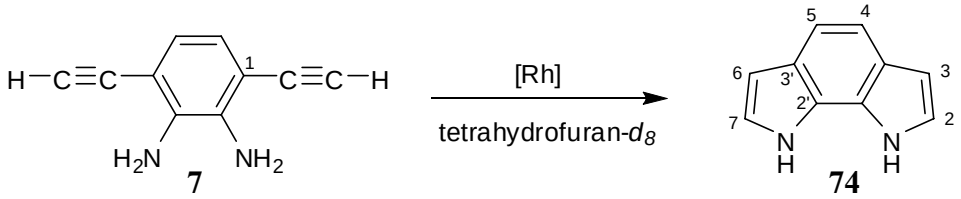
[Rh(bim)(CO)$_2$][BPh$_4$] (**1**) (20.4 mg, 31.2 μmol) (26 mol%) was added to 1, 4-diamino-4, 5-*bis*(phenylethynyl)benzene (**6**) (37 mg, 0.12 mmol) in tetrahydrofuran-d_8 (0.5 mL) in an NMR tube under an atmosphere of nitrogen. The mixture was heated at 60 °C and ^{1}H spectra were recorded at regular intervals. The product (**73**) was formed after 36 min. No resonances for the insoluble product (**73**) or starting material (**6**) were identifiable in the ^{1}H NMR spectrum.

The NMR tube was opened to the atmosphere and the solid precipitate formed was washed repeatedly with tetrahydrofuran to give

2, 6-diphenyl-1, 5-dihydro-pyrrolo[2, 3-*f*]indole (**73**) as a fine flaky yellow solid (9.0 mg, 24%), m.p. 300 °C (dec).

^{1}H NMR (400 MHz, tetrahydrofuran-d_8): δ 10.10 (bs, 2H, N**H**), 7.83 (dd, $^{3}J_{H2'\text{-}H3'}$ = 8.2 Hz, $^{4}J_{H2'\text{-}H4'}$ = 1.0 Hz, 4H, **H2'**), 7.45 (s, 2H, **H4** and **H8**), 7.40 (app. t, $^{3}J_{H3'\text{-}H2'/\,H4'}$ = 7.2 Hz, 4H, **H3'**), 7.24 (app. t, $^{3}J_{H4'\text{-}H3'}$ = 7.6 Hz, 2H, **H4'**), 6.81 (d, $^{4}J_{H3\text{-}HN}$ = 2.0 Hz, 2H, **H3** and **H7**) ppm.
^{13}C{H} NMR (100 MHz, tetrahydrofuran-d_8): δ 139.0, 136.1, 134.5, 129.3 (**C3'**), 128.7, 127.3 (**C4**'), 125.5 (**C2'**), 100.1 (**C4** and **C8**), 99.0 (**C3** and **C7**) ppm.
m/z (EI): 308 (M^+, 100%).
Anal. Found: C, 85.51; H, 5.07; N, 9.16. $C_{22}H_{16}N_2$ requires C, 85.69; H, 5.23; N, 9.08%. Geise *et al*.[35] reported poor microanalysis results for compound **73**.
ν (KBr): 3426m (N-H), 3099w, 3040w, 3031w (aromatic C-H), 1454m, 846m, 754s, 702m, 504m cm^{-1}.

6.7.3 Cyclisation of 2, 3-Diamino-1, 4-diethynylbenzene (7) to 1, 8-Dihydro-pyrrolo[2, 3-*g*]indole (74)



7 **74**

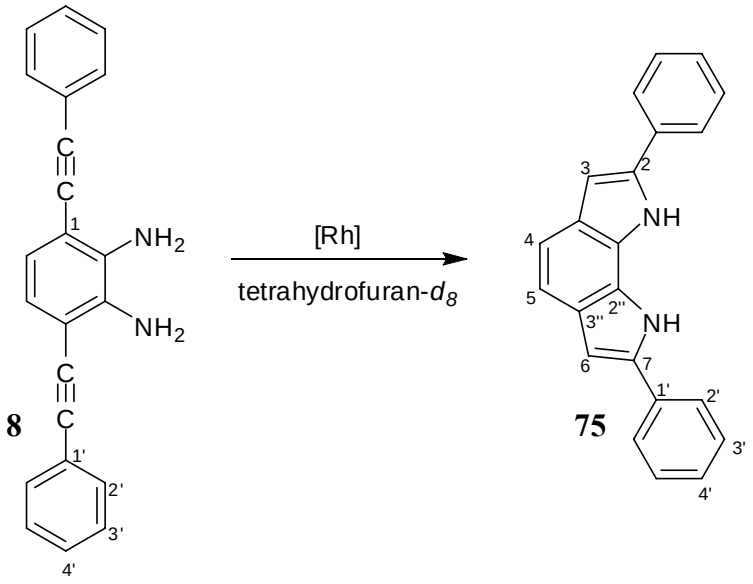
The rhodium(I) complex (**1**) catalysed cyclisation of 2, 3-diamino-1, 4-diethynylbenzene (**7**) and led to the formation of 1, 8-dihydro-pyrrolo[2, 3-*g*]indole (**74**) as the sole product.

[Rh(bim)$(CO)_2$][BPh_4] (**1**) (144 mg, 0.219 mmol) (16 mol%) was added to 2, 3-diamino-1, 4-diethynylbenzene (**7**) (0.214 g, 1.37 mmol) in tetrahydrofuran (7 mL) in a straight schlenk flask under an atmosphere of nitrogen. The mixture was heated at 60 °C and ^{1}H NMR spectra were recorded at regular intervals. The product (**74**) was formed after 34 h.

Once the reaction was complete, the flask was opened to the atmosphere. The insoluble precipitate was filtered and washed with ethyl acetate and acetone. The filtrate was then adsorbed onto silica and purified by column chromatography (hexane: ethyl acetate, 3:2) (TLC, hexane: ethyl acetate, 3:2, $R_f = 0.45$) to give **74** as a brown solid (66 mg, 31%).

^{1}H NMR (400 MHz, tetrahydrofuran-d_8): δ 9.73 (bs, 2H, **NH**), 7.19 (s, 2H, **H4** and **H5**), 7.03 (dd, $^3J_{H2\text{-}H3} = 2.4$ Hz, $^3J_{H2\text{-}NH} = 0.5$ Hz, 2H, **H2** and **H7**), 6.47 (dd, $^3J_{H3\text{-}H2} = 2.4$ Hz, $^4J_{H3\text{-}NH} = 0.9$ Hz, 2H, **H3** and **H6**) ppm.
^{13}C{^{1}H} NMR (100 MHz, tetrahydrofuran-d_8): 124.6 (**C3**'), 123.9 (**C2'**), 121.3 (**C2** and **C7**), 113.7 (**C4** and **C5**), 104.0 (**C3** and **C6**) ppm.
m/z (EI): 156 (M^+, 100%).
High resolution mass spectrum: calculated for $C_{10}H_8N_2$ (M^+) 156.0687, found 156.0685.

6.7.4 Cyclisation of 2, 3-Diamino-1, 4-*bis*(phenylethynyl)benzene (8) to 1, 8-Dihydro-2, 7-diphenyl-pyrrolo[2, 3-*g*]indole (75)



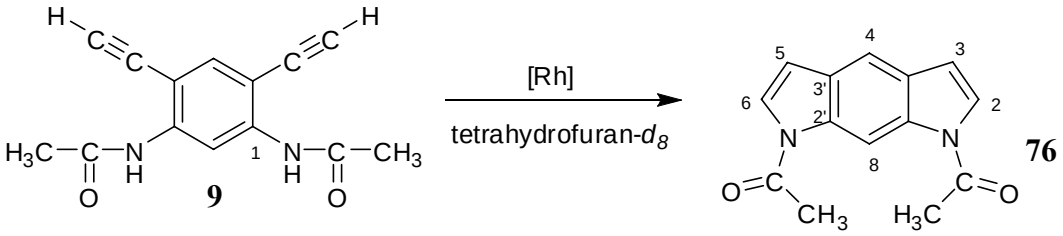
The rhodium(I) complex (**1**) catalysed cyclisation of 2, 3-diamino-1, 4-*bis*(phenylethynyl)benzene (**8**) and led to the formation of 1, 8-dihydro-2, 7-diphenyl-pyrrolo[2, 3-*g*]indole (**75**) as the sole product.

$[Rh(bim)(CO)_2][BPh_4]$ (**1**) (8.64 mg, 13.2 μmol) (20 mol%) was added to 2, 3-diamino-1, 4-*bis*(phenylethynyl)benzene (**8**) (20.3 mg, 0.066 mmol) in tetrahydrofuran-d_8 (0.5 mL) in an NMR tube under an atmosphere of nitrogen. The mixture was heated at 60 °C and ^{1}H NMR spectra were recorded at regular intervals. The product (**75**) was formed after 44 h.

Once the reaction was complete, the NMR tube was opened to the atmosphere. The residue was poured into ethyl acetate (10 mL) then adsorbed onto silica and purified by column chromatography (hexane: dichloromethane, 1:1) (TLC, hexane: dichloromethane, 1:1, $R_f = 0.4$) to give 1, 8-dihydro-2, 7-diphenyl-pyrrolo[2, 3-*g*]indole (**75**) as an orange solid (8.3 mg, 41%).

^{1}H NMR (400 MHz, tetrahydrofuran-d_8): δ 10.12 (bs, 2H, N**H**) 7.70 (m, 4H, **H2'**), 7.40 (m, 4H, **H3'**), 7.21 (m, 4H, **H4**, **H5** and **H4'**), 6.91 (d, $^4J_{H3\text{-}NH} = 2.8$ Hz, 2H, **H3** and **H6**) ppm.
^{13}C{^{1}H} NMR (100 MHz, tetrahydrofuran-d_8): 135.5 (**C1'**), 134.5, 129.6 (**C3'**), 127.2 (**C4'**), 126.4, 125.0 (**C2'**), 124.8, 114.5 (**C4** and **C5**), 102.0 (**C3** and **C6**) ppm.
m/z (EI): 308 (M^+, 100%).
High resolution mass spectrum: calculated for $C_{22}H_{16}N_2$ (M^+) 308.1313, found 308.1308.
ν (KBr): 3370m (N-H), 3055m (aromatic C-H), 2960m, 2922m, 2852m, 1602s, 1487s, 1450w, 1406w,1261w, 1094w, 1026s, 808s, 745s, 689s cm^{-1}.

6.7.5 Cyclisation of 1, 5-*Bis*(acetamido)-2, 4-diethynylbenzene (9) to 1, 7-Diacetyl-pyrrolo[3, 2-*f*]indole (76)



9 **76**

The rhodium(I) complex (**1**) catalysed cyclisation of 1, 5-*bis*(acetamido)-2, 4-diethynylbenzene (**9**) led to 1, 7-diacetyl-pyrrolo[3, 2-*f*]indole (**76**) as the single product. The product was fully characterised.

$[Rh(bim)(CO)_2][BPh_4]$ (**1**) (48.0 mg, 73.1 μmol) (30 mol%) was added to 1, 5-*bis*(acetamido)-2, 4-diethynylbenzene (**9**) (60.1 mg, 250 μmol) in tetrahydrofuran-d_8 (0.5 mL) in an NMR tube under an atmosphere of nitrogen. The mixture was heated at 60 °C and ^{1}H NMR spectra were recorded at regular intervals. The product (**76**) was formed after 72 h.

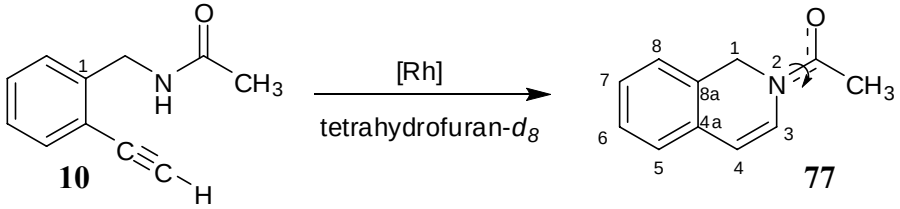
Once the reaction was complete, the NMR tube was opened to the atmosphere. The residue was poured into a mixture of hexane (2.5 mL) and ethyl acetate (7.5 mL) to give a solid precipitate. The supernatant liquid was isolated and the precipitate was washed with hexane: ethyl acetate (1:3) (8 × 20 mL). The solvent fractions were combined, reduced and purified by column chromatography (hexane: ethyl acetate, 1:3) (TLC, hexane: ethyl acetate, 1:3, $R_f = 0.71$) to give 1, 7-diacetyl-pyrrolo[3, 2-*f*]indole (**76**) as an orange solid (22 mg, 36%), m.p. 205-207 °C.

