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The synthesis of Benzo[C]carbazoles

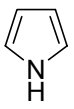
Nhlapo, Johanna Mepeng

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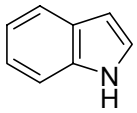
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CHAPTER 1: INTRODUCTION

A research field in chemistry which has also elicited huge interest amongst synthetic chemists is heterocyclic chemistry. The attraction of this area stems from the significance of heterocycles in medicine, agriculture, industry and academic research and teaching. The interesting and often intriguing structural and electronic properties of heterocyclic compounds often naturally occurring, has led to their intense study by researchers especially because a number of important pharmaceutical and agrochemical compounds are derived from heterocycles. Heterocyles such as pyrrole **(1)** and indole **(2)**, formed by fusion of a benzene ring to the 2 and 3 positions of pyrrole, are found extensively as subunits in complex biologically active compounds.[1]



(1)



(2)

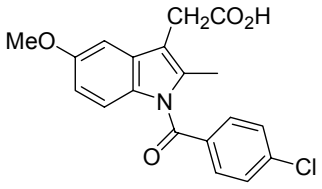
Owing to the immensity of the scope of heterocycles, a comprehensive discussion is not possible in this dissertation but a general discussion on some systems related to those used in this dissertation will be used to highlight the importance of heterocycles.

1.1 COMPOUNDS CONTAINING AN INDOLE CORE

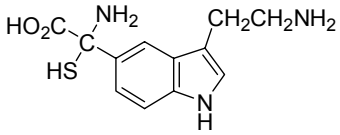
For thousands of years the sick were cured world-wide, by remedies obtained from 'nature's own drugstore', comprising such sources as leaves, fruits, barks and herbs.[1] It was later realised that many successful traditional treatments were frequently as a result of the presence of various heterocyclic compounds in extracts derived from these plants, and even sometimes animals.

The first preparation of indole dates from the 1800s and the Fischer indole synthesis, which probably remains the most versatile method for preparing indoles, was first reported in 1833.[2] The principal commercial source of simple indoles is by extraction

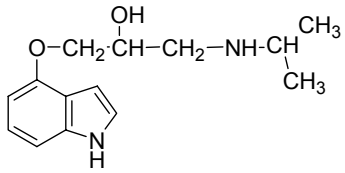
from coal tar, although the feasibility of industrial synthesis from starting material such as aniline and ethylene glycol, *N*-ethylaniline or 2-ethylaniline has been demonstrated.[2] Indole as a sub-structure is present in a vast number of complex natural compounds such as complex alkaloids, fungal metabolites and marine natural products as well as in pharmaceutical compounds, such as indomethacin **(3)**, which is one of the first non-steroidal anti-inflammatory agents.[2] Other indole derivatives which have been used as drugs include sumatriptan **(4)**, which is used in the treatment of migraine headaches and pindolol **(5)**, one of the β–adrenergic blockers.[2]



(3)

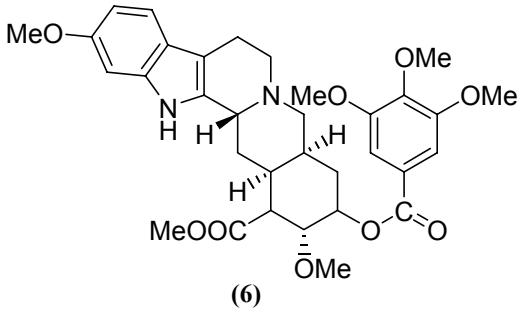


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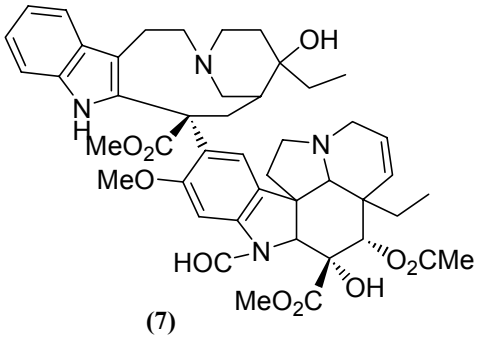
Several naturally occurring indole derivatives have also important clinical applications. The shrub *Rauvolfia serpentia*, native to South and South Eastern Asia, contains the indole alkaloid reserpine (**6**), which although currently not a major drug, was one of the first compounds to show beneficial effects in the treatment of mental disorders[2], and was also used as a tranquilizing agent.[1] It was also found that reserpine can also be used to decrease blood pressure and is also useful in the treatment of hypertension.



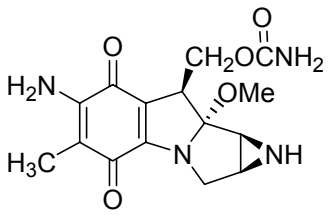
(6)

Some of indole alkaloids have been used in therapeutic treatment of cancer and as anti-tumor agents. The dimeric *vinca* vincristine alkaloid **(7)** was among the first of the anti-

miotic class of chemotherapeutic agents for the treatment of cancer,[2] whilst mitomycin C, an oxidised dihydroindole **(8)** is an example of compounds having anti-tumor activity.[2]



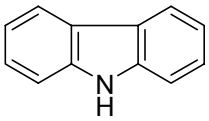
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1.2 NATURALLY OCCURRING, SYNTHETIC CARBAZOLES AND MEDICINE

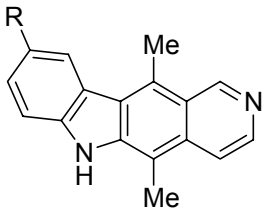
Carbazoles, like indoles were initially isolated from coal tar in 1872 by Graebe and Glaser.[3] The first simple carbazoles from plant sources, *e.g* carbazole **(9)** was not discovered until the 1960's.[4,5] This group has now grown into a large class of alkaloids. Carbazoles are biologically active and display properties ranging from antifungal, antimicrobal, through antitumour, to hypertensive effects.[6,7] Of course the indole nucleus is found embedded in this class of compounds and thus indole and substituted indoles have been used widely by chemists as precursors for the synthesis of carbazoles.



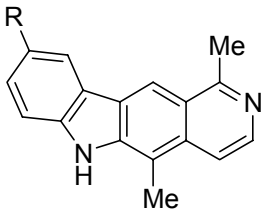
(9)

Important members of this class include the benzo- and pyrido-fused carbazoles, either as naturally occurring products or as compounds derived by synthesis.[7-10] Methods for efficient, regio-selective synthesis of benzo- and pyrido-fused carbazoles are of interest to synthetic chemists because these systems occur as subunits of biologically active products,[11] or are themselves biologically active, or have potential for the development of compounds with antitumour activity.[12] Some of the more important compounds that

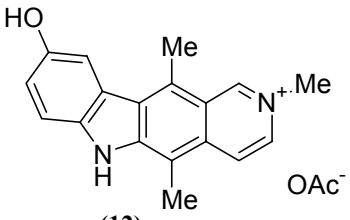
belong to this class include the 6*H*-pyrido[4,3-*b*]carbazole alkaloids ellipticine **(10a)**, 9-methoxyellipticine **(10b)**, and olivacine **(11)**, which display pronounced antitumour-activity in several animal and human tumour systems.[12,13] A derivative of 9-methoxyellipticine **(10c)**, namely 2-methyl-9-hydroxyellipticine acetate **(12)** ('elliptinium'), is a clinically proven anticancer drug for the treatment of matastatic breast cancer, mycoblastic leukaemia, and some solid tumours.[7,8] This compound has a high DNA binding affinity and it is a DNA intercalating compound.[10] The size and the shape of the carbazole ring of **(10a,b)**, **(11)** and **(12)** leads to an almost perfect overlap of the aromatic ring with that of a DNA base pair.[14] Therefore, the pyrido[*b*]carbazole system appears as an appropriate skeleton in the design of DNA intercalating drugs.[14]



(10 a) R= H
(10 b) R= OMe
(10 c) R= OH

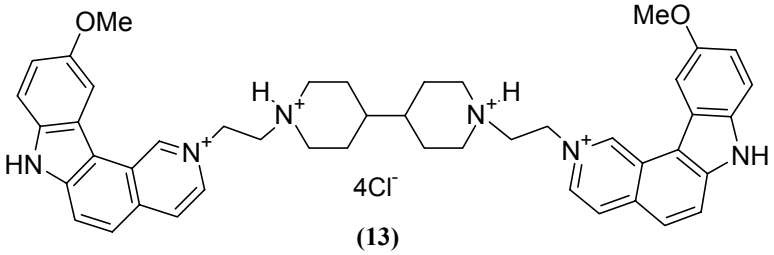


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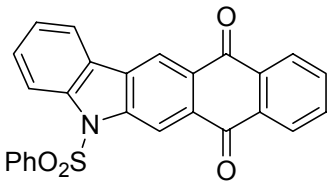


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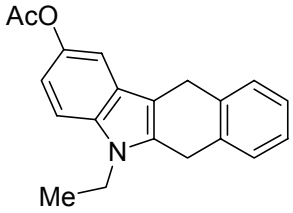
Another important member of this class of pyrido-fused carbazoles is a pyrido[*c*]-fused carbazole ditercalinium **(13)**, which has been used clinically for the treatment of cancers,[10] while the naphtho[2,3-*a*]carbazole **(14)** is responsible for significant cell growth inhibition in a range of tumour cell lines.[10] Simple benzo[*a*]carbazoles such as **(15)** have been shown to bind to estrogen receptors and inhibit the growth of mammary tumours in rats.[14]



(13)

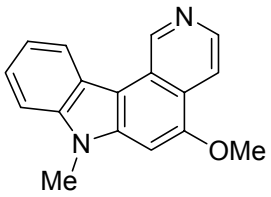


(14)



(15)

Owing to the continuing need for anti-HIV agents with novel structures and mechanisms of action, some pyridocarbazoles have been screened for anti-HIV activity.[15] Several substituted 7*H*-pyrido[4,3-*c*]carbazoles have been screened. These compounds are related in structure to the antitumour alkaloid ellipticine[16] and its synthetic analogues.[17] Several of these derivatives showed promising inhibition of HIV replication in H9 lymphocytes, especially the *c*-face fused 5-methoxy-7-methyl-7*H*-pyrido[4,3-*c*]carbazole **(16)**.[15]



(16)

1.3 INDOLE CONTAINING COMPOUNDS IN AGRICULTURE[1]

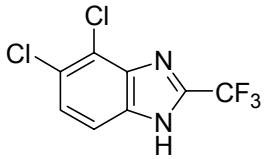
Malnutrition has shown itself to be one of the dangers to the human population. Many people world-wide suffer from diseases as a direct consequence of malnutrition. The world's population is increasing drastically, exerting ever-increasing demands for food and meeting the need for such amounts of food requires dramatic improvements in the productivity of modern agriculture.

Exacerbating these demographic problems are the losses of agricultural production due to pests such as rodents, insects, microorganisms and weeds. Biological methods of plant protection are of great potential importance, but chemical control is currently the main

approach utilised. Chemical pest control is carried out by using compounds known as pesticides, which include herbicides (substances used to kill weeds), insecticides, fungicides (agents used against fungal pathogens) and rodenticides stimulators and regulators of plant growth and development are also of great importance.

The indole ring, which is present in the amino acid tryptophan and metabolites of tryptophan, appears to be important in the biological chemistry of both plants and animals. The agricultural application of compounds with regulatory activity began more than half a century ago. Their small percentage (5% by weight) in the overall production of pesticides is largely accounted for by their effectiveness at low concentrations.

Although not an indole based product, typical applications of heterocyclic compounds as herbicides, such as chloroflurazole **(17)** include the destruction of weeds in cotton, sugar beet, turnips, soya beans and sunflower crops, and also in vineyards, berry plantations and orchards.



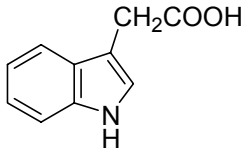
(17)

Plant growth regulators have been used mainly to create favourable conditions for the development of cultivated plants rather than to combat weeds. Plant regulators can accelerate or slow the growth, flowering or ripening of plants, and make crops more drought or frost resistant.

Indol-3-ylacetic acid (heteroauxin) **(18)** is one of the chief growth hormones. This auxin diffuses readily along the plant stem, and its hormonal action results in the lengthening of plant cells and stimulation of their division by increasing the rate of DNA replication. The acid induces the formation of the side roots, stem sprouts and leaves, but inhibits plant growth when used in high concentrations. This acid also regulates and coordinates the growth of all plant components including roots, stems and buds. Heteroauxin usually

accumulates in the growing tissues of the plant. The same hormone is also found in mushrooms and some symbiotic plants. The practical uses of this acid are extensive: the implantation of grafts during the vegetative propagation of fruit and berry cultures, as well as the promotion of an increased number of shoots and seedless fruits.

Many other synthetic regulators of plant growth and development have been prepared, each designed specifically to influence a particular biological process, such as activating or regulating photosynthesis, interfering with chlorophyll biosynthesis or stimulating plant respiration.



(18)

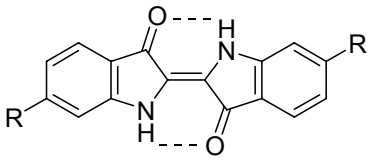
1.4 INDOLE CONTAINING COMPOUNDS IN INDUSTRY AND TECHNOLOGY[1]

Once more, heterocyclic compounds have proven to be very important in our everyday life. It is not surprising to have heterocyclic compounds in the developments of science and technology with numerous applications, including communications and aerospace technology. They are also enormously important in other branches of industry such as the dyestuff industry.

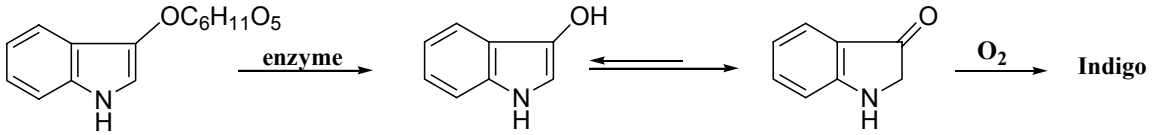
1.4.1 Industrial Applications of Indoles as Dyes[1]

Since ancient times, people have used dyes obtained from various natural sources to adorn their dwellings and clothes and to prepare cosmetics. The blue dye indigo **(19)** was separated from leaves of *Indigofera tinctoria*. The purple dye **(20)** 6,6`-dibromoindigo, known as “Tyrian” or “Royal Purple”, was obtained from the Mediterranean sea mollusk *Murex brabdaris*. This dye got its name, Royal Purple, since it does not occur readily in

nature and is expensive to manufacture. It was mainly used to colour the cloaks of pharaohs, emperors and high priests. Though it does not occur in nature it is formed during the processing from natural precursors. The leaves of the indigo plant contain indican **(21)** (3-hydroxylindole O-glycoside) and when the leaves are destroyed, indican is first transformed enzymatically into 3-hydroxyindole (indoxyl, which exists predominantly in the tautomeric oxoform), and which is then converted into indigo by the action of enzymes and oxygen.



(19) R=H
(20) R=Br

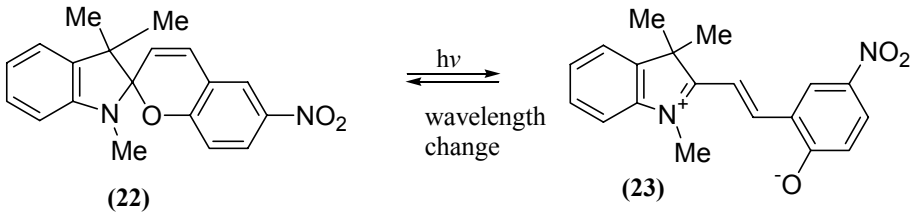


(21)

1.4.2 Industrial Applications in Photographic Materials[1]

The versatile array of chemicals available for use in photographic processes is largely based on heterocyclic compounds. Silver-free photographic materials are eagerly sought, in part owing to fears of a shortage of, and increased price of silver. Heterocyclic compounds play a leading role in creation of another type of silver-free reprographic material. This material is based on photochromic substances, which reversibly change colour, by action of light. Indoylspiropyrans are distinguished by their quality and effectiveness among the various classes of organic photochromes. An example is compound **(22)**, which is produced from the condensation of 1,2,3,3-tetramethylindolium iodide with 5-nitrosalicylic aldehyde. Upon irradiation with light of the appropriate wavelength, spiropyran **(22)** is transformed into the intensely purple valence isomer **(23)**, which structurally resembles the cyanine dyes. Compound **(23)** is sufficiently stable for

the colour of a picture to be preserved over long periods. The reverse reaction, *i.e*. closure of the pyran cycle to give the colourless form **(22)**, is possible only upon repeated irradiation of isomer **(22)** by a powerful light source of a different wavelength.



(22) **(23)**

Despite their comparatively low light sensitivity, photochromes possess a few remarkable advantages over silver halide-based materials. Firstly, photochromic transformations have a molecular nature that provides exceptionally high clarity and large information storage capacity to the image. Thus, the use of micro imaging enables the information contained in a large library to be stored in compact format. Another advantage is that as a clear colour image of the subject is received immediately following exposure. Last but not least, photochromic materials can be highly economical as in some cases they can be utilised repeatedly after deletion of the original image.

1.5 SOME REACTIONS OF INDOLE AND ITS DERIVATIVES[1]

1.5.1 Substitution at Nitrogen

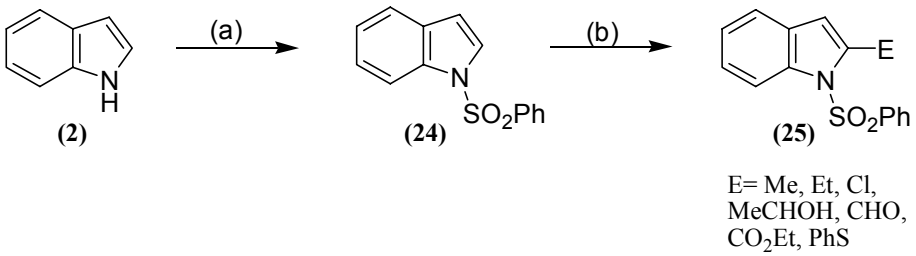
The indole-NH is weakly acidic with the neutral indole ring not very nucleophilic at the nitrogen but the anion generated by deprotonation is a good nucleophile. One method of deprotection is to use one or more equivalents of a strong base in a polar aprotic solvent. Indole will thus react with the base forming indolyl anion. When the counter ion is an alkali metal, these salts have considerable ionic character and react with electrophiles at the nitrogen, affording a practical route for *N*-alkylation (or acylation) of indole nitrogen. Bases that are normally used include *n*-butyllithium, sodium hydride and alkali metal hydroxides. Other methods of *N*-substitution involve phase transfer catalysis. The

alkylating reagent must be able to undergo an S_N2 substitution reaction, consequently, primary alkyl, benzyl and allyl halides and sulfonates are usually excellent electrophiles.

1.5.2 Substitution at C2 and C3 Positions

The *N*-substituted indoles are very important in the synthesis of many important compounds in organic synthesis. The regiospecific metallation of *N*-protected indoles is well known. Nitrogen-protected 2-lithioindoles have been widely used in synthesis since the pioneering work of Sundberg and Russel,[18] with phenylsulfonyl protecting group used extensively.[19] From *N*-protected indoles, deprotonation (lithiation) can be effected at C-2, which can result in various C-2 substituted indoles that subsequently act as precursors in the synthesis of biological active compounds.

Scheme 1 below show examples of C-2 substituted indoles from *N*-phenylsulfonyl protected indole. Thus, 1-(phenylsulfonyl)indole **(24)** is prepared from indole **(2)** with *n*-butyllithium and benzenesulfonyl chloride (91%). This is then lithiated at C-2 with lithium diisopropylamide (LDA), and the resulting 2-lithiospecies treated with various electrophiles to afford C-2 substituted indoles **(25)**.[20]



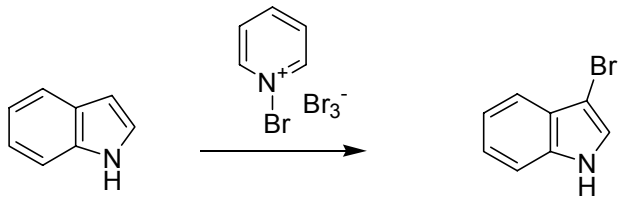
Scheme 1: (a) *n*-BuLi, $PhSO_2Cl$, 91%; (b) (i) LDA, THF, -78 ˚C (ii) EX, 50-93%.

Many other protecting groups have been used such as *tert*-butoxycarbonyl, benzyl, tosyl and methyl, and are capable of directing lithiation at C-2, although in this series *tert*-butoxycarbonyl is often the best director and has the advantage of being easily removed.

Indole is a very reactive π-excessive heterocycle and reacts with halogens and other electrophiles rapidly, preferentially at C3 position.[21] Nature has exploited this property to produce more than 300 halogenated indoles, mainly bromoindoles in marine organisms.[22]

Of the two rings of indole, the heterocyclic ring is very electron-rich, by comparison with the fused benzene ring, so attack by electophiles always takes place on the five-membered ring, except in special circumstances. Of the three positions on the heterocyclic ring, attack at nitrogen would destroy aromaticity of the five-membered ring, and produce a localised cation; both of the remaining positions 2- and 3- can be attacked by electrophiles, leading to C-substituted products, but the 3-position is preferred by a considerable margin.[23] Like *N*-protected indoles C-substituted indoles are also precursors to biologically active compounds.

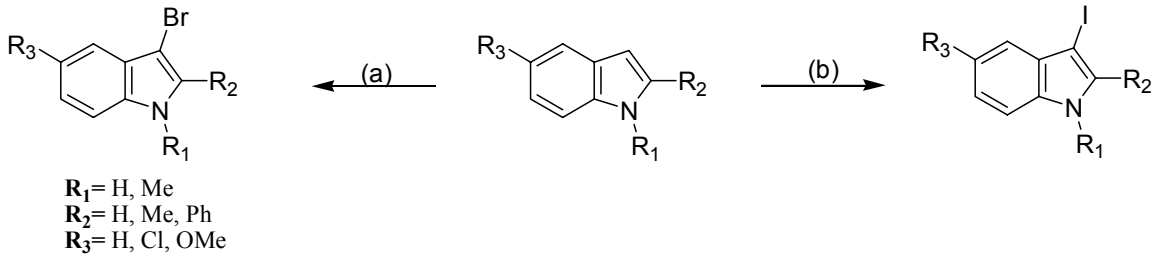
The early synthesis of haloindoles involved direct halogenation with chlorine, bromine or iodine. In some cases, this approach was reasonably successful, but the instability of the resulting 3-haloindoles made product isolation and further chemistry difficult.[24] For an example, 3-bromoindole **(26)**, as shown in **Scheme 2**, can be prepared in 64% yield by treatment of indole **(2)** with pyridinium bromide perbromide. The product decomposes at 65 ˚C and should be stored at –20 ˚C.[24]



(2) **(26)**

Scheme 2: Pyridine, 0-2 ˚C, 64 %.

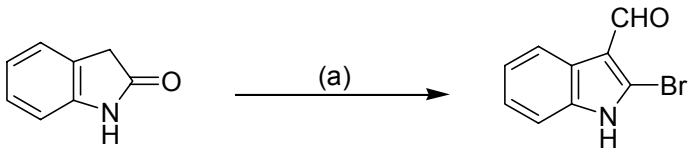
A vast improvement in the synthesis of both 3-bromo and 3-iodoindole, using DMF as a solvent, was described by Bocchi and Palla,[25] as summarised in **Scheme 3** below.



R_1= H, Me
R_2= H, Me, Ph
R_3= H, Cl, OMe

Scheme 3: (a) Br_2, DMF, rt, 94-98%; (b) I_2, DMF, KOH, rt, 93-98%.

Many other C-substitution groups are used to yield precursors to valuable compounds. The C-substitution of indoles can also be achieved from 2-oxindole **(27)** as shown in **Scheme 4**. The treatment of this compound with phosphorus oxybromide and DMF to a variation of Schulte's procedure,[26,27] resulted in a disubstituted indole **(28)**.



(27) **(28)**

Scheme 4: (a) (i) $POBr_3$, DMF, $CHCl_3$, 18h; (ii) $NaOH_{(aq.)}$.

1.6 PALLADIUM IN INDOLE CHEMISTRY

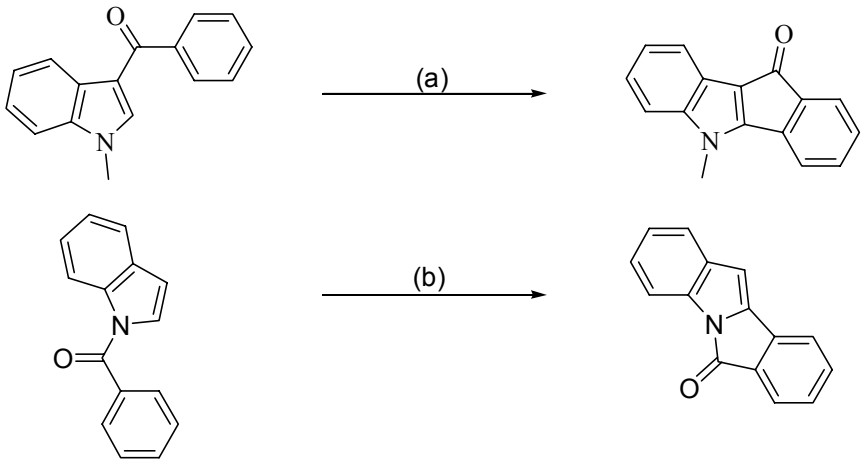
Transition metal-catalysed reactions are probably the most rapidly expanding area of organic chemistry and these reactions have been used extensively in both the ring synthesis and functionalisation of indoles.[23] The transition metal-catalysed reactions of organometallic reagents with organic halides has been extensively studied to provide a new approach to the selective formation of C-C bonds. Due to the enormity of this topic, only a few selected topics will be highlighted with a few chosen examples to provide reasonable scope for this dissertation.

Palladium associated with a variety of ligands in a zero or plus two oxidation state is by far the most important and widely used catalyst due to the wide range of reaction types in which it can function. In general, indole and its derivatives can undergo palladium-catalysed reactions in a way analogous to carbocycles; heterocylic sulfur and nitrogen atoms seldom interfere with these (homogenous) palladium catalysts, which must be contrasted with the well-known supposed poisoning of hydrogenation catalysts such as palladium metal on carbon by sulfur and nitrogen containing compounds.[23]

1.6.1 Oxidative Coupling/Cyclisation

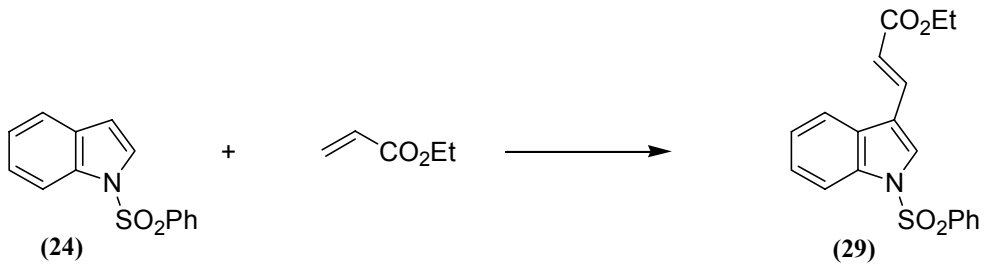
Most early applications of palladium to indole chemistry involved oxidative coupling or cyclisation using stochiometric Pd(II).[28] The source of Pd(II) in oxidative coupling was mostly $Pd(OAc)_2$. Such oxidative couplings have been extensively used in the synthesis of a wide range of carbazoles and carbazolequinone alkaloids.[29]

Trost is reported to be the first to apply a palladium-catalysed cyclisation reaction to the synthesis of indole alkaloids.[30-33] Itahara established the utility of $Pd(OAc)_2$ in oxidative cyclisation of *C*- and *N*-benzoylindoles,[34-36] as shown by the selected examples in **Scheme 5** below.