^{1}H NMR (400 MHz, chloroform-*d*): δ 9.47 (bs, 1H, **H8**), 7.65 (d, $^4J_{H4\text{-}H3/H5} = 0.77$ Hz, 1H, **H4**), 7.50 (d, $^3J_{H2\text{-}H3} = 3.8$ Hz, 2H, **H2** and **H6**), 6.67 (dd, $^3J_{H3\text{–}H2} = 3.8$ Hz, $^4J_{H3\text{–}H4} = 0.77$ Hz, 2H, **H3** and **H5**), 2.67 (s, 6H, C**H**$_3$) ppm.
^{13}C{H} NMR (100 MHz, chloroform-*d*): δ 168.4 (**C**=O), 134.3 (**C2'**), 128.0 (**C3**'), 126.2 (**C2** and **C6**), 111.9 (**C4**), 109.1 (**C3** and **C5**), 104.6 (**C8**), 24.3 (**C**H$_3$) ppm.
m/z (EI): 240 (M^+, 53%), 198 (32), 156 (100).

High resolution mass spectrum: calculated for $C_{14}H_{12}N_2O_2$ (M^+) 240.0899, found 240.0899.

ν (KBr): 1704s, 1688s (C=O), 1263s, 1213s, 1094m, 1029s (C-N), 1378s, 805s cm^{-1}.

6.7.6 Cyclisation of *N*-(Acetyl)-2-ethynylbenzylamine (10) to *N*-(Acetyl)-1, 2-dihydroisoquinoline (77)



The rhodium(I) complex (**1**) catalysed cyclisation of *N*-(acetyl)-2-ethynylbenzylamine (**10**) and led to the formation of *N*-(acetyl)-1, 2-dihydroisoquinoline (**77**) as the sole product.

$[Rh(bim)(CO)_2][BPh_4]$ (**1**) (6.08 mg, 9.30 μmol) (10 mol%) was added to *N*-(acetyl)-2-ethynylbenzylamine (**10**) (16.1 mg, 93.0 μmol) in tetrahydrofuran-d_8 (0.5 mL) in an NMR tube under an atmosphere of nitrogen. The mixture was heated at 60 °C and ^{1}H NMR spectra were recorded at regular intervals. The product (**77**) was formed after 48 h.

Once the reaction was complete, the NMR tube was opened to the atmosphere. The residue was poured into acetone (10 mL) then adsorbed onto silica and purified by column chromatography (hexane: ethyl acetate, 1:1) (TLC, hexane: ethyl acetate, 1:1, $R_f = 0.5$) to give *N*-(acetyl)-1, 2-dihydroisoquinoline (**77**) as an orange oil (10 mg, 62%).

^{1}H NMR (400 MHz, tetrahydrofuran-d_8): a mixture of two isomers of the amide bond in a ratio of 84:16. δ 7.29 and 6.82 (each d, $^3J_{H4\text{-}H3} = 7.8$ and 8.0 Hz respectively, 1H, **H4**) 7.11 (m, 3H, Ar-**H**), 7.01 (m, 1H, Ar-**H**), 5.81 and 5.78 (each d, $^3J_{H3\text{-}H4}$ 7.8 and 8.0 Hz respectively, 1H, **H3**), 4.85 and 4.82 (each s, 2H,

H1), 2.18 and 2.13 (each s, 3H, C**H**$_3$) ppm.

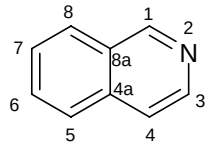
^{13}C{^{1}H} NMR (100 MHz, tetrahydrofuran-d_8): δ 168.6 (**C**=O), 134.0 and 133.2 (**C8a**), 131.2 and 130.8 (**C4a**), 129.1, 128.8, 128.6, 128.2, 128.0, 127.2, 127.0, 126.9 (Ar-**C**), 125.7 and 125.7 (**C3**), 109.6 and 109.4 (**C4**), 49.0 and 45.3 (**C1**), 22.4 and 21.6 (**C**H$_3$) ppm.

m/z (EI): 173 (M^+, 35%), 130 (100).

High resolution mass spectrum: calculated for $C_{11}H_{11}NO$ (M^+) 173.0841, found 173.0840.

6.7.6.1 Isoquinoline (79)

The synthesis of isoquinoline (**79**) was undertaken by a method based on the procedure described by McDonald *et al.*[36]



When 2, 3-dichloro-5, 6-dicyano-benzoquinone (88 mg, 0.38 mmol) was added to *N*-(acetyl)-1, 2-dihydroisoquinoline (**77**) in tetrahydrofuran-d_8 (0.5 mL), there was an instant colour change from a pale peach to a dark green. The reaction was monitored *in situ* by ^{1}H NMR. The solvent was removed by evaporation, aqueous sodium hydroxide (1M, 30 mL) added and the mixture was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined then dried over magnesium sulfate. The filtrate was evaporated to dryness to give isoquinoline (**79**) as a red/ black solid (0.5 mg, 2%).

Assignment of the product was based on comparison of the ^{1}H NMR spectra of **79** with the ^{1}H NMR spectra of an authentic sample of isoquinoline (**79**).

^{1}H NMR (400 MHz, chloroform-*d*): δ 9.25 (bs, 1H, **H1**), 8.49 (m, 1H, **H3**), 8.01 (m, H1, **H8**), 7.86 (m, H1, **H5**), 7.75 (m, **H6**) 7.71 (m, 1H, **H4**), 7.65 (m, **H7**) ppm.

^{13}C{^{1}H} NMR (100 MHz, tetrahydrofuran-d_8): δ 150.9 (**C1**), 139.87 (**C3**), 139.86 (**C4a**), 136.7 (**C8a**), 132.1 (**C6**), 128.5 (**C8**), 128.4 (**C7**), 126.8 (**C5**), 121.9 (**C4**) ppm.

m/z (EI): 130 (M^+, 14%), 129 (100).

6.8 Attempted Cyclisation

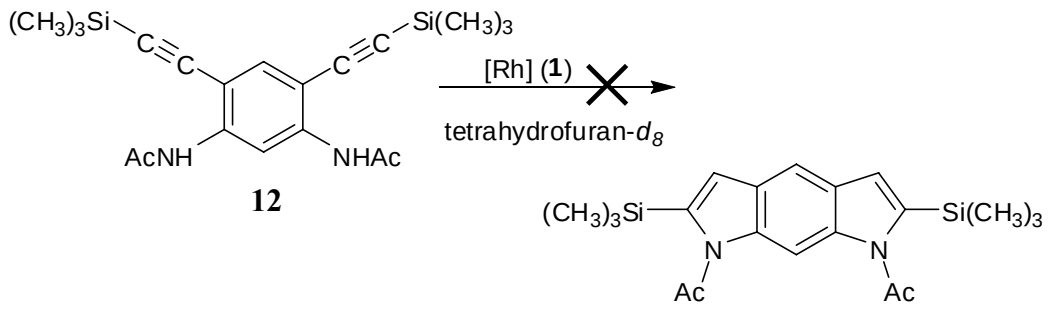
6.8.1.1 The Attempted Cyclisation of 5-Hexyn-1-amide (4).

The cyclisation of 5-hexyn-1-amide (**4**) was attempted with rhodium(I) complex (**1**) using 6, 10, 15, 20 and 30 mol%.

$[Rh(bim)(CO)_2][BPh_4]$ (**1**) (22.0 mg, 33.5 μmol) 10 mol% was added to 5-hexyn-1-amide (**4**) (37.6 mg, 338 μmol) in tetrahydrofuran-d_8 (0.5 mL) in an NMR tube under an atmosphere of nitrogen. The mixture was heated at 60 °C and ^{1}H spectra were recorded at regular intervals. At catalyst loadings of 6, 10 and 15 mol%, most of the starting material remained unchanged. Small amounts (~1%) of cyclised products were detected in the ^{1}H NMR spectra however due to the low conversion, the products have yet to be isolated or identified conclusively. High catalyst loading of rhodium(I) complex (**1**) (20 and 30 mol%) led to extensive decomposition of the starting material.

6.8.1.2 The Attempted Cyclisation of 1, 5-*Bis*(acetamido)-2, 4-*bis*(trimethylsilylethynyl)benzene (12)

The cyclisation of 1, 5-*bis*(acetamido)-2, 4-*bis*(trimethylsilylethynyl)benzene (**12**) was attempted using 30 mol%, 15 mol% and 5 mol% of the rhodium(I) complex. 1, 7-Diacetyl-pyrrolo[3, 2-*f*]indole (**76**) was identified by ^{1}H NMR as the main product amongst a complex mixture of products. The desired tricyclic *bis*(trimethylsilyl) product was not observed.



12

$[Rh(bim)(CO)_2][BPh_4]$ (**1**) (3.7 mg, 5.5 μmol) (15 mol%) was added to 1, 5-*bis*(acetamido)-2, 4-*bis*(trimethylsilylethynyl)benzene (**12**) (14.3 mg, 37.2 μmol) in tetrahydrofuran-d_8 (0.5 mL) in an NMR tube under an atmosphere of nitrogen. The mixture was heated at 60 °C in the NMR spectrometer and ^{1}H NMR spectra were acquired using an automated time course program.

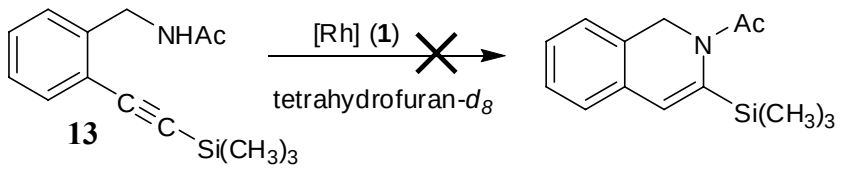
6.8.1.3 The Attempted Cyclisation of *N*-(Acetyl)-2-(phenylethynyl)benzylamine (11)

The cyclisation of *N*-(acetyl)-2-(phenylethynyl)benzylamine (**11**) was attempted using 12 mol% and 30 mol% of rhodium(I) complex (**1**). No new products were detected.

$[Rh(bim)(CO)_2][BPh_4]$ (**1**) (12 mg, 18 μmol) (12 mol%) was added to *N*-(acetyl)-2-(phenylethynyl)benzylamine (**11**) (38 mg, 0.15 mmol) in tetrahydrofuran-d_8 (0.5 mL) in a NMR tube under an atmosphere of nitrogen. The mixture was heated at 60 °C in the NMR spectrometer and ^{1}H NMR spectra were acquired using an automated time course program. No cyclised products were detected in the ^{1}H NMR spectra, the starting material remained unchanged after 5 days.

6.8.1.4 The Attempted Cyclisation of *N*-(Acetyl)-2-(trimethylsilylethynyl)benzylamine (13)

The cyclisation of *N*-(acetyl)-2-(trimethylsilylethynyl)benzylamine (**13**) was attempted using 10 mol% of the rhodium(I) complex (**1**). *N*-(Acetyl)-1, 2-dihydroisoquinoline (**77**) was identified by ^{1}H NMR as the main product amongst a complex mixture of products. The desired trimethylsilyl product was not observed.

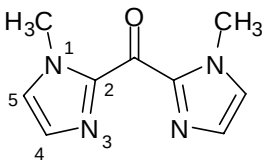


$[Rh(bim)(CO)_2][BPh_4]$ (**1**) (4.6 mg, 7.1 μmol) (10mol%) was added to 1, 5-*bis*(acetamido)-2, 4-*bis*(trimethylsilylethynyl)benzene (**12**) (17.4 mg, 70.9 μmol) in tetrahydrofuran-d_8 (0.5 mL) in an NMR tube under an atmosphere of nitrogen. The mixture was heated at 60 °C in the NMR spectrometer and ^1H NMR spectra were acquired using an automated time course program.