Scheme 5: (a) $Pd(OAc)_2$, AcOH, 110 ˚C, 15h, 60%; (b) $Pd(OAc)_2$, AcOH, 110 ˚C, 7h, 45%.

The formation of C-C bonds at C-3 position is possible using these conditions with AgOAc or other re-oxidants to make these reactions catalytic,[37] as discovered by Itahara and co-workers. Ethyl acrylate was reacted under these conditions with *N*-(phenylsulfonyl)indole (**24**) to give ethyl (*E*)-3-[1-(phenylsulfonyl)-1*H*-indol-3-yl]-2-propenoate (**29**).



(24) **(29)**

Scheme 6: $Pd(OAc)_2$, AgOAc, AcOH, 100 ˚C, 98%.

1.6.2 Negishi Coupling

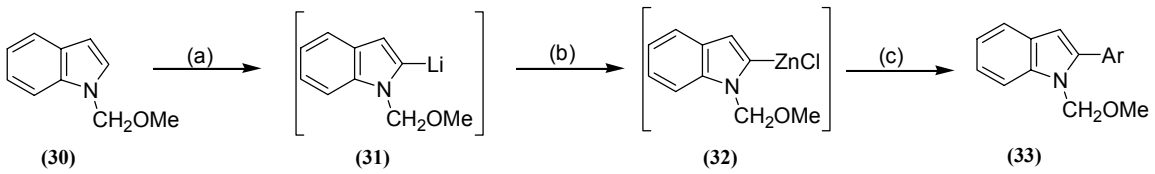
Organozinc derivatives have importance in synthetic organic chemistry because of their reduced reactivity compared with organolithium or organomagnesium halides and their compatibility with functional groups such as alkoxycarbonyls.[38] Their use has included chemoselective carbon-carbon bond forming reactions including palladium-catalysed cross-coupling.[38,39] Organozinc halides have been prepared, in general, by transmetallation of organolithium or organomagnesium halides with zinc chloride, although this method is essentially limited to the preparation of organozinc halides without functional groups.[38] However, organozinc halides can also be directly prepared by oxidative addition of activated zinc to organic iodides or bromides.[40]

1.6.2.1 Indoyl Chlorides from Lithioindoles by Transmetallation with Zinc Chloride

Sakamoto and co-workers studied extensively, the generation and coupling of *N*-protected 2- and 3-indoylzinc halides.[41,42] The selective removal of the proton at the 2- or 3- position in indole requires the absence of the much more acidic hydrogen on the

nitrogen atom. Thus, to achieve this, a protecting group attached to nitrogen must be capable of coordination to an electron deficient metal such as lithium. Thus, groups like methyl, or if required, removable groups such as phenylsulfonyl, *tert*-butoxycarbonyl, methoxymethyl, and trimethylsilylethoxymethyl have been used.

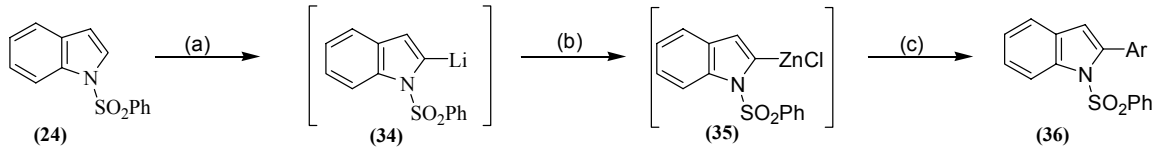
In some cases lithiation of indoles at the 2-position is achieved by directed metallation. This is achieved by the use of *n*-butyllithium or *tert*-butyllithium which abstracts a proton from 1-(methoxymethyl)indole **(30)** to afford 2-litho-1-methoxymethylindole **(31)**. 2-Lithio-1-methoxymethylindole **(31)** was prepared from the reaction of 1-(methoxymethyl)indole **(30)** with *tert*-butyllithium in THF at –70 ^{o}C.[38] The resulting lithiated intermediate compound **(31**) was treated with zinc chloride at room to temperature give 1-(methoxymethyl-9-indol-2-yl)zinc chloride **(32)**[38] which was further reacted with iodobenzene in the presence of tetrakis(triphenylphosphine)palladium(0) in THF, under reflux, to give 1-methoxymethyl-2-phenylindole **(33)** in 28%,[38] as shown in **Scheme 7** below.



(30) **(31)** **(32)** **(33)**

Scheme 7: (a) ^{t}BuLi, THF, -70 ˚C; (b) ZnCl, rt; (c) $Pd(PPh_3)_4$, ArI.

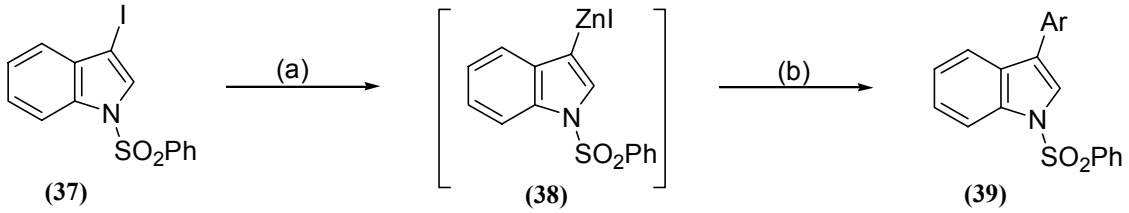
The use of strong bases such as *n*-butyllithium and *tert*-butyllithium in some cases gives inseparable mixtures as in lithiation of 1-phenylsulfonylindole **(24)**.[38] Lithiation of 1-phenylsulfonylindole **(24)** by lithium diisopropylamide instead of *tert*-butyllithium at –78 ^{o}C followed by the transmetallation and the cross-coupling gave no products.[38] Lithiation by diisopropylamide at –20 to 0 ^{o}C, however, proceeded smoothly to afford 1-(2-phenyl-phenylsulfonyl)indole **(36)** in 51%,[38] as shown in **Scheme 8** below.



Scheme 8: (a) LDA, THF, -20 - 0 ˚C; (b) $ZnCl_2$, rt; (c) $Pd(PPh_3)_4$, ArI.

1.6.2.2 Indoylzinc Iodides from Iodoindoles by Oxidative Addition with active Zinc

3-Iodo-1-phenylsulfonylindole **(37)** was reacted with activated zinc in THF at room temperature to give the indolylzinc iodide **(38)**.[38] This was coupled with iodobenzene to give the 3-phenylindole **(39)** in 83% without any 2-phenylindole, **Scheme 9**.[38] Similar reaction with 2-bromopyridine, 3-iodopyridine or iodothiazole afforded the corresponding products in good yields.[38]

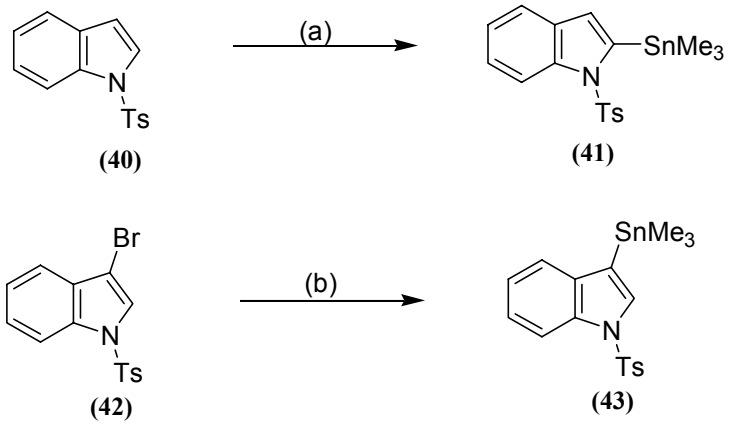


Scheme 9: (a) Activated Zn, THF, rt; (b) $Pd(PPh_3)_4$, ArI.

1.6.3 Stille Coupling

Despite the well-documented toxicity of organotin compounds, the use of these reagents in palladium-catalysed cross-coupling reactions continues unabated, following the pioneering work of Stille. Stannanes are usually prepared by treating the appropriate lithioindoles with a trialkyltin halide or by halogen-tin exchange with, for example,

hexamethylditin in the presence of a source of palladium(0).[22] For example, 1-(4-toluenesulfonyl)indole **(40)** was lithiated with LDA and quenched with trimethylstannyl chloride to give a 2-trimethylstannylindole **(41)**.[43,44] The corresponding 3-trimethylstannylindole **(43)** was prepared by lithiation of 3-bromo-1-substituted indole **(42)** with ^{t}BuLi [44] and similar reaction with palladium-catalysed coupling reaction with hexamethylditin,[45] as shown in **Scheme 10**.

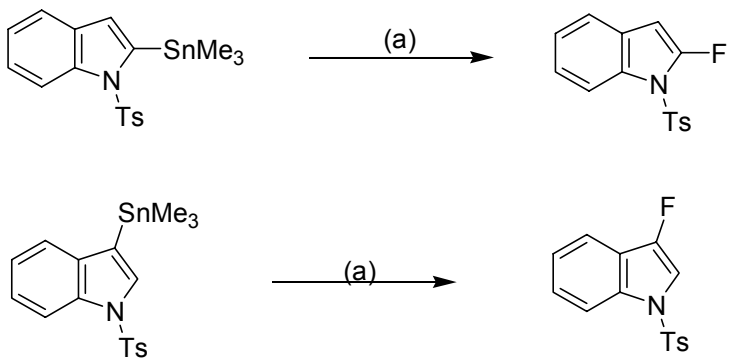


Scheme 10: (a) LDA, THF, Me_3SnCl; (b) ^{t}BuLi, THF, MeSnCl or $Pd(PPh_3)_4$ and $(Me_3Sn)_2$.

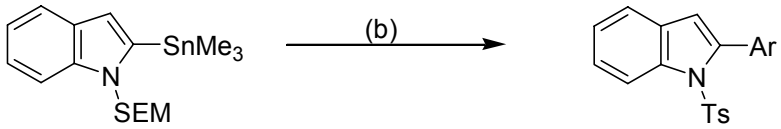
The Stille reaction should, in pinciple, serve as an alternative (and complementary) route to the synthesis of important intermediates that can be used in the formation of alkaloids.[46] Some of these intermediates such as 2-vinyl-1*H*-indoles were investigated as 2π or 4π components in some Diels-Alder cycloadditions.[47]

Indolystannane compounds can be used in the direct synthesis of fluorinated indoles[44] and selective C-C bond formation,[48] **Scheme 11**

Fluorination



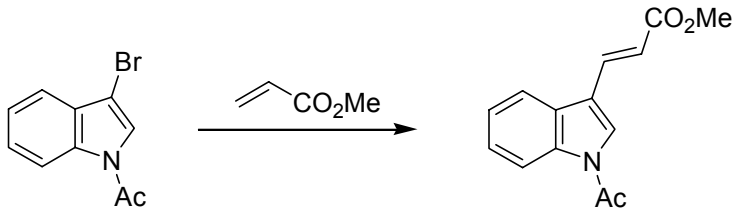
Selective C-C Bond Formation



Scheme 11: (a) CFS, MeOH, MeCN; (b) ArX, $Pd(PPh_3)_4$, DMF, 100 ˚C.

1.6.4 The Heck Reaction

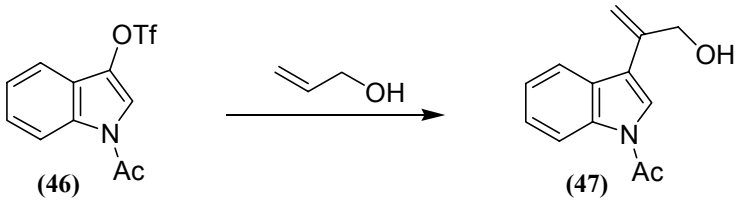
The vinylic substitution reaction with heterocyclic halides is of considerable synthetic value. Heck and co-workers were among the first to use Pd-catalysed vinyl substitution reactions of electron poor vinyl systems with haloindoles,[49] and this has since become the renowned Heck reaction. As an example (**Scheme 12)**, 1-acetyl-3-bromoindole **(44)** on reaction with methyl acrylate gave 3-indolylacrylate **(45)** in the presence of 1 mol of $Pd(OAc)_2$ and added phosphine ligand [2-4% mol of P(*o*-tol)$_3$].[49]



(44) **(45)**

Scheme 12: $Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N, 100 ˚C, 6h.

Triflates also undergo the Heck reaction and Mérour explored the Heck reaction of indoyl triflates with allylic alcohols.[33] Gribble [34-36] has also described numerous Heck reactions of triflate **(46)** and since its reaction with allylic alcohols was not described, Mérour and co-workers choose to react the indole triflate **(46)** with allyl alcohol under traditional conditions [7% $Pd(OAc)_2$, 2.5% Et_3N, 2 eq. DMF, 100 ˚C], leading to the formation of the substituted alcohol **(47)**[33] (**Scheme 13**).

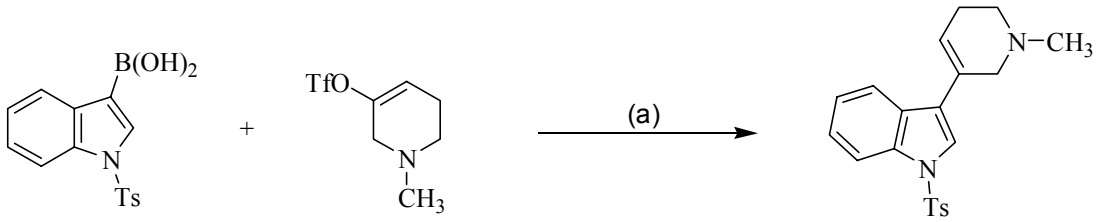


Scheme 13: $Pd(OAc)_2$, PPh_3, DMF, Et_3N, 100 ˚C, 18h.

1.6.5 Suzuki Coupling

Gribble [37-39] and others have shown that 3-haloindoles are useful intermediates in the synthesis of indole alkaloids *via* halogen-metal exchange reactions or by using palladium carbon-carbon cross-coupling methodologies. Prior to that, functionalisation of existing indole ring systems tended to rely heavily on well-established electrophilic substitution reactions.[40] However, when employed to introduce alkenyl groups onto an indole ring, many of the classical electrophilic substitution lead to regioselectivity problems.

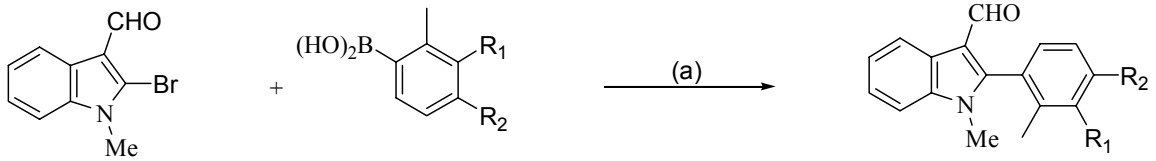
One other way of avoiding the regioselectivity problem is to use palladium(0)-catalysed cross-coupling reactions between aryl boronic acids and vinyl triflates or halides. In addition to no ambiguity in regiochemistry, other advantages of this reaction are the mild reaction conditions and usually good to excellent product yields.[41-42] A typical example of the utilisation of boronic acid under classical Suzuki reaction conditions is shown in **Scheme 14** below. Indoleboronic acid **(48)** was coupled with vinyl triflate **(49)** in the presence of Na_2CO_3 and $Pd(PPh_3)_4$ to give substituted indole **(50)** in good yield.[41,42]



(48) **(49)** **(50)**

Scheme 14: (a) $Pd(PPh_3)_4$, DME, LiCl, Na_2CO_3.

In our laboratories, the Suzuki reaction has also been utilised to achieve substituted indole intermediates for use in the synthesis of benzo[*a*]carbazoles.[5] As shown in **Scheme 15**, treatment of **(51)** with different boronic acids **(52a-c)** in the presence of a catalytic amount of $Pd(PPh_3)_4$ in dimethoxyethane and ethanol together with aqueous Na_2CO_3, to afford high yields of the desired products (**53a-c**).[5]



(51) **(52a-b)** **(53a-b)**

53 (a): R_1 = Me, R_2 = H

53 (b): R_1 = H, R_2 = OMe

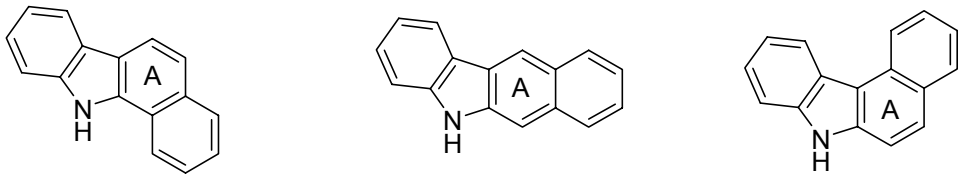
Scheme 15: (a) $Pd(PPh_3)_4$, DME, EtOH, aq. Na_2CO_3

CHAPTER 2: SYNTHETIC APPROACHES TO BENZO-FUSED CARBAZOLE

Benzo-annulated carbazole ring systems are found rarely in natural products. However, their potential as antitumour agents has attracted wide interest and has resulted in the development of numerous synthetic approaches to these compounds. Moreover, many benzocarbazole type frameworks display further useful pharmacological properties. However, many of the general approaches to annellated carbazoles are low yielding, or require the synthesis of complex starting materials and subsequent reactions under harsh conditions to facilitate aromatisation.

A number of research groups have made important contributions to this area, notably those of Moody,[3] Gribble[60], Dötz,[61-63] Knölker[64,65] and our own Wits Organic research group.[10,66] However due to the scope of this dissertation only a few approaches will be discussed.

The benzocarbazole frameworks are divided into the benzo[*a*]carbazoles **(54)**, benzo[*b*]carbazoles **(55)**, and benzo[*c*]carbazoles **(56)**, depending on the position of the benzo ring fused at the A-ring of the 9*H*-carbazole nucleus, as shown in **Scheme 16**.



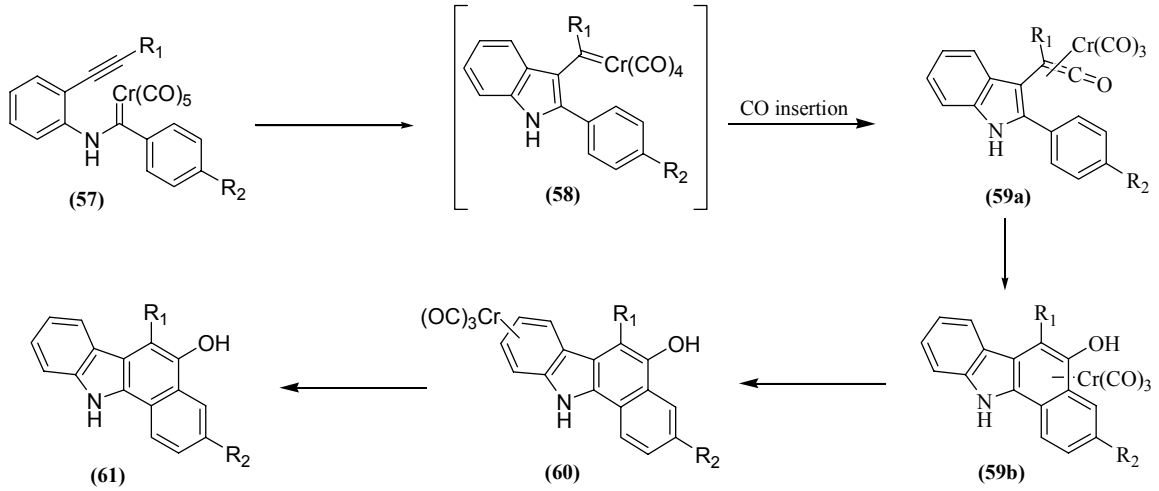
(54) **(55)** **(56)**

Scheme 16: The three kinds of ring fusion in carbazoles.

The methods that were employed for the synthesis of various benzocarbazoles derivatives range from polar through radical to pericyclic type of reactions.[67,68] Complementary to these more classical synthetic strategies, various transition metal-mediated reactions have also been applied.[64,67]

2.1 BENZANNULATION OF CHROMIUM-CARBENE COMPLEXES

Dötz and co-workers initially reported the use of metal-carbene complexes in the synthesis of substituted hydroquinones.[69] Wulff and co-workers extended this further and proceeded to describe the use of indoylcarbene complexes for the synthesis of carbazolequinones.[70] Dötz continued to explore this field and has described the synthesis 11*H*-benzo[*a*]carbazoles **(61)**, from the aminocarbene-chromium complexes **(57)**. Upon heating in toluene at 90 ^{o}C, the alkynylanilinocarbene complexes **(57)** undergo a tandem alkyne carbonylation reaction to give directly, the 11*H*-benzo[*a*]carbazoles **(61)** *via* the indol-3-ylketene complexes **(59a)**. The formation of the 11*H*-benzo[*a*]carbazoles **(61)** is rationalised by an insertion of the alkyne into the chromium-carbene bond to generate an intermediate 3-indoylcarbene complex **(58)**, **Scheme 17**. A carbonyl insertion affords the 3-indoylketenes **(59a)**, which in turn undergoes an electrocyclic ring closure to yield complex **(59b)**, followed by a haptotropic migration of the transition metal fragment to generate the chromiumtricarbonyl-coordinated benzo[*a*]carbazole **(60)** which upon decomplexation, provides the 11*H*-benzo[*a*]carbazole (**61**).[63, 67]



R_1= propyl; C_6H_5; 4-MeC_6H_4; 2,4,6-$(Me)_3C_6H_2$; 2,6-$(MeO)_2C_6H_3$; 3,4,5-$(MeO)_3C_6H_2$

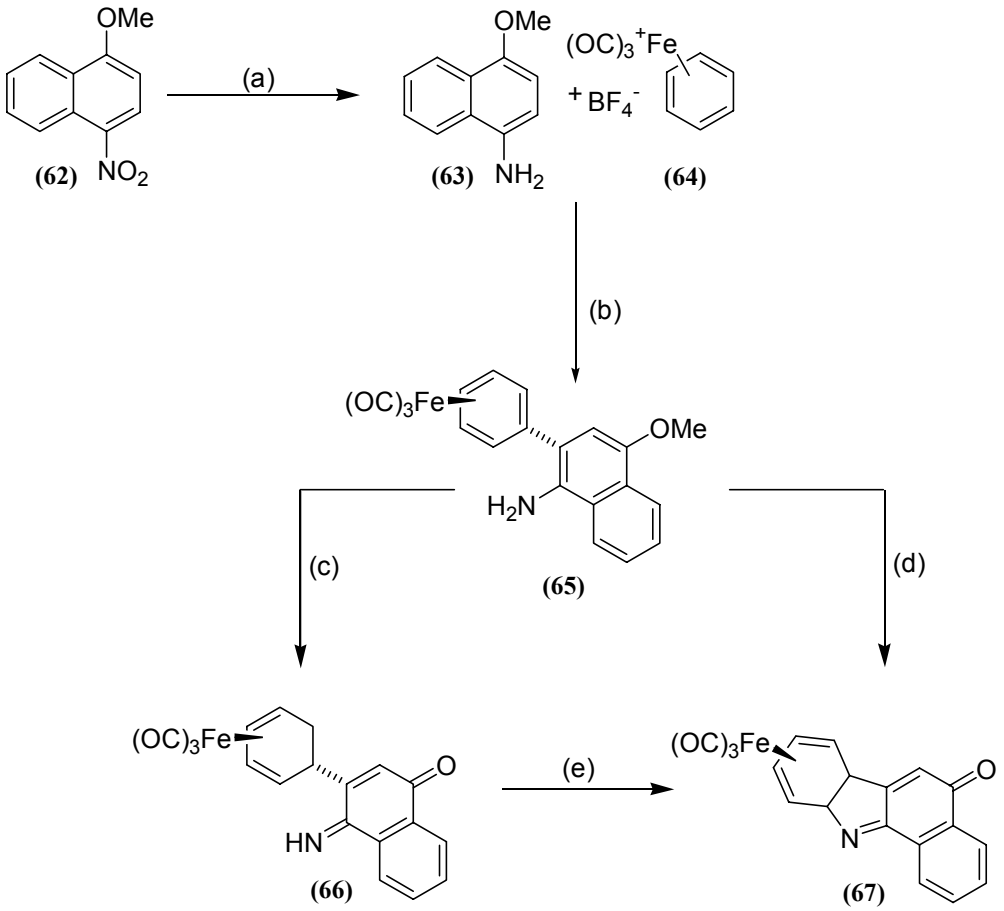
R_2= H; Me

Scheme 17: Reaction conditions and mechanistic sequence of Dotz's synthesis of benzo[*a*]carbazoles.

The yield of the benzo[*b*]carbazole depends on the solvent and on the steric crowding of the substituent at the alkyne terminus of the anilinocarbene complex.