6.9 Nitrogen Donor Ligand

6.9.1 *Bis*(*N*-methylimidazol-2-yl)ketone, (bik) (91)

The synthesis of *bis*(*N*-methylimidazol-2-yl)ketone (**91**) was undertaken by a method based on the procedures reported by Byers and Canty[37] and Burling.[38]



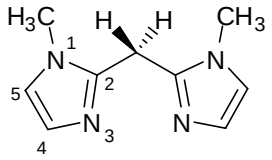
A solution of *n*-butyllithium (1.6M, 100 mL, 250 mmol) in hexane was added dropwise to a solution of *N*-methylimidazole (20.5 g, 250 mmol) in tetrahydrofuran (300 mL) at -78 °C under nitrogen and stirred for 2.5 h. A solution of diethyl carbonate (14.2 mL, 120 mmol) in tetrahydrofuran (40 mL) was added very slowly over 2 h to the mixture and then stirred for a further 2 h after the addition. The reaction was quenched by the addition of solid carbon dioxide and allowed to warm to room temperature. Addition of water (80 mL) was followed by hydrochloric acid solution (3M, 150 mL) to acidify the aqueous layer. The mixture was filtered, the organic layer separated and extracted with hydrochloric acid (3M, 3 × 40 mL). The combined aqueous phases were neutralized with sodium carbonate, filtered and extracted continuously with chloroform for 32 h in a liquid-liquid extractor. Solvent was removed *in vacuo* and the resulting brown solid was recrystallised from dichloromethane/ hexane to yield *bis*(*N*-methylimidazol-2-yl)ketone (**91**) as a creamy/ white crystalline solid (15 g, 65%), m.p. 147-148 °C (lit.[37] 145-148 °C).

^{1}H NMR (chloroform-*d*): δ 7.14 (s, 2H, **H4**), 7.12 (s, 2H, **H5**), 4.00 (s, 6H, N-C**H**$_3$) ppm.

^{13}C{^{1}H} NMR (chloroform-*d*): δ 174.2 (**C**=O), 143.5 (**C2**), 130.1 (**C4**), 127.2 (**C5**), 36.3 (N-**C**H$_3$) ppm.

m/z (EI): 191 ([M+H]$^+$, 98%), 190 (35), 162 (100), 161 (59), 127 (23), 96 (20), 83 (75), 81 (21), 54 (20).

6.9.2 *Bis*(*N*-methylimidazol-2-yl)methane, (bim) (2)



The synthesis of *bis*(*N*-methylimidazol-2-yl)methane (**2**) was undertaken by a method based on the procedures reported by Burling.[39]

Bis(*N*-methylimidazol-2-yl)ketone (3.52 g, 18.5 mmol), hydrazine monohydrate (25 mL, 515 mmol) and sodium hydroxide (1.8 g, 45 mmol) were loaded into a stainless steel high pressure reaction vessel. The vessel was sealed and heated for 24 h at 150 °C in an oil bath. After the reaction vessel had cooled, the residue was dissolved in dichloromethane. The solution was dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The solid was recrystallised from acetone to give *bis*(*N*-methylimidazol-2-yl)methane (**2**) as a creamy solid (2.0 g, 62%), m.p. 149-151 °C (lit.[39] 151-153 °C).

^{1}H NMR (400 MHz, chloroform-*d*): δ 6.88 (d, $^{3}J_{H4\text{-}H5}$ = 1.1 Hz, 2H, **H4**), 6.76 (d, $^{3}J_{H5\text{-}H4}$ = 1.1 Hz, 2H, **H5**), 4.20 (s, 2H, C**H**$_2$), 3.63 (s, 6H, N-C**H**$_3$) ppm.

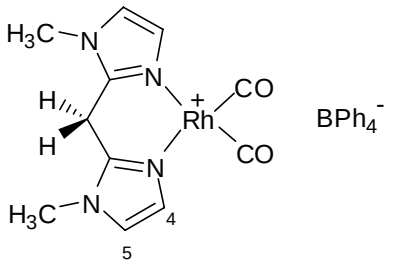
^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 144.0 (**C2**), 127.3 (**C4**), 121.6 (**C5**), 33.2 (N-**C**H$_3$), 27.0 (**C**H$_2$) ppm.

m/z (EI): 176 (M$^+$, 70%), 161 (17), 134 (9), 121 (9), 107 (14), 95 (100), 81 (28), 66 (7), 54 (85).

6.10 Rhodium(I) Complex

6.10.1 [Rh(bim)(CO)$_2$][BPh$_4$] (1)

The synthesis of [Rh(bim)(CO)$_2$][BPh$_4$] (**1**) was undertaken by a method based on the procedures reported by Burling.[39]



A solution of *bis*(*N*-methylimidazol-2-yl)methane (**2**) (179 mg, 1.02 mmol) in methanol (5 mL) was added to a solution of [Rh(CO)$_2$Cl]$_2$[2, 40] (180 mg, 0.460 mmol) in methanol (20 mL) at room temperature under an atmosphere of nitrogen. The mixture was stirred for 30 min before an excess of sodium tetraphenylborate (356 mg, 1.04 mmol) in methanol (5 mL) was added. The resulting precipitate was isolated by filtration and washed with methanol to give (*bis*(*N*-methylimidazol-2-yl)methane)dicarbonylrhodium(I) tetraphenylborate (**1**) as a bright yellow solid (0.55 g, 91%), m.p. 175-176 °C dec. (lit.[38] 175 °C dec.).

^{1}H NMR (400 MHz, tetrahydrofuran-d_8): δ 7.40 (m, 8H, *o*-**H**), 7.28 (d, $^3J_{H4\text{-}H5}$ = 1.5 Hz, 1H, **H4**), 7.16 (d, $^3J_{H4\text{-}H5}$ = 1.5 Hz, 1H, **H5**), 6.92 (m, 8H, *m*-**H**), 6.68 (m, 4H, *p*-**H**), 3.70 (s, 2H, C**H**$_2$), 3.30 (s, 6H, N-C**H**$_3$) ppm.

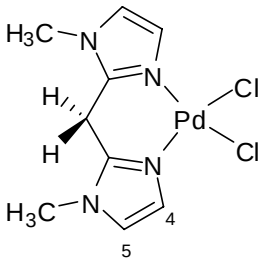
^{13}C{^{1}H} NMR (100 MHz, tetrahydrofuran-d_8): δ 185.6 (d, $^1J_{Rh\text{-}CO}$ = 68.2 Hz, Rh-**C**O), 165.7-164.3 (m, B-**C**), 143.2 (**C2**), 137.1 (*o*-**C**), 130.9 (**C4**), 125.8 (*m*-**C**), 124.1 (**C5**), 122.1 (*p*-**C**), 34.2 (N-**C**H$_3$), 24.1 (**C**H$_2$) ppm.

m/z (ESI$^+$, methanol): 334 ([M-BPh$_4$-H]$^+$, 100%).

6.11 Palladium Complexes

6.11.1 [Pd(bim)Cl$_2$] (15)

The synthesis of [Pd(bim)Cl_2] (**15**) was undertaken by a method based on the procedures reported by Burling and by Cavell *et al*.[39, 41]



A solution of *bis*(*N*-methylimidazol-2-yl)methane (**2**) (243 mg, 1.38 mmol) in methanol (20 mL) was added to a suspension of [Pd(COD)Cl_2][3] (260 mg, 1.50 mmol) in methanol (20 mL) at room temperature under an atmosphere of nitrogen. The resulting precipitate was stirred overnight before the principate was isolated by filtration and washed with hexane to give (*bis*(*N*-methylimidazol-2-yl)methane)dichloropalladium(II) (**15**) as a creamy/ peach solid (0.38 g, 85%), m.p. >300 °C.

^{1}H NMR (400 MHz, dimethyl-d_6 sulfoxide): δ 7.32 (d, $^3J_{H4\text{-}H5}$ = 1.7 Hz, 2H, **H4**), 7.28 (d, $^3J_{H4\text{-}H5}$ = 1.7 Hz, 2H, **H5**), 4.43 (s, 2H, C**H**$_2$), 3.75 (s, 6H, N-C**H**$_3$) ppm.

^{13}C{^{1}H} NMR (100 MHz, dimethyl-d_6 sulfoxide): δ 140.0 (**C2**), 126.2 (**C4**), 121.4 (**C5**), 34.0 (N-**C**H$_3$), 23.2 (**C**H$_2$) ppm.

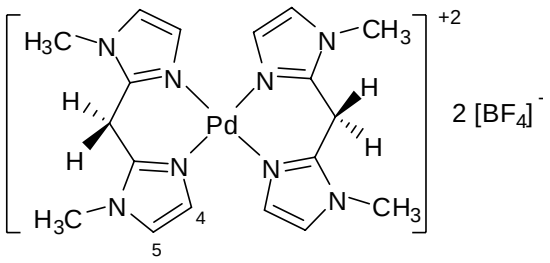
m/z (ESI$^+$, methanol): 635 ([{Pd(bim)Cl}$_2$-H]$^+$, 53%), 351 (100), 349 (85), 176 (65)

High resolution mass spectrum: calculated for $C_{18}H_{23}Cl_2N_8Pd_2$ ([{Pd(bim)Cl}$_2$-H]$^+$) 634.9647, found 634.9515.

Anal. Found: C, 30.80; H, 3.42; N, 15.78. $C_9H_{12}Cl_2N_4Pd$ requires C, 30.58; H, 3.42; N, 15.85%.

6.11.2 [Pd(bim)$_2$][BF$_4$]$_2$ (17)

The methanol filtrate from the synthesis of **15** was treated with sodium tetrafluoroborate (150 mg, 1.4 mmol). The precipitate that formed was collected and dried



in vacuo to afford (di-*bis*(*N*-methylimidazol-2-yl)methane)palladium(II) *bis*(tetrafluoroborate) (**17**) as an off-white solid (70 mg, 8.7%), m.p. >300 °C.

^{1}H NMR (300 MHz, dimethyl-d_6 sulfoxide): δ 7.43 (s, 4H, **H4**), 6.68 (s, 4H, **H5**), 4.65 (s, 4H, C**H**$_2$), 3.86 (s, 12H, N-C**H**$_3$) ppm.

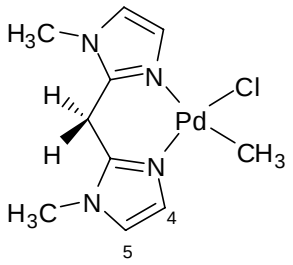
^{13}C{^{1}H} NMR (75 MHz, dimethyl-d_6 sulfoxide): δ 142.4 (**C2**), 126.5 (**C4**), 123.1 (**C5**), 34.4 (N-**C**H$_3$), 23.5 (**C**H$_2$) ppm.

m/z (ESI$^+$, acetonitrile): 457 ([M-BF$_4$]$^+$, 50%), 229 (100).

High resolution mass spectrum: calculated for $C_{18}H_{23}N_8Pd$ ([{Pd(bim)$_2$}-H-BF$_4$]$^+$) 457.1081, found 457.1079.

6.11.3 [Pd(bim)(Cl)(CH$_3$)] (14)

The synthesis of [Pd(bim)(Cl)(CH$_3$)] (**14**) was undertaken by a method based on the procedures reported by Cavell *et al*.[41]



A solution of *bis*(*N*-methylimidazol-2-yl)methane (**2**) (175 mg, 0.993 mmol) in dichloromethane (20 mL) was added to a solution of [Pd(COD)(Cl)(CH$_3$)][4] (239 mg, 0.905 mmol) in dichloromethane (20 mL) at room temperature under an atmosphere of nitrogen. The resulting mixture was stirred overnight before the precipitate was isolated by filtration and washed with hexane to give (*bis*(*N*-methylimidazol-2-yl)methane)chloromethylpalladium(II) (**14**) as a white solid (0.22 g, 71%).

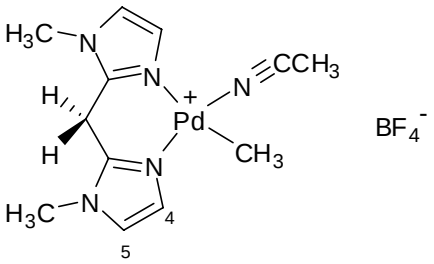
^{1}H NMR (400 MHz, dimethyl-d_6 sulfoxide): δ 7.31 (s, 1H, Im-**H**), 7.16 (s, 1H, Im-**H**), 7.13 (s, 1H, Im-**H**), 6.92 (s, 1H, Im-**H**), 4.29 (s, 2H, C**H**$_2$), 3.76 (s, 3H, N-C**H**$_3$), 3.70 (s, 3H, N-C**H**$_3$), 0.47 (s, 3H, Pd-C**H**$_3$) ppm.