2.2 IRON-MEDIATED SYNTHESIS

Knölker *et al*. developed an iron-mediated method for the synthesis of substituted carbazoles.[65.67] Two alternative procedures were used towards the synthesis of benzo[*a*]carbazole skeleton **(67)**. The first procedure involves the oxidative cyclisation of an iron complex **(65)** made from naphthalene **(63)**, by two different routes. Firstly, treatment with activated manganese dioxide results in the isolation of a non-cyclised intermediate, quinone imine **(66)**. The second procedure is a direct oxidative cyclisation of the iron complex **(65)** by treatment of thallium(III) trifluoroacetate without isolation of an intermediate, **Scheme 18**.[65,67] The synthesis of the iron complex **(65)** was achieved over two steps from the commercially available 1-methoxy-4-nitronaphthalene **(62)**. The methoxynitronaphthalene was reduced using H_2, Pd/C in ethanol at room temperature to give 4-methoxy-1-naphthalenamine **(63)** in 96%. This was followed by the electrophilic substitution of the arylamine by the iron-complexed cation **(64)** to give the tricarbonyliron complex **(65)**.[64,65,67]



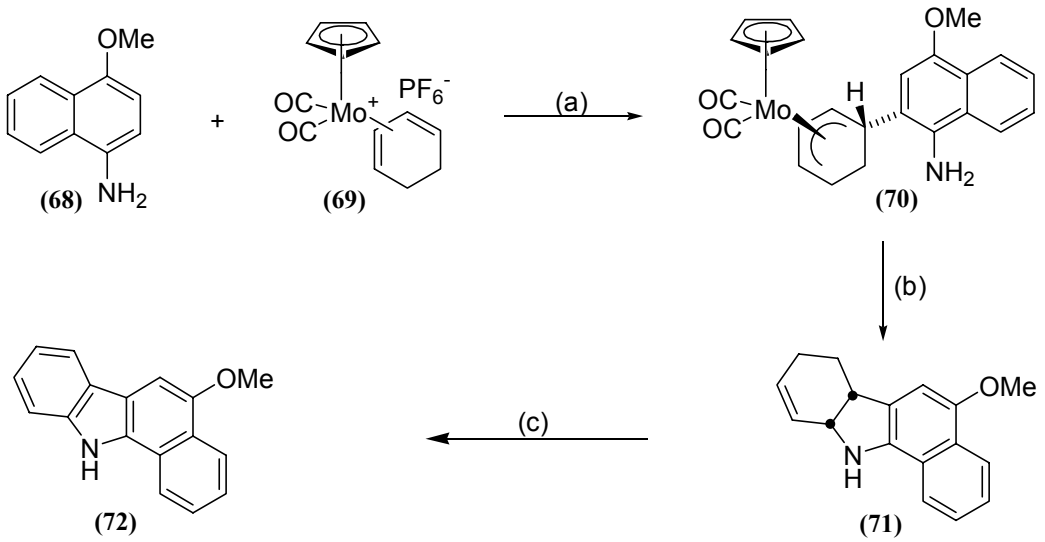
Scheme 18: (a) H_2, Pd/C, EtOH, 25 ^oC; (b) MeCN, 82 ^oC; (c) MnO_2, Toluene, 25 ^oC; (d) $Tl(OCOCF_3)_3$, $NaHCO_3$, EtOH/CH_2Cl_2, -15 ^oC; (e) Activated MnO_2, CH_2Cl_2, 25 ^oC.

2.3 MOLYBDENUM-MEDIATED SYNTHESIS

In this synthesis dicarbonyl(η^5-cyclopentadienyl)molybdenum coordinated cyclohexadiene was used in an electrophilic substitution reaction of an arylamine to afford the intermediate complex regio- and stereoselectively. This was followed by an oxidative cyclisation of the complex and subsequently, aromatisation to give the desired benzo-fused carbazole.

Knölker *et al*. have synthesised benzo[*a*]carbazole **(72)** from reaction of dicarbonyl(η^4-cyclohexa-1,3-diene)(η^5-cyclopentadienyl)molybdenum hexafluorophosphate **(69)** with

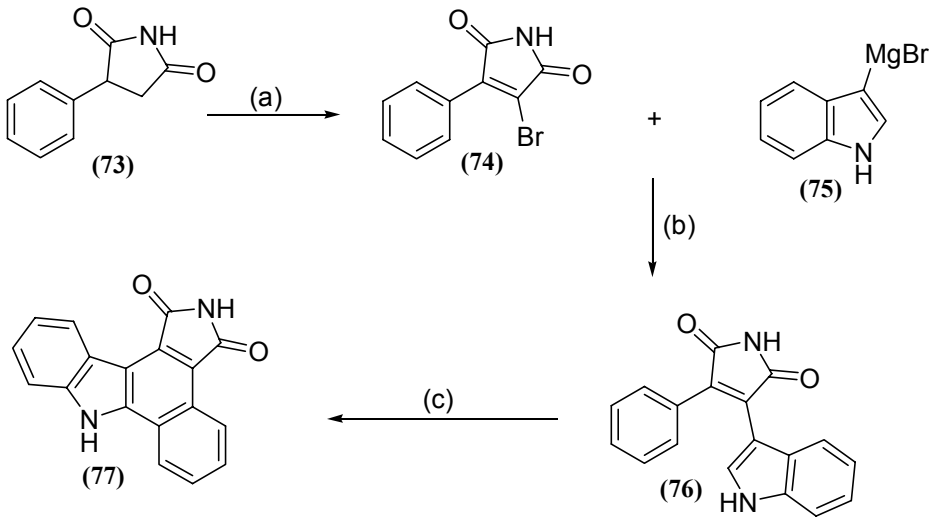
naphthylamine **(68)** to give complex **(70)**. The oxidative cyclisation of the complex **(70)** using iodine in acetonitrile at room temperature (with concomitant decomplexation) gave the tetrahydrobenzocarbazole **(71)**. Subsequent aromatisation of this compound with DDQ afforded the benzo[*a*]carbazole **(72)**[67,71] as shown in **Scheme 19**.



Scheme 19: (a) MeCN, 25 ^{o}C;(b) I_2, MeCN, 25 ^{o}C; (c) DDQ, THF, 25 ^{o}C.

2.4 PALLADIUM-MEDIATED SYNTHESIS

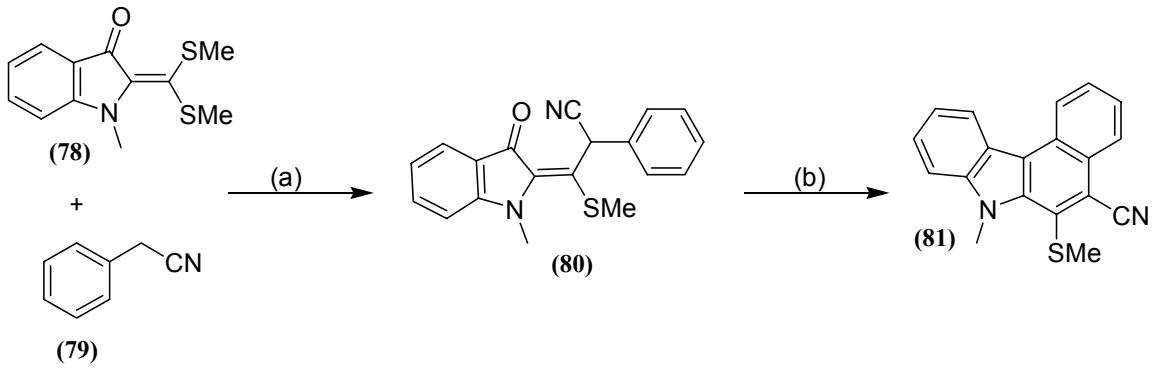
A palladium-mediated cyclisation has been employed by Hill *et al*. in the synthesis of maleimidobenzo[*a*]carbazole **(77)**. Bromination of 3-phenylsuccinimide **(73)** followed by the reaction of the brominated product **(74)** with indolylmagnesium bromide **(75)** gave 3-(indol-3-yl)-4-phenylmaleimide **(76)**. Finally, the oxidative cyclisation of the latter with palladium(II) acetate gave 5,6-maleimido-11*H*-benzo[a]carbazole **(77)**[72] as shown in **Scheme 20**.



Scheme 20: (a) Br_2, 120 ^oC, NH_4OAc, 200 ^oC; (b) Benzene, reflux; (c) $Pd(OAc)_2$, AcOH, 110 ^oC.

2.5 BENZANNULATION OF INDOLES

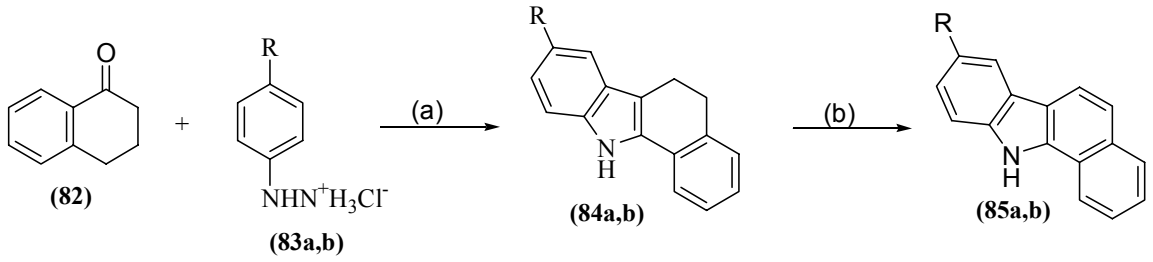
Rao *et al*. have reported the synthesis of benzo[*c*]carbazole **(81)** from 3-oxoindole **(78)** as shown in **Scheme 21**.[73] Reaction of **(78)** with the anion of phenylacetonitrile **(79)** afforded compound **(80)** by elimination of methanethiol. Cycloaromatisation of the latter was achieved by heating compound **(80)** in the presence of phosphoric acid to give benzo[*c*]carbazole **(81)**.[73]



Scheme 21: (a) NaH, DMF, 0 ^oC, H_3PO_4, Heat.

2.6 FISCHER INDOLISATION OF PHENYLHYDRAZONES

Kirsch and coworkers have applied the Fischer-Borsche method, described by Rogers and Corson,[74] of arylhydrazines and tetralones in their synthesis of annellated carbazoles.[75] As shown in **Scheme 22**, condensation of α-tetralone **(82)** and arylhydrazine hydrochlorides (**83a,b**) afforded 5,6-dihydro-11*H*-benzo[*a*]carbazoles (**84a,b)**. This was followed by the dehydrogenation of the dihydrobenzocarbazoles **(84a,b)** with DDQ in refluxing benzene to give the 11*H*-benzo[*a*]carbazoles **(85a,b)**.[75]



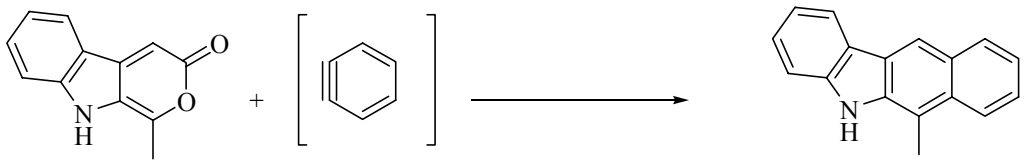
(82) **(83a,b)** **(84a,b)** **(85a,b)**

R = **H (a)** R = **OMe (b)**

Scheme 22: (a) AcOH, HCl, reflux; (b) DDQ, benzene, reflux.

2.7 DIELS –ALDER REACTIONS

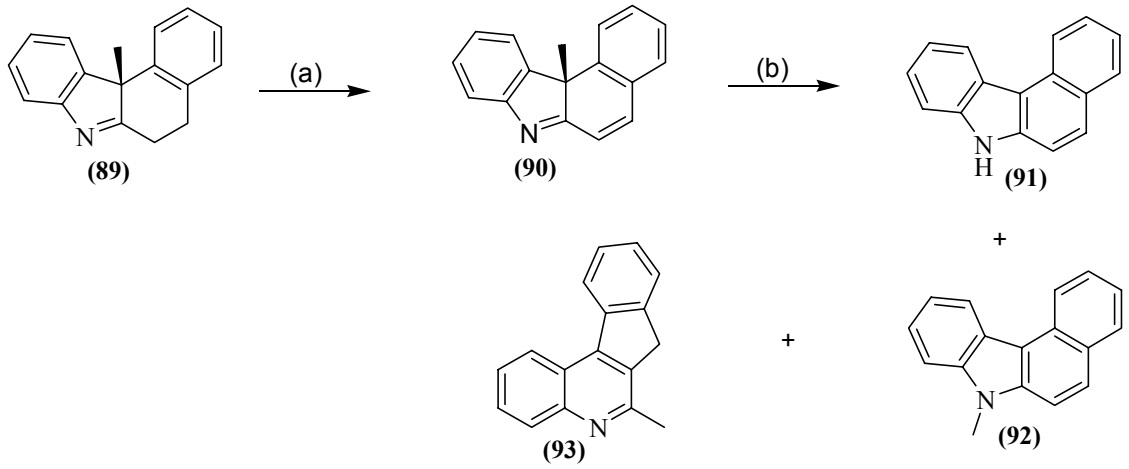
Moody and co-workers used Diels–Alder reactions in their synthesis of benzoannellated carbazoles.[76] As shown in **Scheme 23**, the pyranoindole **(86)** (diene), generated from reaction of acetic anhydride with indole-3-acetic acid,[77] reacted with benzyne **(87)** (dienophile), generated from benzenediazonium 2-carboxylate,[76] to afford 5*H*-benzo[*b*]carbazole **(88)**.[76]



(86) **(87)** **(88)**

Scheme 23: Dichloroethane, reflux.