^{13}C{^{1}H} NMR (100 MHz dimethyl-d_6 sulfoxide): δ 141.8 (**Cq**), 139.9 (**Cq**), 125.4 (**C-Im**), 125.1 (**C-Im**), 121.8 (**C-Im**), 121.1 (**C-Im**), 33.9 (N-**C**H$_3$), 33.8 (N-**C**H$_3$), 22.7 (**C**H$_2$), 6.2 (Pd-**C**H$_3$) ppm.

m/z (ESI$^+$, methanol): 282 ([M-CH$_3$-Cl]$^+$, 100%).

6.11.4 [Pd(bim)(CH$_3$)(NCCH$_3$)][BF$_4$] (16)

The synthesis of [Pd(bim)(CH$_3$)(NCCH$_3$)][BF$_4$] (**16**) was undertaken by a method based on the procedure reported by Cavell *et al*.[41]



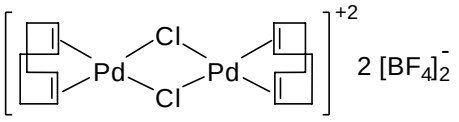
A solution of silver tetrafluoroborate (0.11 g, 0.59 mmol) in acetonitrile: dichloromethane (1:1, 8 mL) was added to a suspension of (*bis*(*N*-methylimidazol-2-yl)methane)chloromethylpalladium (**14**) (0.16 g, 0.49 mmol) in acetonitrile: dichloromethane (1:1, 10 mL) at room temperature. The mixture was stirred for a further 1 hour after addition. The mixture was filtered through Celite and the filtrate evaporated to afford a grey solid. The solid was redissolved in dichloromethane (15 mL), and the resulting solution filtered and evaporated to dryness. The residue was washed with hexane (3 × 5 mL) to give acetonitrile(*bis*(*N*-methylimidazol-2-yl)methane)methylpalladium(II) tetrafluoroborate (**16**) as a white solid (0.15 g, 70%).

^{1}H NMR (300 MHz, acetonitrile-d_3): δ 7.10 (m, 2H, Im-**H**), 6.98 (m, 2H, Im-**H**), 4.16 (s, 2H, C**H**$_2$), 3.73 (s, 3H, N-C**H**$_3$), 3.70 (s, 3H, N-C**H**$_3$), 1.97 (s, 3H, C**H**$_3$CN), 0.74 (s, 3H, Pd-C**H**$_3$) ppm.

m/z (ESI$^+$, acetone): 338 ([M-BF$_4$]$^+$, 19%), 314 (26), 282 (100).

6.11.5 $[Pd(COD)Cl]_2[BF_4]_2$ (20)

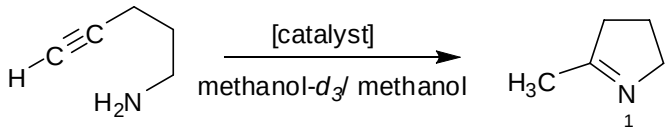
The synthesis of $[Pd(COD)Cl]_2[BF_4]_2$ (**20**) was undertaken by a method based on the procedure reported by Eaborn *et al*.[42]



Triethyloxonium tetrafluoroborate (0.213 g, 1.12 mmol) in dichloromethane (10 mL) was added to a suspension of $[Pd(COD)Cl_2]$[3] (0.350 g, 0.930 mmol) in dichloromethane at reflux. The mixture was refluxed for a further 15 min after addition. The mixture was cooled on ice and then stored in a refrigerator overnight. The resulting precipitate was isolated by filtration, washed with cold dichloromethane (2 × 10 mL) then dried under vacuum to give di-μ-chloro-*bis*[(η-cyclo-octa-1,5-diene)palladium(II)] *bis*(tetrafluoroborate) (**20**) as a yellow/ orange crystalline solid (0.19 g, 30%).

^{1}H NMR (400 MHz, acetone-d_6): δ 6.43 (bs, 4H, **H1, H2, H6** and **H5**), 3.07 (m, 4H, **H3** and **H8**), 2.76 (m, 4H, **H4** and **H7**) ppm.
m/z (ESI$^+$, methanol): 531 ([{M-$(BF_4)_2$}+OCH_3]$^+$, 60%), 277 (54), 245 (92).

6.12 Cyclisation of 4-Pentyn-1-amine (21) to 2-Methyl-1-pyrroline (22)



21 **22**

Palladium(II) catalysed cyclisation of 4-pentyn-1-amine (**21**) led to the formation of 2-methyl-1-pyrroline (**22**) as the sole product. Assignment of the product was based on comparison of the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **22** with literature values.[43]

6.12.1 Cyclisation of 4-pentyn-1-amine (21) in methanol-d_3 and methanol at 60 °C

The cyclisation of 4-pentyn-1-amine (**21**) in methanol-d_3 and methanol at 60 °C was catalysed by $[Rh(bim)(CO)_2][BPh_4]$ (**1**), $[Pd(bim)Cl_2]$ (**15**), $[Pd(bim)(Cl)(CH_3)]$ (**14**), $[Pd(bim)(CH_3)(NCCH_3)][BF_4]$ (**16**), $[Pd(bim)_2][BF_4]_2$ (**17**), $[Pd(COD)Cl_2]$ (**18**), $[Pd(COD)(Cl)(CH_3)]$ (**19**) and $[Pd(COD)Cl]_2[BF_4]_2$ (**20**). A typical reaction was performed as follows:

4-Pentyn-1-amine (**21**) (55 mg, 0.66 mmol) was added to $[Pd(COD)Cl_2]^3$ (**18**) (2.8 mg, 9.8 μmol) (1.5 mol%) in methanol-d_3 (0.1 mL) and methanol (0.4 mL) in a NMR tube at -78 °C. All reactions were performed under an atmosphere of nitrogen. The mixture was heated at 60 °C and ^{1}H NMR spectra were recorded at regular intervals. The product, 2-methyl-1-pyrroline (**22**) was formed in 97% after 7.7 h.

^{1}H NMR (400 MHz, methanol-d_3): δ 3.69 (m, 2H, **H3**), 2.50 (t, $^{3}J_{H5\text{-}H4}$ = 8.0 Hz, 2H, **H5**), 1.97 (s, 3H, C**H**$_3$), 1.86 (m, 2H, **H4**) ppm.

$^{13}C\{^{1}H\}$ NMR (75 MHz, methanol-d_3): δ 178.9 (**C2**), 61.0 (**C**5), 39.4 (**C**3), 23.6 (**C**4), 19.2 (**C**H_3) ppm.

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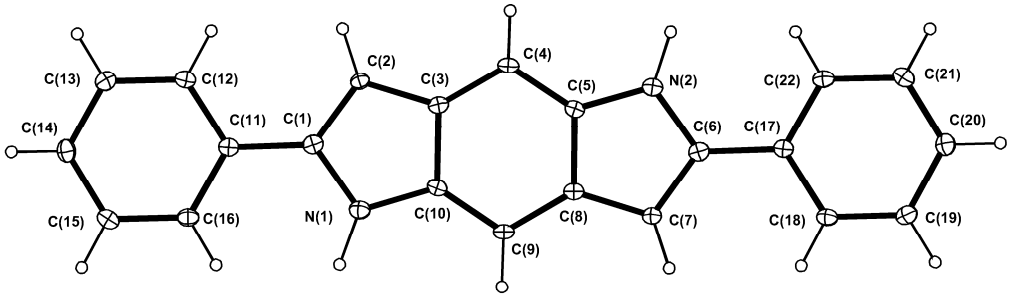
Appendix 1

X-ray Crystallographic Data

A1.1 X-ray Crystal Structure of 1, 5-Dihydro-2, 6-diphenyl-pyrrolo[2, 3-*f*]indole (73)



The crystal structure was solved by Dr. Peter Tuner, (School of Chemistry, The University of Sydney).

A pale yellow blade like crystal was attached with Exxon Paratone N, to a short length of fibre supported on a thin piece of copper wire inserted in a copper mounting pin. The crystal was quenched in a cold nitrogen gas stream from an Oxford Cryosystems Cryostream. A Bruker SMART 1000 CCD diffractometer employing graphite monochromated MoKα radiation generated from a sealed tube was used for the data collection. The reciprocal lattice display program RLATT[1*] was used to remove a small set of reflections, arising from a minor twin component, from the reflections used to obtain an orientations matrix and unit cell. Cell constants were obtained from a least squares refinement against 858 reflections located between 7.03 and 56.01º 2θ. Data were collected at 150(2) Kelvin with ω scans to 56.62º 2θ. The data integration and reduction were undertaken with SAINT and XPREP,[1] and subsequent computations were carried out with the teXsan,[2] WinGX[3] and XTAL[4] graphical user interfaces. The intensities of 49 standard reflections recollected at the end of the experiment did not change significantly during the data collection. A Gaussian absorption correction[1, 5] was applied to the data.

The structure was solved in the space group $P2_1/n$(#14) by direct methods with SIR97,[6] and extended and refined with SHELXL-97.[7] The non-hydrogen atoms in the asymmetric unit were modelled with anisotropic displacement parameters, and in general a riding atom model was used for the hydrogen atoms. The amine hydrogen sites were located and modelled with isotropic displacement parameters. An ORTEP[8] depiction of the molecule with 20% displacement ellipsoids is provided.

[*] References begin on page A1-18.

A1.1.1 Results

Formula $C_{22}H_{16}N_2$, *M* 308.37, monoclinic, space group $P2_1/n$(#14), *a* 5.704(3), *b* 7.465(4), *c* 34.893(17) Å, β 94.659(8), *V* 1481.0(12) $Å^3$, D_c 1.383 g cm^{-3}, *Z* 4, crystal size 0.431 by 0.352 by 0.043 mm, colour pale yellow, habit blade, temperature 150(2) Kelvin, λ(MoKα) 0.71073 Å, μ(MoKα) 0.082 mm^{-1}, *T*(Gaussian)$_{min,max}$ 0.963, 0.996, $2\theta_{max}$ 56.62, *hkl* range -7 7, -9 9, -44 44, *N* 14154, N_{ind} 3493(R_{merge} 0.0467), N_{obs} 2287(I > 2σ(I)), N_{var} 225, residuals † *R*1(*F*) 0.0540, *wR*2(F^2) 0.1369, GoF(all) 1.008, $\Delta\rho_{min,max}$ -0.239, 0.294 e^- $Å^{-3}$.

Table A1.1.1 Non-Hydrogen Atom Coordinates, Isotropic Thermal Parameters and Occupancies for 1, 5-dihydro-2, 6-diphenyl-pyrrolo[2, 3-*f*] (**73**)

atom	x	y	z	U_{eq}($Å^2$)	Occ
N(1)	0.7535(3)	0.0071(2)	0.18589(5)	0.0280(4)	1
N(2)	0.2534(3)	0.1549(2)	0.31009(5)	0.0279(4)	1
C(1)	0.6119(3)	0.0786(2)	0.15542(6)	0.0244(4)	1
C(2)	0.4149(3)	0.1488(2)	0.16967(5)	0.0220(4)	1
C(3)	0.4290(3)	0.1235(2)	0.21012(5)	0.0220(4)	1
C(4)	0.2820(3)	0.1713(2)	0.23838(5)	0.0231(4)	1
C(5)	0.3601(3)	0.1294(2)	0.27582(5)	0.0220(4)	1
C(6)	0.3926(3)	0.0813(3)	0.34029(6)	0.0251(4)	1
C(7)	0.5914(3)	0.0129(2)	0.32610(5)	0.0219(4)	1
C(8)	0.5782(3)	0.0400(2)	0.28585(5)	0.0221(4)	1
C(9)	0.7255(3)	-0.0078(2)	0.25749(5)	0.0221(4)	1
C(10)	0.6477(3)	0.0344(2)	0.21997(5)	0.0219(4)	1
C(11)	0.6729(3)	0.0753(2)	0.11559(5)	0.0230(4)	1
C(12)	0.5217(3)	0.1509(3)	0.08633(6)	0.0262(4)	1
C(13)	0.5736(4)	0.1443(3)	0.04847(6)	0.0301(5)	1
C(14)	0.7798(4)	0.0630(3)	0.03853(6)	0.0306(5)	1
C(15)	0.9327(4)	-0.0106(3)	0.06704(6)	0.0298(5)	1
C(16)	0.8801(3)	-0.0047(3)	0.10504(6)	0.0267(5)	1
C(17)	0.3266(3)	0.0788(2)	0.37996(5)	0.0227(4)	1
C(18)	0.4709(3)	-0.0063(3)	0.40902(6)	0.0267(5)	1
C(19)	0.4122(4)	-0.0078(3)	0.44648(6)	0.0300(5)	1
C(20)	0.2071(4)	0.0753(3)	0.45629(6)	0.0296(5)	1