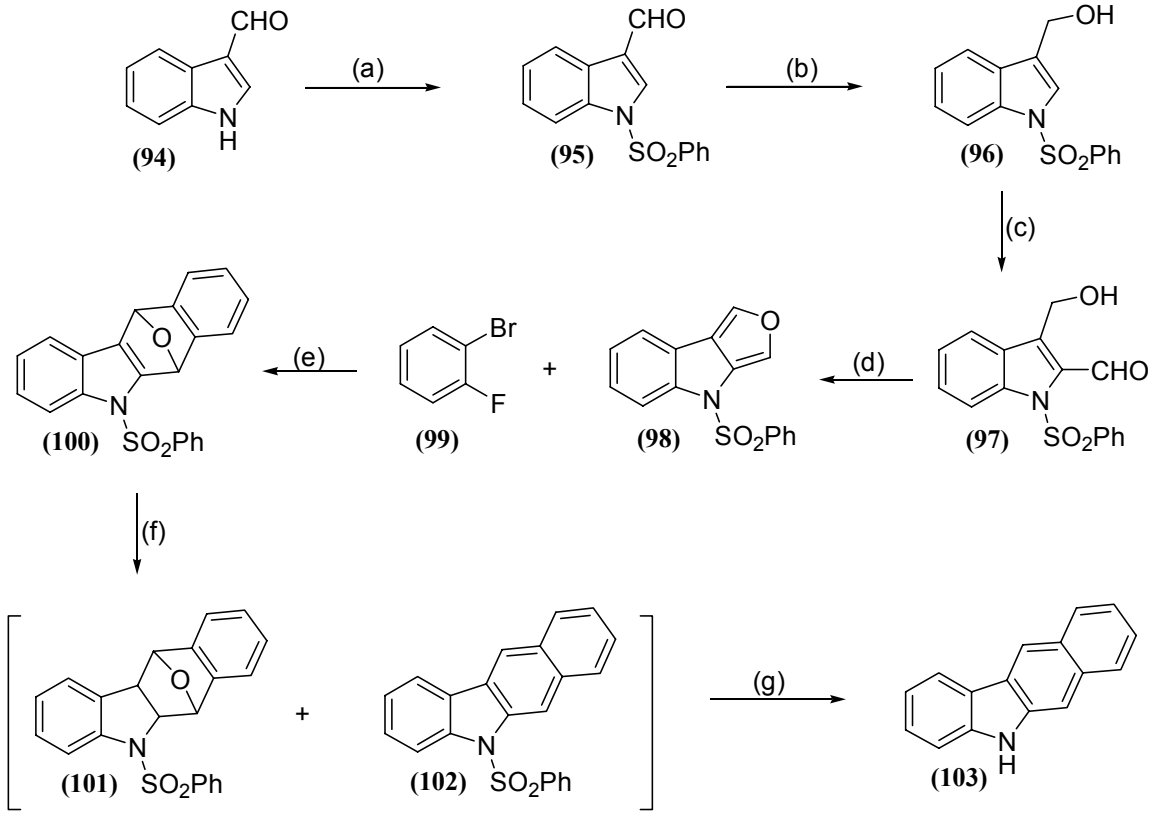
Moody *et al*. extended their synthesis of benzoannellated carbazoles by using flash vacuum pyrolysis of 11b-methyl-11b*H*-benzo[*c*]carbazole **(90)**,[78,79] obtained from dehydrogenation of dihydro-11*H*-benzo[*c*]carbazole **(89**) with benzeneselenic anhydride and iodobenzene in refluxing benzene.[80] Subjection of compound **(90)** to flash vacuum pyrolysis at 640 ^{o}C and 0.03mmHg gave the 7*H*-benzo[*c*]carbazoles **(91)** and **(92**) along with the angular indenoquinoline **(93)** in good yields , as shown in **Scheme 24**.[78,79]



Scheme 24: (a) Benzeneselenic anhydride, PhI, Benzene, reflux; (b) FVP, 640 ^{o}C.

Gribble *et al*. have also employed Diels-Alder reactions in their synthesis of 5*H*-benzo[*b*]carbazole **(103).** The furo[3,4-*b*]indole **(98)** was prepared from the commercially available 3-formylindole **(94)** which was converted to the *N*-phenylsulfonyl derivative **(95)**. Subsequent reduction with sodium borohydride gave the alcohol **(96)** which upon dilithiation with *tert*-butyllithium followed by quenching with dimethylformamide

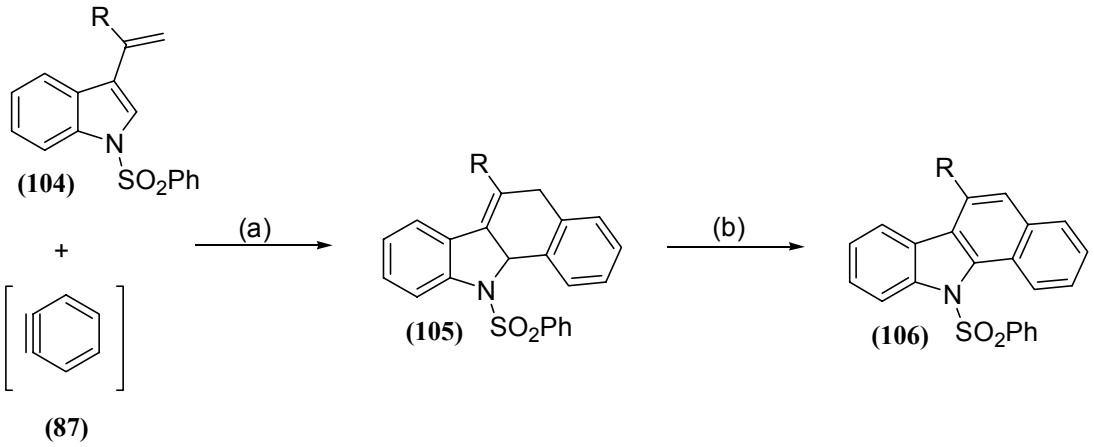
afforded regioselectively, indole-2-carbaldehyde **(97)**. The desired diene **(98)** was obtained by heating the indole-carbaldehyde (**97**) with glacial acetic acid in the presence of potassium fluoride and hydroquinone. The furo[3,4-*b*]indole **(98)** was reacted with benzyne **(87)** as dienophile, generated from 1-bromo-2-fluorobenzene **(99)** and magnesium,[81] to give the corresponding Diels-Alder adduct **(100)**. Reduction of this adduct with sodium borohydride in trifluoroacetic acid gave a mixture of products **(101)** and **(102)**. Treatment of this mixture with base gave 5*H*-benzo[*b*]carbazole (**103**) in good yields as shown in **Scheme 25**.[60,82]



Scheme 25: (a) LDA, THF, -78 ^{o}C, $PhSO_2Cl$; (b) $NaBH_4$, $THF_{(aq.)}$/EtOH, 0-5 ^{o}C; (c) ^{t}BuLi, THF, -40 to 23 ^{o}C then DMF, THF, -78 ^{o}C; (d) AcOH, KF, hydroquinone, 100 ^{o}C; (e) Mg, THF, reflux; (f) $NaBH_4$, CF_3COOH; (g) $MeOH/NaOH_{(aq.)}$, THF, reflux.

Pindur and co-workers is another research group that employed Diels-Alder reactions for their synthesis for the 11*H*-benzo[*a*]carbazole, as shown in **Scheme 26**. Using 1,1-

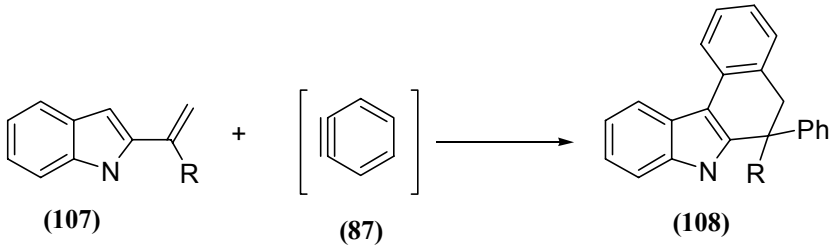
bis(indo-3-yl)ethene **(104)** as a diene, a Diels-Alder reaction with benzyne **(92)** afforded the cycloadduct **(105)** which was further dehydrogenated to the 11*H*-benzo[*a*]carbazole.[83]



R = 1-phenylsulfonylindol-3-yl

Scheme26: (a) THF, 40 to 45 ^{o}C; (b) [1,3]-H, then $-H_2$.

Pindur and co-workers extended their methodology to the synthesis of 7*H*-benzo[*c*]carbazoles. Using 2-vinylindoles **(107)**, a Diels-Alder reaction with benzyne **(87)** added *in situ* in dimethoxyethane at –60 ^{o}C gave the 5,6-dihydro-7*H*-benzo[*c*]carbazoles **(108)** with a phenyl group in the 6-position. These products are believed to be the result of an ene reaction of the initially formed cyclo-adduct with a second molecule of benzyne, as depicted in **Scheme 27**.[84]

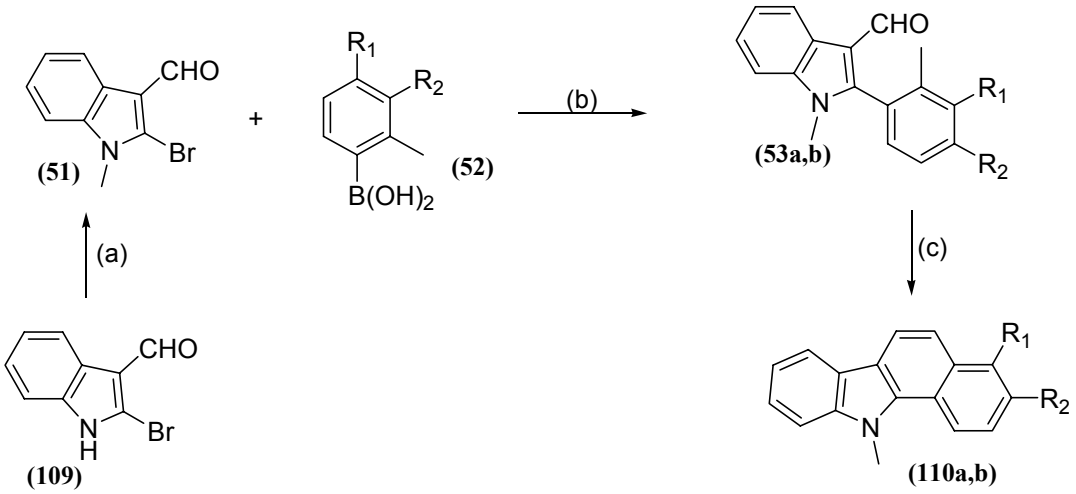


R = H, Me

Scheme 27: DME, -60 ^{o}C.

2.8 WITS'S NOVEL APPROACH TO BENZO-ANNELLATED CARBAZOLES

The Wits research group has also embarked on the synthesis of benzoannellated carbazoles. The method involves two key steps as outlined in **Scheme 28** below. The first entails palladium-mediated Suzuki coupling reaction, and the second is a base and light-induced ring closure. This affords the desired targets in relatively few, high yielding steps.[10,11] Alkylation of 2-bromoindol-3-carbaldehyde **(109)** with potassium bis(trimethylsilyl)amide and methyliodide gave the *N*-methyl derivative **(51)**. A palladium-mediated Suzuki coupling of this compound with boronic acids afforded the corresponding 2-arylindoles **(53)**, which were subjected to base/light-induced ring closure to give 11*H*-benzo[*a*]carbazoles **(110)**.[10,11]



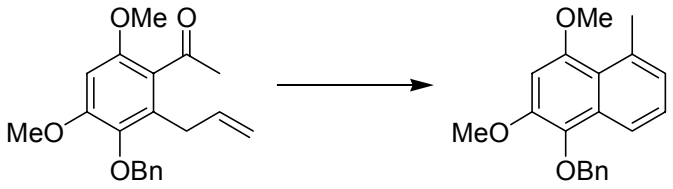
R_1 = H, Me, R_2 = H, OMe

Scheme 28: (a) KHMDS, MeI; (b) $Pd(PPh_3)_4$, Na_2CO_3, DME/EtOH; (c) ^tBuOK, DMF, hν, 70 to 80 ^oC.

2.9 BACKGROUND AND AIMS

Work in the course of 1995 by de Koning and co-workers led to the discovery of a novel cyclisation reaction that afforded naphthalene products. In an attempt to isomerise (internalise) the double bond of 2-allyl-3-benzyloxy-4,6-dimethoxybenzene **(111)** under

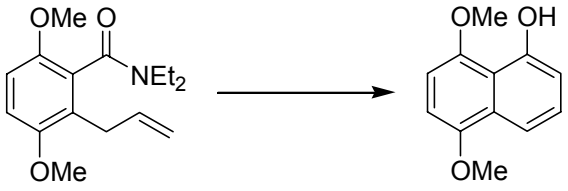
the classical potassium *t*-butoxide catalytic conditions,[85] an unexpected cyclisation reaction affording naphthalene product **(112)** was observed as shown in **Scheme 29**.



(111) **(112)**

Scheme 29: ^{t}BuOK, DMF, 48%.

A comprehensive literature search was done so as to establish whether this cyclisation reaction had ever been achieved under similar reaction conditions. Gratifyingly, the literature search revealed that the cyclisation reaction was new and was related to work done by Snieckus and co-workers.[86] The latter had previously treated *o*-allylbenzamides such as **(113)** with methyllithium or LDA to afford the corresponding 1-naphthols such as **(114)** (**Scheme 30**) [86] rather than naphthalenes generated by the Wits cyclisation reaction.

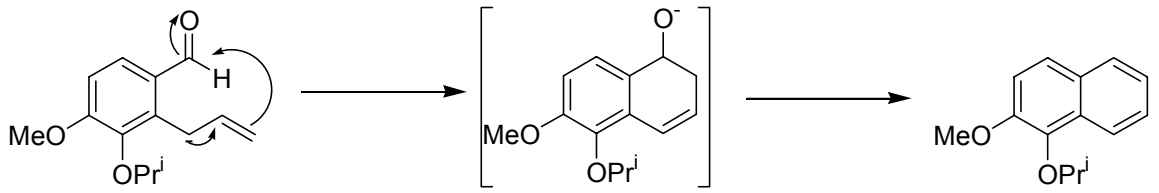


(113) **(114)**

Scheme 30: MeLi or LDA.