† $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ for $F_o > 2\sigma(F_o)$; $wR2 = (\Sigma w(F_o^2 - F_c^2)^2/\Sigma(wF_c^2)^2)^{1/2}$ all reflections

$w=1/[\sigma^2(F_o^2)+(0.05P)^2+1.0P]$ where $P=(F_o^2+2F_c^2)/3$

C(21)	0.0620(4)	0.1586(3)	0.42813(6)	0.0290(5)	1
C(22)	0.1202(3)	0.1602(3)	0.39034(6)	0.0264(4)	1

Table A1.1.2 Hydrogen Atom Coordinates, Isotropic Thermal Parameters and Occupancies for 1, 5-dihydro-2, 6-diphenyl-pyrrolo[2, 3-*f*] (**73**)

atom	**x**	**y**	**z**	**U_{eq}(Å^2)**	**Occ**
H(1N)	0.914(5)	-0.045(4)	0.1834(7)	0.060(8)	1
H(2N)	0.094(4)	0.211(3)	0.3116(6)	0.032(6)	1
H(2)	0.2889	0.2055	0.1548	0.026	1
H(4)	0.1358	0.2298	0.2323	0.028	1
H(7)	0.7175	-0.0436	0.3409	0.026	1
H(9)	0.8716	-0.0664	0.2636	0.027	1
H(12)	0.3809	0.2077	0.0927	0.031	1
H(13)	0.4680	0.1956	0.0290	0.036	1
H(14)	0.8151	0.0582	0.0124	0.037	1
H(15)	1.0744	-0.0655	0.0605	0.036	1
H(16)	0.9866	-0.0560	0.1243	0.032	1
H(18)	0.6113	-0.0639	0.4027	0.032	1
H(19)	0.5122	-0.0657	0.4658	0.036	1
H(20)	0.1672	0.0747	0.4822	0.035	1
H(21)	-0.0784	0.2152	0.4347	0.035	1
H(22)	0.0184	0.2173	0.3712	0.032	1

Table A1.1.3 Anisotropic Thermal Parameters (Å^2) for 1, 5-dihydro-2, 6-diphenyl-pyrrolo[2, 3-*f*] (**73**)

atom	**U(1,1)**	**U(2,2)**	**U(3,3)**	**U(1,2)**	**U(1,3)**	**U(2,3)**
N(1)	0.0263(9)	0.0254(9)	0.0319(10)	0.0015(7)	0.0008(7)	-0.0011(7)
N(2)	0.0258(9)	0.0266(9)	0.0313(10)	0.0023(7)	0.0017(7)	0.0001(7)
C(1)	0.0257(10)	0.0175(9)	0.0295(11)	-0.0037(8)	-0.0007(8)	-0.0006(8)
C(2)	0.0209(9)	0.0201(9)	0.0244(10)	-0.0008(7)	-0.0020(7)	0.0000(8)
C(3)	0.0201(9)	0.0168(9)	0.0284(10)	-0.0036(7)	-0.0026(8)	-0.0005(8)
C(4)	0.0167(9)	0.0184(9)	0.0334(11)	0.0010(7)	-0.0016(8)	-0.0005(8)
C(5)	0.0190(9)	0.0170(9)	0.0300(11)	-0.0029(7)	0.0022(8)	-0.0021(8)
C(6)	0.0259(10)	0.0196(9)	0.0292(11)	-0.0033(8)	-0.0011(8)	-0.0018(8)
C(7)	0.0202(9)	0.0192(9)	0.0259(10)	-0.0010(7)	-0.0006(7)	-0.0017(8)

C(8)	0.0195(9)	0.0165(9)	0.0299(11)	-0.0022(7)	-0.0009(8)	-0.0010(8)
C(9)	0.0166(9)	0.0175(9)	0.0316(11)	0.0012(7)	-0.0021(8)	0.0002(8)
C(10)	0.0194(9)	0.0165(9)	0.0297(11)	-0.0013(7)	0.0022(8)	-0.0025(8)
C(11)	0.0222(9)	0.0176(9)	0.0289(11)	-0.0030(7)	0.0007(8)	-0.0011(8)
C(12)	0.0219(9)	0.0237(10)	0.0330(11)	0.0006(8)	0.0021(8)	0.0003(8)
C(13)	0.0296(11)	0.0293(11)	0.0308(12)	-0.0001(9)	-0.0006(9)	0.0030(9)
C(14)	0.0357(12)	0.0287(11)	0.0283(11)	-0.0046(9)	0.0078(9)	-0.0009(9)
C(15)	0.0251(10)	0.0269(11)	0.0380(13)	0.0005(8)	0.0069(9)	-0.0037(9)
C(16)	0.0228(10)	0.0230(10)	0.0336(12)	-0.0003(8)	-0.0012(8)	-0.0004(8)
C(17)	0.0218(9)	0.0170(9)	0.0289(11)	-0.0026(7)	0.0003(8)	-0.0022(8)
C(18)	0.0232(10)	0.0231(10)	0.0333(12)	0.0033(8)	-0.0003(8)	-0.0023(8)
C(19)	0.0308(11)	0.0272(11)	0.0308(12)	0.0026(9)	-0.0041(9)	0.0002(9)
C(20)	0.0317(11)	0.0288(11)	0.0283(11)	-0.0047(9)	0.0029(9)	-0.0039(9)
C(21)	0.0245(10)	0.0270(11)	0.0358(12)	-0.0007(8)	0.0048(9)	-0.0049(9)
C(22)	0.0236(10)	0.0220(10)	0.0327(12)	0.0013(8)	-0.0022(8)	-0.0003(8)

Table A1.1.4 Non Hydrogen Bond Lengths (Å) for 1, 5-dihydro-2, 6-diphenyl-pyrrolo[2, 3-*f*] (**73**)

atom	**atom**	**Distance**	**atom**	**atom**	**Distance**
N(1)	C(1)	1.389(3)	N(1)	C(10)	1.391(3)
N(2)	C(6)	1.381(3)	N(2)	C(5)	1.398(3)
C(1)	C(2)	1.369(3)	C(1)	C(11)	1.460(3)
C(2)	C(3)	1.420(3)	C(3)	C(4)	1.392(3)
C(3)	C(10)	1.431(3)	C(4)	C(5)	1.382(3)
C(5)	C(8)	1.430(3)	C(6)	C(7)	1.372(3)
C(6)	C(17)	1.463(3)	C(7)	C(8)	1.415(3)
C(8)	C(9)	1.396(3)	C(9)	C(10)	1.384(3)
C(11)	C(16)	1.400(3)	C(11)	C(12)	1.401(3)
C(12)	C(13)	1.378(3)	C(13)	C(14)	1.392(3)
C(14)	C(15)	1.383(3)	C(15)	C(16)	1.384(3)
C(17)	C(22)	1.398(3)	C(17)	C(18)	1.405(3)
C(18)	C(19)	1.376(3)	C(19)	C(20)	1.391(3)
C(20)	C(21)	1.380(3)	C(21)	C(22)	1.386(3)

Symmetry Operators: (1) x, y, z (2) -x+1/2, y+1/2, -z+1/2 (3) -x, -y, -z (4) x-1/2, -y-1/2, z-1/2

Table A1.1.5 Non Hydrogen Bond Angles (º) for 1, 5-dihydro-2, 6-diphenyl-pyrrolo[2, 3-*f*] (**73**)

atom	**atom**	**atom**	**angle**
C(1)	N(1)	C(10)	109.41(17)
C(6)	N(2)	C(5)	109.58(17)
C(2)	C(1)	N(1)	108.23(17)
C(2)	C(1)	C(11)	128.18(18)
N(1)	C(1)	C(11)	123.60(18)
C(1)	C(2)	C(3)	109.14(17)
C(4)	C(3)	C(2)	132.95(18)
C(4)	C(3)	C(10)	120.85(18)
C(2)	C(3)	C(10)	106.17(17)
C(5)	C(4)	C(3)	116.44(17)
C(4)	C(5)	N(2)	130.41(17)
C(4)	C(5)	C(8)	122.99(18)
N(2)	C(5)	C(8)	106.57(16)
C(7)	C(6)	N(2)	108.25(17)
C(7)	C(6)	C(17)	128.31(18)
N(2)	C(6)	C(17)	123.43(18)
C(6)	C(7)	C(8)	109.04(17)
C(9)	C(8)	C(7)	132.91(18)
C(9)	C(8)	C(5)	120.52(18)
C(7)	C(8)	C(5)	106.53(16)
C(10)	C(9)	C(8)	116.58(17)
C(9)	C(10)	N(1)	130.33(17)
C(9)	C(10)	C(3)	122.62(18)
N(1)	C(10)	C(3)	107.04(17)
C(16)	C(11)	C(12)	117.62(18)
C(16)	C(11)	C(1)	121.94(17)
C(12)	C(11)	C(1)	120.44(17)
C(13)	C(12)	C(11)	121.12(19)
C(12)	C(13)	C(14)	120.40(19)
C(15)	C(14)	C(13)	119.38(19)
C(14)	C(15)	C(16)	120.22(19)
C(15)	C(16)	C(11)	121.26(18)
C(22)	C(17)	C(18)	117.76(18)
C(22)	C(17)	C(6)	121.73(17)
C(18)	C(17)	C(6)	120.51(18)
C(19)	C(18)	C(17)	121.04(18)

C(18)	C(19)	C(20)	120.31(19)
C(21)	C(20)	C(19)	119.58(19)
C(20)	C(21)	C(22)	120.33(19)
C(21)	C(22)	C(17)	120.98(18)

Symmetry Operators: (1) x, y, z (2) -x+1/2, y+1/2, -z+1/2 (3) -x, -y, -z (4) x-1/2, -y-1/2, z-1/2

Table A1.1.6 Torsion Angles (º) for 1, 5-dihydro-2, 6-diphenyl-pyrrolo[2, 3-*f*] (**73**)

atom	**atom**	**atom**	**atom**	**angle**
C(10)	N(1)	C(1)	C(2)	-0.9(2)
C(10)	N(1)	C(1)	C(11)	179.05(17)
N(1)	C(1)	C(2)	C(3)	0.3(2)
C(11)	C(1)	C(2)	C(3)	-179.65(18)
C(1)	C(2)	C(3)	C(4)	178.47(19)
C(1)	C(2)	C(3)	C(10)	0.4(2)
C(2)	C(3)	C(4)	C(5)	-177.38(19)
C(10)	C(3)	C(4)	C(5)	0.5(3)
C(3)	C(4)	C(5)	N(2)	-178.26(18)
C(3)	C(4)	C(5)	C(8)	-0.6(3)
C(6)	N(2)	C(5)	C(4)	176.34(19)
C(6)	N(2)	C(5)	C(8)	-1.6(2)
C(5)	N(2)	C(6)	C(7)	1.7(2)
C(5)	N(2)	C(6)	C(17)	-177.44(17)
N(2)	C(6)	C(7)	C(8)	-1.0(2)
C(17)	C(6)	C(7)	C(8)	178.00(18)
C(6)	C(7)	C(8)	C(9)	-177.4(2)
C(6)	C(7)	C(8)	C(5)	0.1(2)
C(4)	C(5)	C(8)	C(9)	0.7(3)
N(2)	C(5)	C(8)	C(9)	178.79(16)
C(4)	C(5)	C(8)	C(7)	-177.20(17)
N(2)	C(5)	C(8)	C(7)	0.9(2)
C(7)	C(8)	C(9)	C(10)	176.68(19)
C(5)	C(8)	C(9)	C(10)	-0.5(3)
C(8)	C(9)	C(10)	N(1)	179.02(18)
C(8)	C(9)	C(10)	C(3)	0.4(3)
C(1)	N(1)	C(10)	C(9)	-177.65(19)
C(1)	N(1)	C(10)	C(3)	1.1(2)