With the aim of elucidating the probable mechanism of this unusual outcome as well as developing this into a novel method for the synthesis of condensed aromatic compounds, Rousseau conducted an extensive investigation of this reaction in her work, which resulted in the formation of naphthalenes,[87] phenanthrenes,[88] benzo[*a*]carbazoles and pyrido[*a*]carbazoles.[10,11] Manzini continued with the investigation in the synthesis of other polyaromatic compounds, the anthracenes.[89]

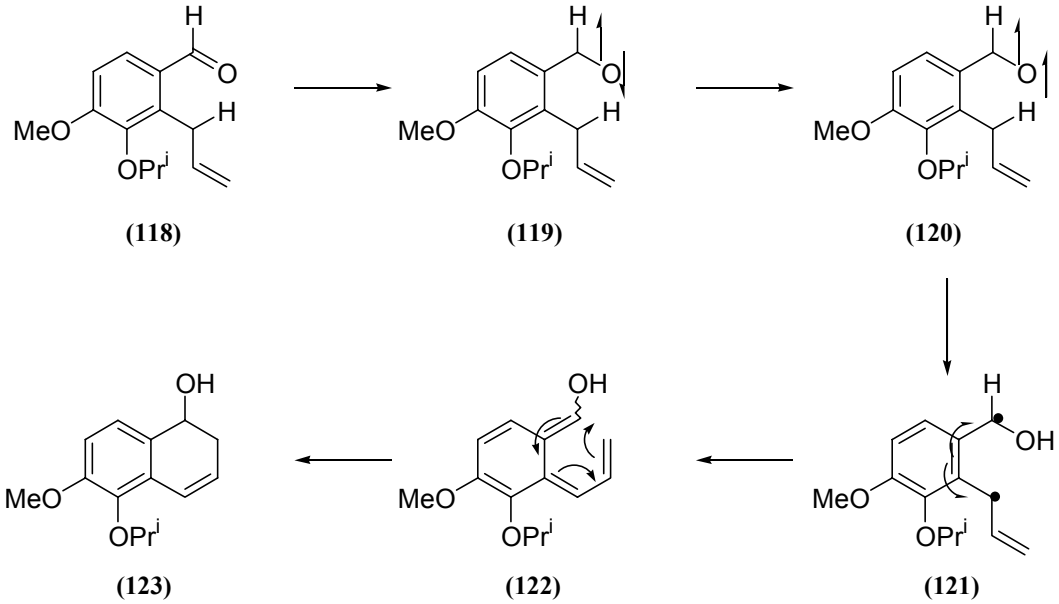
Detailed studies culminated in the proposal of two possible mechanisms. The first is anionic (**Scheme 31**) and the second involves photoenolisation (**Scheme 32**).[88] Taking compound **(115)** as a model for the investigations, the removal of benzylic protons by potassium *t*-butoxide is likely to generate an anion at this position and this anion would thus initiate an intramolecular nucleophilic attack on the carbonyl group to afford the cyclised intermediate **(116)**. Protonation on the intermediate followed by elimination of water would result in the naphthalene product **(117)**.



(115) **(116)** **(117)**

Scheme 31: ^{t}BuOK, DMF, 80 ˚C, 54%.

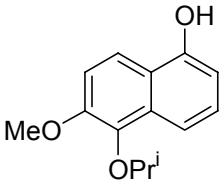
An interesting observation made during this reaction was that each time upon the addition of potassium *t*-butoxide to the reaction mixture there was a prominent colour change. The reaction mixture colour would change normally from colourless to a dark purple colour. Due to this observation the possibility of a radical intermediate involvement in the reaction was envisaged. A Norrish type II radical process resulting in photoenolisation of compound **(115)** was considered as a possible pathway. The use of radical promoters was envisaged and experiments were then conducted in the presence of a high pressure mercury lamp of shorter wavelength than visible light.[88,90] When irradiation from a 400W high-pressure mercury lamp through a quartz filter was applied during the reaction (**Scheme31**), the desired product was obtained in considerably shorter times (from 90 min. to 10 min.) and an improved yield of 81% (from 54%). Reasonably so, this was taken as an indication that there is involvement of photochemically generated intermediates in the reaction, resulting in the proposal of the second mechanism as depicted in **Scheme 32** below.



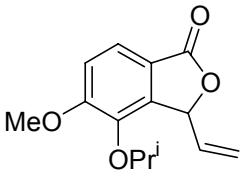
Scheme 32:

Irradiation of **(118)** is thought to result in excitation of the carbonyl group to an excited singlet state **(119)**.[88] The excited singlet state rapidly transforms to the triplet state **(120)** by intersystem crossing.[90] Due to the triplet state the benzylic proton is abstracted, forming a diradical species **(121)**, which then rearranges to the photoenol intermediate **(122)**. The formation of the alcohol (**123**) follows by a π^6 electrolytic process, followed by dehydration to give naphthalene product **(117)**.

Further studies were carried out to investigate the mechanism of the reaction. The reaction was carried out in excess oxygen, known to quench radical formation. This was done with the hope of trapping intermediates. Bubbling oxygen in the solution of compound **(118)** in DMF for five minutes followed by the addition of potassium *t*-butoxide and then radiation from 400W high-pressure mercury lamp through a quartz filter for 30 minutes afforded **(117)** in a much lower yield of 42% and two other products **(124)** and **(125)** as shown below, in 2% and 4% yields respectively.[88,90]

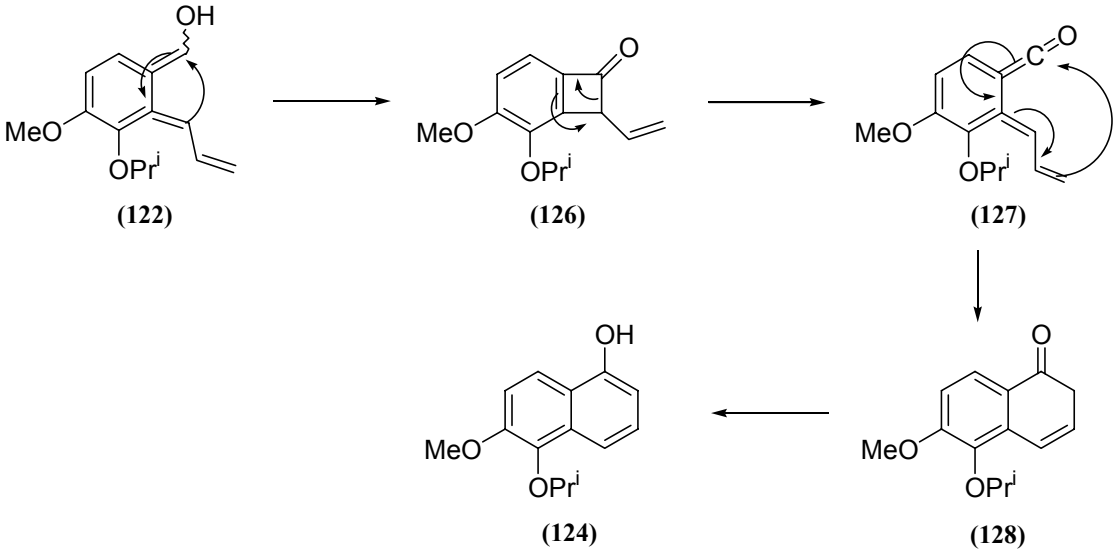


(124)



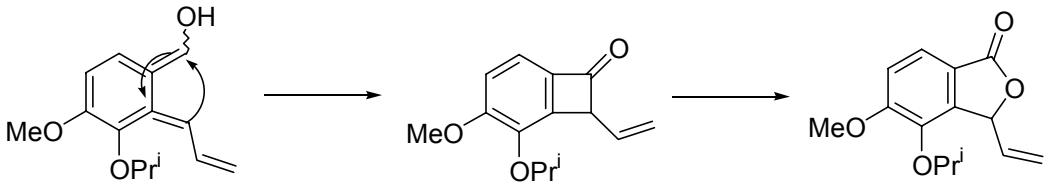
(125)

The formation of product **(124)** was thought to have resulted from the rearrangement of the cyclobutanone intermediate **(126)** to a highly unstable ketene intermediate **(127)**, which in turn goes through a π^6 electrocyclic process to form a ketone **(128)**. Keto-enol tautomerism favours the more stable enol form product **(124)** as shown in **Scheme 33**.



Scheme 33:

The formation of product **(125)** possibly resulted from a π^4 electrocyclic process of the suspected photoenol intermediate **(122)** to form cyclobutanone intermediate **(126)** after oxidation, which then went through an oxygen insertion reaction[91,92] to afford product **(125)** as depicted in **Scheme 34**.

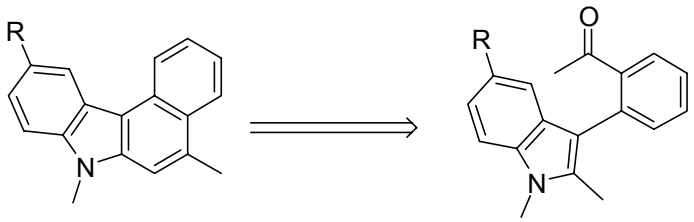


(122) **(126)** **(125)**

Scheme 34

When the reaction was conducted under the same reaction conditions as before save the addition of potassium *t*-butoxide, only starting material was recovered with no desired products. This thus proved the indispensable role of potassium *t*-butoxide with all the other information pointing towards the possible dual mechanisms as explained above. This methodology was extended towards the synthesis of benzo[*a*]- and pyrido[*a*]carbazoles.[10]

The aim of the present MSc project therefore was to extend on this methodology towards the synthesis of benzo[*c*]carbazoles as shown in **Figure 1**. This would require the formation of phenyl-substituted indoles, like compound **(130)**, formed by biaryl coupling methods. Thus, the initial aim of the project was to investigate Suzuki coupling reactions of related indoles with suitable boronic acids.



(129) **(130)**

Figure 1

CHAPTER 3: EXPERIMENTAL RESULTS: THE SYNTHESIS OF BENZO[*C*]CARBAZOLES

3.1. RETROSYNTHETIC ANALYSIS TOWARDS BENZO[*C*]CARBAZOLES

With the foregoing in mind, we hoped to extend our cyclisation reaction methodology to include the synthesis of benzo[*c*]carbazoles. Retrosynthesis of benzo[*c*]carbazole nucleus **(129)** led to the aldehyde **(130)** as shown in **Figure 2**. This aldehyde could be obtained from the Vilsmeier-Haack formylation of the biaryl precursor **(131)**. We envisaged applying Suzuki coupling methodology developed and used for the synthesis of phenanthrenes,[11] benzo[*a*] and pyrido[*a*]carbazoles[10,11] to the synthesis of the required precursor **(131)**. Retrosynthesis of **(131)**, also shown in **Scheme 36**, led back to suitably substituted bromoindole **(132)** and toluneboronic acid **(133)**.

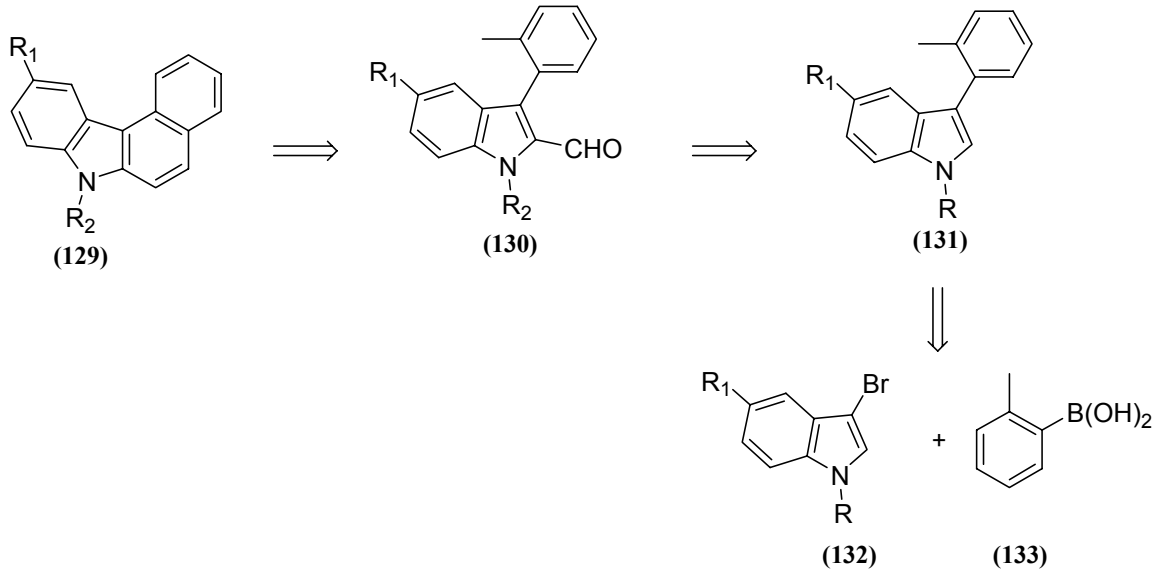
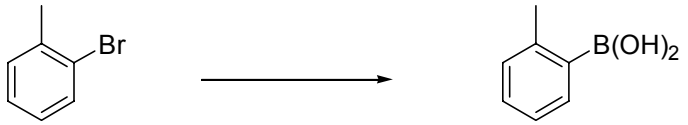


Figure 2:

3.2. PREPARATION OF ARYLBORONIC ACID

Arylboronic acid **(133)** was synthesised in quantitative yield from bromotoluene **(134)** by metal-halogen exchange with butyllithium followed by quenching with trimethyl borate and acidification,[90,93] as shown in **Scheme 36**.



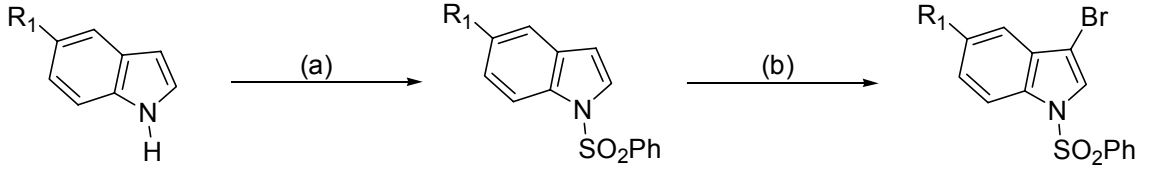
(134) **(133)**

Scheme 36: *n*BuLi, THF, ─78 ^{o}C, $B(OMe)_3$, HCl.