C(4)	C(3)	C(10)	C(9)	-0.4(3)
C(2)	C(3)	C(10)	C(9)	177.97(17)
C(4)	C(3)	C(10)	N(1)	-179.29(17)
C(2)	C(3)	C(10)	N(1)	-0.9(2)
C(2)	C(1)	C(11)	C(16)	-178.77(19)
N(1)	C(1)	C(11)	C(16)	1.3(3)
C(2)	C(1)	C(11)	C(12)	0.3(3)
N(1)	C(1)	C(11)	C(12)	-179.69(17)
C(16)	C(11)	C(12)	C(13)	0.9(3)
C(1)	C(11)	C(12)	C(13)	-178.14(18)
C(11)	C(12)	C(13)	C(14)	-0.5(3)
C(12)	C(13)	C(14)	C(15)	-0.2(3)
C(13)	C(14)	C(15)	C(16)	0.5(3)
C(14)	C(15)	C(16)	C(11)	-0.1(3)
C(12)	C(11)	C(16)	C(15)	-0.6(3)
C(1)	C(11)	C(16)	C(15)	178.41(18)
C(7)	C(6)	C(17)	C(22)	177.76(19)
N(2)	C(6)	C(17)	C(22)	-3.3(3)
C(7)	C(6)	C(17)	C(18)	-2.2(3)
N(2)	C(6)	C(17)	C(18)	176.74(18)
C(22)	C(17)	C(18)	C(19)	-0.7(3)
C(6)	C(17)	C(18)	C(19)	179.21(18)
C(17)	C(18)	C(19)	C(20)	0.2(3)
C(18)	C(19)	C(20)	C(21)	0.3(3)
C(19)	C(20)	C(21)	C(22)	-0.2(3)
C(20)	C(21)	C(22)	C(17)	-0.4(3)
C(18)	C(17)	C(22)	C(21)	0.8(3)
C(6)	C(17)	C(22)	C(21)	-179.10(18)

Symmetry Operators: (1) x, y, z (2) -x+1/2, y+1/2, -z+1/2 (3) -x, -y, -z (4) x-1/2, -y-1/2, z-1/2

Table A1.1.7 Hydrogen Bond Lengths (Å) for 1, 5-dihydro-2, 6-diphenyl-pyrrolo[2, 3-*f*] (**73**)

atom	atom	Distance	atom	atom	Distance
N(1)	H(1N)	1.00(3)	N(2)	H(2N)	1.01(2)
C(2)	H(2)	0.9500	C(4)	H(4)	0.9500
C(7)	H(7)	0.9500	C(9)	H(9)	0.9500
C(12)	H(12)	0.9500	C(13)	H(13)	0.9500
C(14)	H(14)	0.9500	C(15)	H(15)	0.9500
C(16)	H(16)	0.9500	C(18)	H(18)	0.9500
C(19)	H(19)	0.9500	C(20)	H(20)	0.9500
C(21)	H(21)	0.9500	C(22)	H(22)	0.9500

Symmetry Operators: (1) x, y, z (2) -x+1/2, y+1/2, -z+1/2 (3) -x, -y, -z (4) x-1/2, -y-1/2, z-1/2

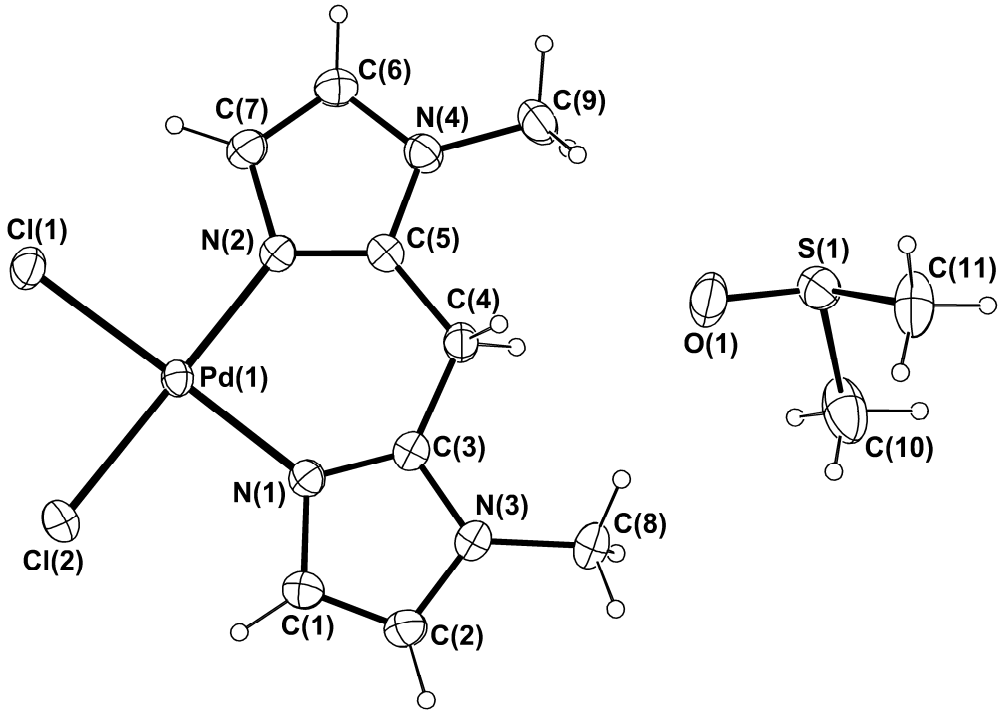
Table A1.1.8 Hydrogen Bond Angles (º) for 1, 5-dihydro-2, 6-diphenyl-pyrrolo[2, 3-*f*] (**73**)

atom	atom	atom	angle
C(1)	N(1)	H(1N)	124.1(15)
C(10)	N(1)	H(1N)	126.3(15)
C(6)	N(2)	H(2N)	126.3(12)
C(5)	N(2)	H(2N)	124.0(12)
C(1)	C(2)	H(2)	125.4
C(3)	C(2)	H(2)	125.4
C(5)	C(4)	H(4)	121.8
C(3)	C(4)	H(4)	121.8
C(6)	C(7)	H(7)	125.5
C(8)	C(7)	H(7)	125.5
C(10)	C(9)	H(9)	121.7
C(8)	C(9)	H(9)	121.7
C(13)	C(12)	H(12)	119.4
C(11)	C(12)	H(12)	119.4
C(12)	C(13)	H(13)	119.8
C(14)	C(13)	H(13)	119.8
C(15)	C(14)	H(14)	120.3
C(13)	C(14)	H(14)	120.3
C(14)	C(15)	H(15)	119.9
C(16)	C(15)	H(15)	119.9
C(15)	C(16)	H(16)	119.4
C(11)	C(16)	H(16)	119.4

C(19)	C(18)	H(18)	119.5
C(17)	C(18)	H(18)	119.5
C(18)	C(19)	H(19)	119.8
C(20)	C(19)	H(19)	119.8
C(21)	C(20)	H(20)	120.2
C(19)	C(20)	H(20)	120.2
C(20)	C(21)	H(21)	119.8
C(22)	C(21)	H(21)	119.8
C(21)	C(22)	H(22)	119.5
C(17)	C(22)	H(22)	119.5

Symmetry Operators: (1) x, y, z (2) -x+1/2, y+1/2, -z+1/2 (3) -x, -y, -z (4) x-1/2, -y-1/2, z-1/2

A1.2 X-ray Crystal Structure of [Pd(bim)Cl_2] (15)



The crystal structure was solved by Dr. Peter Tuner, (School of Chemistry, The University of Sydney).

An orange prismatic crystal was attached with Exxon Paratone N, to a short length of fibre supported on a thin piece of copper wire inserted in a copper mounting pin. The crystal was quenched in a cold nitrogen gas stream from an Oxford Cryosystems Cryostream. A Bruker SMART 1000 CCD diffractometer employing graphite monochromated MoKα radiation generated from a fine-focus sealed tube was used for the data collection. Cell constants were obtained from a least squares refinement against 1016 reflections located between 6 and 56º 2θ. Data were collected at 150(2) Kelvin with ω scans to 57º 2θ. The data integration and reduction were undertaken with SAINT and XPREP,[1] and subsequent computations were carried out with the WinGX[3] and XTAL[4] graphical user interfaces. The intensities of 244 standard reflections recollected at the end of the experiment did not change significantly during the data collection. An empirical absorption correction determined with SADABS[9, 10] was applied to the data.

The structure was solved in the space group $P2_1/c$(#14) by direct methods with SHELXS-97[7] and extended and refined with SHELXL-97.[7] The non-hydrogen atoms were modelled with anisotropic displacement parameters and a riding atom model with group displacement parameters was used for the hydrogen atoms. An ORTEP[6] depiction of the molecule with 50% displacement

ellipsoids is provided.

A1.2.1 Results

Formula $C_{11}H_{18}Cl_2N_4OPdS$, *M* 431.65, Monoclinic, space group $P2_1/c$(#14), *a* 11.1214(14), *b* 8.5587(11), *c* 16.560(2) Å, β 94.886(2), *V* 1570.5(3) $Å^3$, D_c 1.826 g cm^{-3}, *Z* 4, crystal size 0.464 by 0.347 by 0.312 mm, colour Orange, habit Prism, temperature 150(2) Kelvin, λ(MoKα) 0.71073 Å, μ(MoKα) 1.655 mm^{-1}, *T*(SADABS)$_{min,max}$ 0.818, 1.000, $2\theta_{max}$ 56.58, *hkl* range -14 14, -10 11, -21 21, *N* 14875, N_{ind} 3722(R_{merge} 0.0183), N_{obs} 3509(I > 2σ(I)), N_{var} 185, residuals‡ *R*1(*F*) 0.0163, *wR*2(F^2) 0.0451, GoF(all) 1.058, $\Delta\rho_{min,max}$ -0.412, 0.354 e^- $Å^{-3}$.

Table A1.2.1. Non-Hydrogen Atom Coordinates,Isotropic Thermal Parameters and Occupancies for [Pd(bim)Cl_2] (**15**)

atom	x	y	z	U_{eq}($Å^2$)	Occ
Pd(1)	0.620460(9)	0.554894(12)	0.162971(6)	0.01890(4)	1
Cl(1)	0.65427(3)	0.40954(5)	0.27982(2)	0.02642(8)	1
Cl(2)	0.82477(3)	0.60220(6)	0.17022(3)	0.03457(10)	1
N(1)	0.59370(11)	0.68793(15)	0.06166(7)	0.0213(2)	1
N(2)	0.44195(11)	0.50422(15)	0.15547(7)	0.0208(2)	1
N(3)	0.50851(12)	0.81738(15)	-0.04258(8)	0.0220(2)	1
N(4)	0.24757(12)	0.50251(16)	0.11861(8)	0.0249(3)	1
S(1)	0.03518(4)	0.84514(5)	-0.11192(3)	0.03581(10)	1
O(1)	0.13383(13)	0.8568(2)	-0.04442(8)	0.0490(4)	1
C(1)	0.68320(14)	0.76076(19)	0.02157(10)	0.0266(3)	1
C(2)	0.63097(14)	0.84032(19)	-0.04260(10)	0.0267(3)	1
C(3)	0.48910(13)	0.72482(16)	0.02110(9)	0.0205(3)	1
C(4)	0.36480(13)	0.68012(18)	0.03823(9)	0.0240(3)	1
C(5)	0.35549(14)	0.56344(16)	0.10400(9)	0.0211(3)	1
C(6)	0.26645(15)	0.3985(2)	0.18173(10)	0.0288(3)	1
C(7)	0.38581(15)	0.39991(19)	0.20430(10)	0.0258(3)	1
C(8)	0.41772(15)	0.87744(19)	-0.10391(9)	0.0269(3)	1
C(9)	0.13169(15)	0.5369(2)	0.07305(12)	0.0337(4)	1
C(10)	0.10825(19)	0.8326(3)	-0.20232(12)	0.0532(6)	1

‡ $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ for $F_o > 2\sigma(F_o)$; $wR2 = (\Sigma w(F_o^2 - F_c^2)^2/\Sigma(wF_c^2)^2)^{1/2}$ all reflections

$w=1/[\sigma^2(F_o^2)+(0.023P)^2+0.77P]$ where $P=(F_o^2+2F_c^2)/3$

C(11)	-0.0264(2)	1.0350(2)	-0.12688(13)	0.0438(5)	1

Table A1.2.2 Hydrogen Atom Coordinates, Isotropic Thermal Parameters and Occupancies for [Pd(bim)Cl_2] (**15**)

atom	**x**	**y**	**z**	**U_{eq}(Å^2)**	**Occ**
H(1)	0.7674	0.7555	0.0368	0.032	1
H(2)	0.6710	0.9004	-0.0804	0.032	1
H(4A)	0.3227	0.6378	-0.0122	0.029	1
H(4B)	0.3213	0.7758	0.0525	0.029	1
H(6)	0.2069	0.3375	0.2049	0.035	1
H(7)	0.4251	0.3393	0.2468	0.031	1
H(8A)	0.4020	0.7993	-0.1468	0.040	1
H(8B)	0.4475	0.9737	-0.1273	0.040	1
H(8C)	0.3429	0.8995	-0.0788	0.040	1
H(9A)	0.1261	0.6491	0.0618	0.051	1
H(9B)	0.0656	0.5055	0.1051	0.051	1
H(9C)	0.1259	0.4789	0.0218	0.051	1
H(10A)	0.1650	0.9198	-0.2048	0.080	1
H(10B)	0.0480	0.8376	-0.2490	0.080	1
H(10C)	0.1523	0.7336	-0.2033	0.080	1
H(11A)	-0.0663	1.0663	-0.0789	0.066	1
H(11B)	-0.0854	1.0346	-0.1743	0.066	1
H(11C)	0.0384	1.1091	-0.1357	0.066	1

Table A1.2.3 Anisotropic Thermal Parameters (Å^2) for [Pd(bim)Cl_2] (**15**)

atom	**U(1,1)**	**U(2,2)**	**U(3,3)**	**U(1,2)**	**U(1,3)**	**U(2,3)**
Pd(1)	0.01891(6)	0.02029(7)	0.01712(6)	0.00079(4)	-0.00070(4)	-0.00140(4)
Cl(1)	0.02785(18)	0.03154(19)	0.01934(17)	0.00384(15)	-0.00111(13)	0.00219(14)
Cl(2)	0.01998(18)	0.0515(3)	0.0314(2)	-0.00227(17)	-0.00275(15)	0.00777(18)
N(1)	0.0218(6)	0.0211(6)	0.0208(6)	-0.0015(5)	0.0006(5)	-0.0009(5)
N(2)	0.0224(6)	0.0199(6)	0.0200(6)	-0.0007(5)	0.0012(5)	-0.0004(5)
N(3)	0.0262(6)	0.0196(6)	0.0199(6)	-0.0001(5)	0.0000(5)	0.0001(5)
N(4)	0.0210(6)	0.0243(6)	0.0292(7)	-0.0015(5)	0.0007(5)	0.0008(5)
S(1)	0.0270(2)	0.0360(2)	0.0444(3)	0.00001(17)	0.00263(18)	0.01168(19)
O(1)	0.0406(8)	0.0757(11)	0.0302(7)	0.0221(7)	0.0007(6)	0.0152(7)

C(1)	0.0237(7)	0.0275(8)	0.0288(8)	-0.0028(6)	0.0039(6)	0.0023(6)
C(2)	0.0281(8)	0.0261(8)	0.0264(8)	-0.0031(6)	0.0044(6)	0.0019(6)
C(3)	0.0245(7)	0.0172(6)	0.0195(7)	0.0001(5)	0.0006(5)	-0.0022(5)
C(4)	0.0221(7)	0.0245(7)	0.0245(7)	-0.0002(6)	-0.0021(6)	0.0030(6)
C(5)	0.0204(7)	0.0202(7)	0.0226(7)	0.0002(5)	0.0017(6)	-0.0022(5)
C(6)	0.0281(8)	0.0279(8)	0.0305(8)	-0.0046(6)	0.0037(6)	0.0042(6)
C(7)	0.0293(8)	0.0244(7)	0.0237(7)	-0.0025(6)	0.0020(6)	0.0025(6)
C(8)	0.0326(8)	0.0255(8)	0.0216(7)	0.0017(6)	-0.0039(6)	0.0021(6)
C(9)	0.0197(7)	0.0373(9)	0.0433(10)	-0.0010(7)	-0.0019(7)	0.0063(8)
C(10)	0.0401(11)	0.0844(17)	0.0337(10)	0.0220(11)	-0.0057(8)	-0.0163(10)
C(11)	0.0479(11)	0.0452(11)	0.0358(10)	0.0194(9)	-0.0112(8)	-0.0067(8)

Table A1.2.4 Non Hydrogen Bond Lengths (Å) for [Pd(bim)Cl_2] (**15**)

atom	**atom**	**Distance**	**atom**	**atom**	**Distance**
Pd(1)	N(2)	2.0255(13)	Pd(1)	N(1)	2.0284(13)
Pd(1)	Cl(2)	2.3011(5)	Pd(1)	Cl(1)	2.3042(4)
N(1)	C(3)	1.3307(19)	N(1)	C(1)	1.3903(19)
N(2)	C(5)	1.3297(19)	N(2)	C(7)	1.388(2)
N(3)	C(3)	1.3509(19)	N(3)	C(2)	1.376(2)
N(3)	C(8)	1.4632(19)	N(4)	C(5)	1.349(2)
N(4)	C(6)	1.375(2)	N(4)	C(9)	1.467(2)
S(1)	O(1)	1.5015(15)	S(1)	C(10)	1.766(2)
S(1)	C(11)	1.773(2)	C(1)	C(2)	1.351(2)
C(3)	C(4)	1.485(2)	C(4)	C(5)	1.488(2)
C(6)	C(7)	1.348(2)			

Symmetry Operators: (1) x, y, z (2) -x, y+1/2, -z+1/2 (3) -x, -y, -z (4) x, -y-1/2, z-1/2

Table A1.2.5 Non Hydrogen Bond Angles (º) for [Pd(bim)Cl_2] (**15**)

atom	**atom**	**atom**	**angle**
N(2)	Pd(1)	N(1)	89.74(5)
N(2)	Pd(1)	Cl(2)	177.71(4)
N(1)	Pd(1)	Cl(2)	91.09(4)
N(2)	Pd(1)	Cl(1)	91.43(4)
N(1)	Pd(1)	Cl(1)	178.33(4)
Cl(2)	Pd(1)	Cl(1)	87.786(15)

C(3)	N(1)	C(1)	106.45(12)
C(3)	N(1)	Pd(1)	127.67(10)
C(1)	N(1)	Pd(1)	125.88(10)
C(5)	N(2)	C(7)	106.38(13)
C(5)	N(2)	Pd(1)	127.53(10)
C(7)	N(2)	Pd(1)	126.09(10)
C(3)	N(3)	C(2)	107.93(13)
C(3)	N(3)	C(8)	126.96(13)
C(2)	N(3)	C(8)	125.04(13)
C(5)	N(4)	C(6)	107.81(13)
C(5)	N(4)	C(9)	125.90(14)
C(6)	N(4)	C(9)	126.25(14)
O(1)	S(1)	C(10)	105.97(9)
O(1)	S(1)	C(11)	106.99(10)
C(10)	S(1)	C(11)	97.89(12)
C(2)	C(1)	N(1)	108.92(14)
C(1)	C(2)	N(3)	106.69(13)
N(1)	C(3)	N(3)	110.02(13)
N(1)	C(3)	C(4)	129.08(13)
N(3)	C(3)	C(4)	120.90(13)
C(3)	C(4)	C(5)	115.90(13)
N(2)	C(5)	N(4)	110.09(13)
N(2)	C(5)	C(4)	129.31(14)
N(4)	C(5)	C(4)	120.60(13)
C(7)	C(6)	N(4)	106.74(14)
C(6)	C(7)	N(2)	108.98(14)

Symmetry Operators: (1) x, y, z (2) -x, y+1/2, -z+1/2 (3) -x, -y, -z (4) x, -y-1/2, z-1/2

Table A1.2.6 Torsion Angles (º) for [Pd(bim)Cl_2] (**15**)

atom	**atom**	**atom**	**atom**	**angle**
N(2)	Pd(1)	N(1)	C(3)	5.89(13)
Cl(2)	Pd(1)	N(1)	C(3)	-176.25(12)
Cl(1)	Pd(1)	N(1)	C(3)	-128.2(12)
N(2)	Pd(1)	N(1)	C(1)	-175.08(13)
Cl(2)	Pd(1)	N(1)	C(1)	2.78(12)
Cl(1)	Pd(1)	N(1)	C(1)	50.8(13)

N(1)	Pd(1)	N(2)	C(5)	-6.18(13)
Cl(2)	Pd(1)	N(2)	C(5)	-117.4(9)
Cl(1)	Pd(1)	N(2)	C(5)	172.62(12)
N(1)	Pd(1)	N(2)	C(7)	174.23(13)
Cl(2)	Pd(1)	N(2)	C(7)	63.0(10)
Cl(1)	Pd(1)	N(2)	C(7)	-6.98(13)
C(3)	N(1)	C(1)	C(2)	-0.05(18)
Pd(1)	N(1)	C(1)	C(2)	-179.25(11)
N(1)	C(1)	C(2)	N(3)	0.08(18)
C(3)	N(3)	C(2)	C(1)	-0.09(17)
C(8)	N(3)	C(2)	C(1)	-177.23(14)
C(1)	N(1)	C(3)	N(3)	-0.01(16)
Pd(1)	N(1)	C(3)	N(3)	179.17(9)
C(1)	N(1)	C(3)	C(4)	-179.09(15)
Pd(1)	N(1)	C(3)	C(4)	0.1(2)
C(2)	N(3)	C(3)	N(1)	0.06(16)
C(8)	N(3)	C(3)	N(1)	177.14(13)
C(2)	N(3)	C(3)	C(4)	179.23(13)
C(8)	N(3)	C(3)	C(4)	-3.7(2)
N(1)	C(3)	C(4)	C(5)	-7.8(2)
N(3)	C(3)	C(4)	C(5)	173.21(13)
C(7)	N(2)	C(5)	N(4)	0.58(17)
Pd(1)	N(2)	C(5)	N(4)	-179.08(10)
C(7)	N(2)	C(5)	C(4)	-179.78(15)
Pd(1)	N(2)	C(5)	C(4)	0.6(2)
C(6)	N(4)	C(5)	N(2)	-0.65(18)
C(9)	N(4)	C(5)	N(2)	-178.48(15)
C(6)	N(4)	C(5)	C(4)	179.67(14)
C(9)	N(4)	C(5)	C(4)	1.8(2)
C(3)	C(4)	C(5)	N(2)	7.5(2)
C(3)	C(4)	C(5)	N(4)	-172.93(13)
C(5)	N(4)	C(6)	C(7)	0.45(19)
C(9)	N(4)	C(6)	C(7)	178.26(16)
N(4)	C(6)	C(7)	N(2)	-0.10(19)
C(5)	N(2)	C(7)	C(6)	-0.29(18)
Pd(1)	N(2)	C(7)	C(6)	179.37(11)

Symmetry Operators: (1) x, y, z (2) -x, y+1/2, -z+1/2 (3) -x, -y, -z (4) x, -y-1/2, z-1/2

Table A1.2.7 Hydrogen Bond Lengths (Å) for [Pd(bim)Cl_2] (**15**)

atom	atom	Distance	atom	atom	Distance
C(1)	H(1)	0.9500	C(2)	H(2)	0.9500
C(4)	H(4A)	0.9900	C(4)	H(4B)	0.9900
C(6)	H(6)	0.9500	C(7)	H(7)	0.9500
C(8)	H(8A)	0.9800	C(8)	H(8B)	0.9800
C(8)	H(8C)	0.9800	C(9)	H(9A)	0.9800
C(9)	H(9B)	0.9800	C(9)	H(9C)	0.9800
C(10)	H(10A)	0.9800	C(10)	H(10B)	0.9800
C(10)	H(10C)	0.9800	C(11)	H(11A)	0.9800
C(11)	H(11B)	0.9800	C(11)	H(11C)	0.9800

Symmetry Operators: (1) x, y, z (2) -x, y+1/2, -z+1/2 (3) -x, -y, -z (4) x, -y-1/2, z-1/2

Table A1.2.8 Hydrogen Bond Angles (º) for [Pd(bim)Cl_2] (**15**)

atom	atom	atom	angle
C(2)	C(1)	H(1)	125.5
N(1)	C(1)	H(1)	125.5
C(1)	C(2)	H(2)	126.7
N(3)	C(2)	H(2)	126.7
C(3)	C(4)	H(4A)	108.3
C(5)	C(4)	H(4A)	108.3
C(3)	C(4)	H(4B)	108.3
C(5)	C(4)	H(4B)	108.3
H(4A)	C(4)	H(4B)	107.4
C(7)	C(6)	H(6)	126.6
N(4)	C(6)	H(6)	126.6
C(6)	C(7)	H(7)	125.5
N(2)	C(7)	H(7)	125.5
N(3)	C(8)	H(8A)	109.5
N(3)	C(8)	H(8B)	109.5
H(8A)	C(8)	H(8B)	109.5
N(3)	C(8)	H(8C)	109.5
H(8A)	C(8)	H(8C)	109.5
H(8B)	C(8)	H(8C)	109.5
N(4)	C(9)	H(9A)	109.5
N(4)	C(9)	H(9B)	109.5

H(9A)	C(9)	H(9B)	109.5
N(4)	C(9)	H(9C)	109.5
H(9A)	C(9)	H(9C)	109.5
H(9B)	C(9)	H(9C)	109.5
S(1)	C(10)	H(10A)	109.5
S(1)	C(10)	H(10B)	109.5
H(10A)	C(10)	H(10B)	109.5
S(1)	C(10)	H(10C)	109.5
H(10A)	C(10)	H(10C)	109.5
H(10B)	C(10)	H(10C)	109.5
S(1)	C(11)	H(11A)	109.5
S(1)	C(11)	H(11B)	109.5
H(11A)	C(11)	H(11B)	109.5
S(1)	C(11)	H(11C)	109.5
H(11A)	C(11)	H(11C)	109.5
H(11B)	C(11)	H(11C)	109.5

Symmetry Operators: (1) x, y, z (2) -x, y+1/2, -z+1/2 (3) -x, -y, -z (4) x, -y-1/2, z-1/2

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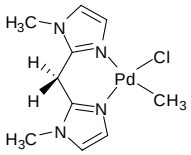
Appendix 2

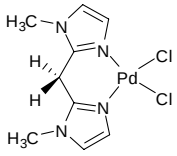
Hydroamination Kinetic Data

A2.1 Cyclisation of 4-Pentyn-1-amine (21) to 2-Methyl-1-pyrroline (22)

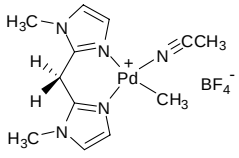
A2.1.1 Catalysed by Palladium Complexes

Complex 14	Reaction Conditions	Time (h)	% Conversion
	**[Pd]** = 3.2 mg, 9.6 μmol **4-pentyn-1-amine** = 53 mg, 0.64 mmol **mol% of catalyst** = 1.5 mol% **Conditions**: methanol-d_3, methanol, 60 °C **N_t (h^{-1})** = 31	0.01	1
		0.03	1
		0.04	2
		0.05	4
		0.07	5
		0.08	6
		0.11	8
		0.14	10
		0.17	11
		0.19	13
		0.22	14
		0.25	16
		0.28	18
		0.31	19
		0.33	21
		0.36	22
		0.46	27
		0.55	32
		0.65	35
		0.74	39
		0.84	42
		0.93	45
		1.03	48
		1.12	50
		1.22	52
		1.31	54
		1.49	57
		1.67	60
		1.84	63
		2.02	65
		2.20	67
		2.38	69
		2.56	71
		2.73	72
		2.91	74
		3.09	75
		3.60	78
		4.11	81
		4.63	83
		5.14	84
		5.65	85

		6.16	86
		6.67	87
		7.18	88
		7.69	89
		8.20	90
		8.72	91
		9.23	91
		9.74	92
		10.25	93
		10.76	94
		11.27	95
		11.78	95
		12.30	96
		12.81	96
		13.32	97
		13.83	97
		14.34	98
		14.85	98
		15.36	99
		15.88	99
		16.39	100
		16.90	100
		17.41	100

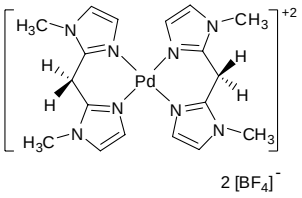
Complex 15	**Reaction Conditions**	**Time (h)**	**% Conversion**
	**[Pd]** = 2.4 mg, 6.8 μmol **4-pentyn-1-amine** = 38 mg, 0.45 mmol **mol% of catalyst** = 1.5 mol% **Conditions**: methanol-d_3, methanol, 60 °C **N_t (h^{-1})** = 16	0.04	1
		0.05	3
		0.07	4
		0.08	5
		0.11	6
		0.14	7
		0.17	9
		0.19	10
		0.22	11
		0.25	13
		0.28	14
		0.31	15
		0.33	16
		0.36	17
		0.46	20
		0.55	24
		0.65	27
		0.74	30
		0.84	32
		0.93	35
		1.03	37
		1.12	38
		1.22	40
		1.31	41

		1.49	44
		1.67	46
		1.84	48
		2.02	50
		2.20	52
		2.38	54
		2.56	55
		2.73	57
		2.91	58
		3.09	60
		3.60	63
		4.11	66
		4.63	68
		5.14	70
		5.65	72
		6.16	74
		6.67	75
		7.18	76
		7.69	77
		8.20	78
		8.72	78
		9.23	79
		9.74	80
		10.25	80
		10.76	81
		11.27	81
		11.78	82
		12.30	82
		12.81	83
		13.32	83
		13.83	83
		14.34	83
		14.85	84
		15.36	83
		15.88	83
		16.39	83
		16.90	83
		17.41	83

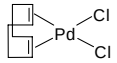
Complex 16	Reaction Conditions	Time (h)	% Conversion
	**[Pd]** = 3.0 mg, 7.1 μmol **4-pentyn-1-amine** = 41 mg, 0.50 mmol **mol% of catalyst** = 1.4 mol% **Conditions**: methanol-d_3, methanol, 60 °C **N_t (h^{-1})** = 4	0.01	6
		0.03	8
		0.04	11
		0.05	13
		0.07	15
		0.08	17
		0.11	20
		0.14	22
		0.17	22

		0.19	23
		0.22	23
		0.25	24
		0.28	25
		0.31	25
		0.33	25
		0.36	26
		0.46	27
		0.55	28
		0.65	28
		0.74	29
		0.84	30
		0.93	31
		1.03	31
		1.12	32
		1.22	33
		1.31	33
		1.49	35
		1.67	35
		1.84	36
		2.02	37
		2.20	38
		2.38	38
		2.56	39
		2.73	40
		2.91	41
		3.09	41
		3.60	42
		4.11	43
		4.63	45
		5.14	45
		5.65	46
		6.16	47
		6.67	48
		7.18	48
		7.69	49
		8.20	50
		8.72	50
		9.23	51
		9.74	52
		10.25	52
		10.76	53
		11.27	53
		11.78	53
		12.30	54
		12.81	54
		13.32	55
		13.83	55
		14.34	56

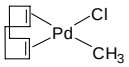
		14.85	56
		15.36	56
		15.88	57
		16.39	57
		16.90	58
		17.41	58

Complex 17	Reaction Conditions	Time (h)	% Conversion
	**[Pd]** = 3.5 mg, 5.5 μmol **4-pentyn-1-amine** = 34 mg, 0.41 mmol **mol% of catalyst** = 1.4 mol% **Conditions**: methanol-d_3, methanol, 60 °C **N_t (h^{-1})** = 6	0.01	5
		0.03	3
		0.04	3
		0.05	3
		0.07	3
		0.08	4
		0.11	5
		0.14	6
		0.17	6
		0.19	7
		0.22	8
		0.25	9
		0.28	10
		0.31	10
		0.33	11
		0.36	12
		0.46	14
		0.55	16
		0.65	18
		0.74	19
		0.84	20
		0.93	22
		1.03	22
		1.12	24
		1.22	25
		1.31	26
		1.49	28
		1.67	29
		1.84	31
		2.02	32
		2.20	33
		2.38	35
		2.56	35
		2.73	37
		2.91	38
		3.09	39
		3.60	41
		4.11	44
		4.63	46
		5.14	48
		5.65	50

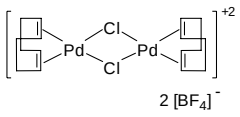
		6.16	52
		6.67	53
		7.18	55
		7.69	57
		8.20	58
		8.72	60
		9.23	61
		9.74	62
		10.25	63
		10.76	65
		11.27	66
		11.78	67
		12.30	68
		12.81	69
		13.32	70
		13.83	70
		14.34	72
		14.85	72
		15.36	73
		15.88	74
		16.39	74
		16.90	74
		17.41	76

Complex 18	Reaction Conditions	Time (h)	% Conversion
	**[Pd]** = 1.3 mg, 4.5 μmol **4-pentyn-1-amine** = 25 mg, 0.30 mmol **mol% of catalyst** = 1.5 mol% **Conditions**: methanol-d_3, methanol, 60 °C **N_t (h^{-1})** = 32	0.46	4
		0.55	17
		0.65	22
		0.74	33
		0.84	39
		0.93	45
		1.03	49
		1.12	55
		1.22	58
		1.31	61
		1.49	66
		1.67	69
		1.84	72
		2.02	75
		2.20	76
		2.38	78
		2.56	79
		2.73	80
		2.91	81
		3.09	83
		3.60	86
		4.11	89
		4.63	90
		5.14	91

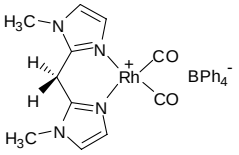
		5.65	94
		6.16	93
		6.67	93
		7.18	94
		7.69	95
		8.20	95
		8.72	95
		9.23	108
		9.74	124
		10.25	129
		10.76	143
		11.27	136
		11.78	123
		12.30	139
		12.81	118
		13.32	108
		13.83	109
		14.34	103
		14.85	106
		15.36	104
		15.88	112
		16.39	106
		16.90	101
		17.41	100

Complex 19	Reaction Conditions	Time (h)	% Conversion
	**[Pd]** = 2.5 mg, 9.4 μmol **4-pentyn-1-amine** = 53 mg, 0.64 mmol **mol% of catalyst** = 1.5 mol% **Conditions**: methanol-d_3, methanol, 60 °C **N_t (h^{-1})** = 52	0.14	1
		0.17	7
		0.19	10
		0.22	14
		0.25	18
		0.28	21
		0.31	24
		0.33	28
		0.36	31
		0.46	38
		0.55	45
		0.65	50
		0.74	55
		0.84	59
		0.93	62
		1.03	64
		1.12	67
		1.22	69
		1.31	71
		1.49	73
		1.67	76
		1.84	77
		2.02	78

		2.20	80
		2.38	80
		2.56	81
		2.73	82
		2.91	83
		3.09	84
		3.60	84
		4.11	86
		4.63	87
		5.14	86
		5.65	88
		6.16	90
		6.67	91
		7.18	92
		7.69	94
		8.20	94
		8.72	95
		9.23	95
		9.74	95
		10.25	95
		10.76	96
		11.27	93
		11.78	93
		12.30	93
		12.81	92
		13.32	90
		13.83	90

Complex 20	**Reaction Conditions**	**Time (h)**	**% Conversion**
	**[Pd]** = 2.6 mg, 3.9 μmol **4-pentyn-1-amine** = 2.8 mg, 0.30 mmol **mol% of catalyst** = 1.3 mol% **Conditions**: methanol-d_3, methanol, 60 °C **N_t (h^{-1})** = 425	0.01	10
		0.03	19
		0.04	26
		0.05	34
		0.07	39
		0.08	43
		0.11	54
		0.14	60
		0.17	65
		0.19	69
		0.33	81
		0.74	91
		1.22	96
		2.02	97
		2.91	98

A2.1.2 Catalysed by Rhodium(I) Complex (1)

Complex 1	Reaction Conditions	Time (h)	% Conversion
	**[Rh]** = 4.0 mg, 6.1 μmol **4-pentyn-1-amine** = 34 mg, 0.41 mmol **mol% of catalyst** = 1.5 mol% **Conditions**: methanol-d_3, methanol, 60 °C **N_t (h^{-1})** = 7	0.25	5
		0.28	6
		0.31	6
		0.33	6
		0.36	8
		0.46	12
		0.55	16
		0.65	19
		0.74	20
		0.84	21
		0.93	22
		1.03	24
		1.12	25
		1.22	26
		1.31	26
		1.49	28
		1.67	30
		1.84	31
		2.02	33
		2.20	34
		2.38	36
		2.56	37
		2.73	38
		2.91	40
		3.09	41
		3.60	44
		4.11	47
		4.63	49
		5.14	51
		5.65	54
		6.16	56
		6.67	58
		7.18	60
		7.69	63
		8.20	64
		8.72	66
		9.23	68
		9.74	69
		10.25	72
		10.76	73
		11.27	74
		11.78	76
		12.30	77
		12.81	77
		13.32	78
		13.83	80
		14.34	81

		14.85	81
		15.36	82
		15.88	84
		16.39	84
		16.90	84
		17.41	84