The required bromoindoles **(136)** and **(137)** were synthesized by firstly converting indole **(2)** and 5-methoxyindole **(135)** to the related *N*-phenylsulfonylindoles **(24)** and **(138)** in good yields as shown in **Scheme 37**. The phenylsulfonyl group was chosen because of its ease of attachment to the indole nitrogen, its well documented role in regiospecific metallation (at C-2) of of indoles as well as its ease of removal at the end of the synthesis. Most of the biological active indole-containing compounds have a free N-H group (*vide supra*) and thus easy removal of the protecting group was important since we wished to submit the final targets in our synthesis for biological testing

Treatment of **(2)** and **(135)** with aqueous sodium hydroxide and phenylsulfonyl chloride under phase transfer catalysis[52,91] afforded the desired products **(24)** and **(138)**. Spectroscopic evidence for the formation of these products **(24)** and **(138)** included the disappearance of the broad singlet due to the N-H group and the increase in the integration for aromatic protons in the region δ 6.64-8.3 and δ 6.57- 7.91 respectively. The ^{13}C NMR spectra also showed an increase in the number of aromatic carbons on both compounds. The next intermediates in the sequence, the bromoindoles (**136**)-(**137**), shown in **Scheme 37** were obtained also in good yields from direct (radical) bromination of compounds (**24**) and (**138**) with bromine in carbontetrachloride. The ^{1}H NMR spectra

showed the disappearance of the multiplets due to the H-3 protons at δ 6.64- 6.70 and δ 6.56-6.59 on both compounds.

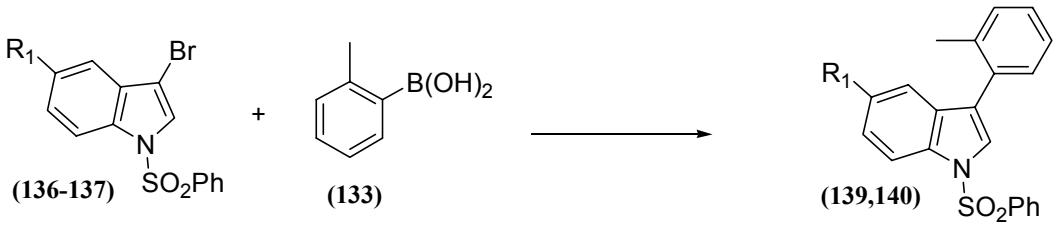


(2,135) **(24,138)** **(136-137)**

Indole	Substituents	Product	Yield	Bromoindole	Yield
(2)	R_1= H	**(24)**	99%	**(136)**	99%
(135)	R_1= OMe	**(138)**	99%	**(137)**	99%

Scheme 37: (a) NaOH, H_2O/CH_2Cl_2, Bu_4NBr, $PhSO_2Cl$; (b) Br_2, CCl_4.

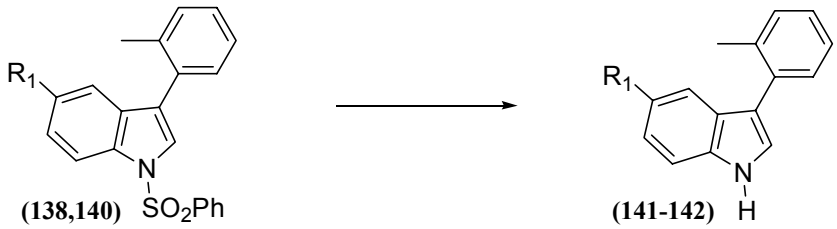
At this point, the stage was now set for the Suzuki coupling of the bromoindoles **(136)-(137)** with arylboronic acid **(133)** using the methodology previously applied in our group for the synthesis of phenanthrenes, benzo[*a*]- and pyrido[*a*]carbazoles precursors. As shown in **Scheme 38**, treatment of **(136)** and **(137)** with arylboronic acid **(133)** in a DME/ethanol mixture in the presence of a catalytic amount of tetrakis(triphenylphoshine)palladium(0) and an aqueous sodium bicarbonate solution afforded the coupled products **(139)** and **(140)** in quantitative yields. The ^{1}H NMR spectra of the products **(139)** and **(140)** showed *inter alia,* a singlet for the methyl protons on the aromatic ring at δ 2.19 and δ 2.18 respectively. The ^{13}C NMR spectra showed signals for the corresponding carbons (methyl) at δ 20.3 and δ 20.3 respectively. These results were corroborated by high-resolution mass spectroscopy, showing the molecular ions at 347.0980 ($C_{21}H_{17}NO_2S$ requires 347.0980) and 377.1078 ($C_{22}H_{19}NO_3S$ requires 377.1086) respectively, providing conclusive evidence for the formation of **(139)** and **(140)**.



Bromoindole	Substituents	Biaryl	Yield
(136)	R_1= H	**(139)**	100%
(137)	R_1= OMe	**(140)**	100%

Scheme 38: $Pd(PPh_3)_4$, DME/EtOH, $Na_2CO_{3(aq.)}$.

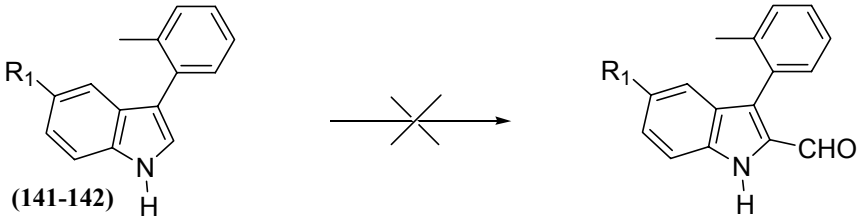
With the successful formation of the 3-benzoindoles **(139)** and **(140)**, an aldehyde functional group had to be introduced at C-2 of the indole nucleus. We envisaged introducing this group by Vilsmeier-Haack formylation. Since position 3 of the indole nucleus was already blocked by a biaryl axis we though that the formylation would simply occur at C-2 marginally more activated than any of the other aryl sites. In that regard, the 3-benzoindoles were subjected to formylation conditions but disappointingly, no reaction occurred in both cases. We thus had to remove the phenylsulfonyl group and this was easily accomplished in high yields, by heating to reflux, the bromoindoles **(138)** and **(140)** in methanol with potassium carbonate[6] to give the deprotected products **(141)-(142)** as shown in **Scheme 39**. The ^{1}H NMR (and ^{13}C NMR) spectra showed the welcome simplification in the aromatic region and appearance of a broad singlet at δ 8.09 and δ 8.08 for the free N-H groups. Further proof was provided by infrared spectroscopy, showing stretching frequencies of 3477 cm^{-1} and 3416 cm^{-1} respectively for the N-H group of compounds **(141)-(142)**.



Product	Substituent	Yield
(141)	R_1= H	93%
(142)	R_1= OMe	96%

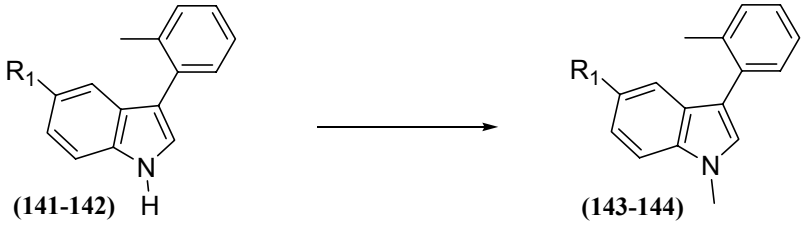
Scheme 39: K_2CO_3, MeOH, reflux.

As with the synthesis of the pyrido[*a*]carbazoles we attempted the Vilsmeier-Haack formylation at C-2 of the indole nucleus on both compound **(141)-(142)** (**Scheme 40**). However, to our disappointment, this proved to be unsuccessful forming material that could not be characterised.



Scheme 40: DMF, $POCl_3$, reflux.

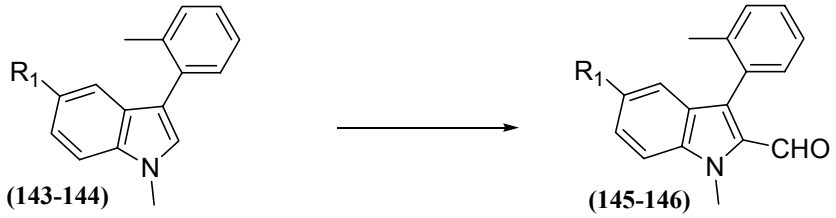
We therefore decided to re-protect the indole nitrogen of both **(141)** and **(142)** before we could carry out the formylation reaction and for this chose in line with literature precedent, the smaller methyl protecting group which at the end of the synthesis would of course present serious deprotection problems. This was accomplished by treatment of **(141)-(142)** with sodium hydride and dimethyl sulfate in THF to afford **(143)-(144)** in good yields in **Scheme 41**. The ^{1}H NMR and ^{13}C NMR spectra showed evidence for the introduction of a methyl group with peaks at δ 3.77, δ 32.7 and δ 3.78, δ 32.9 respectively for compound **(143)** and **(144)**.



Product	Substituent	Yield
(143)	R_1= H	99%
(144)	R_1= OMe	99%

Scheme 41: NaH, THF, Me_2SO_4.

At this point we once more attempted the Vilsmeier-Haack reaction, which proceeded smoothly to afford **(145)-(146)** in fair to moderate yields as shown in **Scheme 42**. Signals for the aldehyde were visible at δ 9.65 and δ 9.59 in the ^{1}H NMR and δ 184.2 and δ 190.4 in the ^{13}C NMR for both products. The signals for the H-2 on the indole nucleus had also disappeared in the spectra of both compounds.

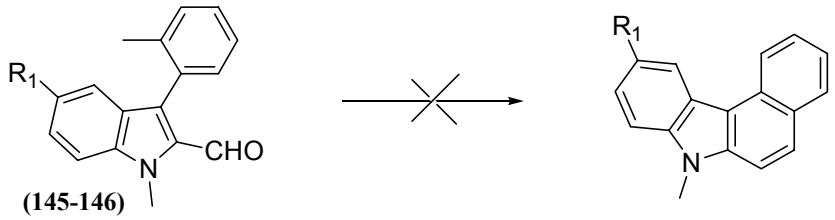


Product	Substituent	Yield
(145)	R_1= H	96%
(146)	R_1= OMe	65%

Scheme 42: DMF, $POCl_3$, Toluene, reflux.

We were now in a position to subject these precursors **(145)-(146)** to the conditions for our novel cyclisation reaction. Treatment of **(145)-(146)** with potassium *t*-butoxide in DMF and with simultaneous irradiation from a mercury lamp for 10 to 30 minutes at 10 minutes intervals proved to be unsuccessful as shown in **Scheme 43**, with only starting material recovered. As this cyclisation strategy had proved to be successful in the synthesis of pyrido[*a*]carbazoles, we felt that the lack of reactivity could not be attributable to steric factors. Looking at the proposed mechanism,[94,95] clearly the electrophilic nature of the carboyl placed in the 2-position of the indole nucleus i.e.

(146)-(147) is different to the carbonyl in (148) and this may play a role in assisting or retarding the reaction. The pKa's of the two different aromatic methyl substituents would also be different.



Scheme 43: ^{t}BuOK, DMF, hν, 70-80 ˚C.

This necessitated a change of strategy, and we investigated another Suzuki coupling in which the indole precursor was made to bear the methyl substituent and the boronic acid the carbonyl group. As depicted in the retrosynthesis in **Figure 3**, we planned to synthesis benzo[*c*]carbazoles **(147)** from indoles such as **(148)** containing substituted aromatic ring at the 3-position. A carbonyl-containing substituent is required *ortho* to the linkage between the benzene ring, and the indole nucleus with a methyl substituent at the 2-position is necessary. The linkage could be formed using Suzuki coupling methodology of bromoindole **(149)** and a carbonyl containing boronic acid **(150)**.

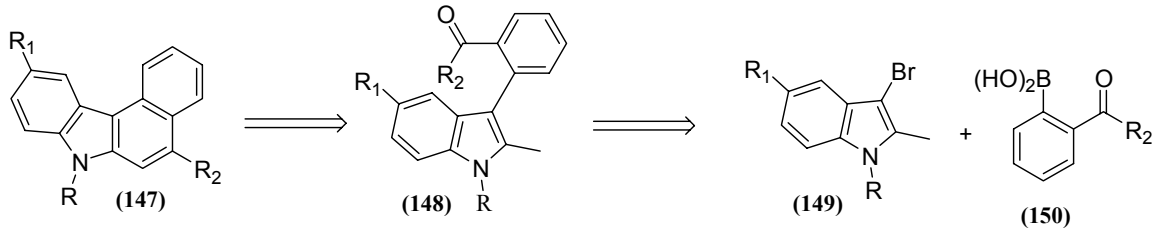
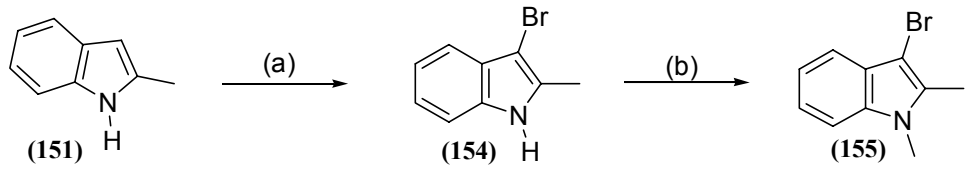


Figure 3

Exposure of 2-methylindole **(151)** to molecular bromine in DMF gave **(154)** in quantitative yield as shown in **Scheme 44**. Also shown in **Scheme 44** is the protection of the indole nitrogen by *N*-methylation to afford **(155)** in 99% yield. This protection was done immediately because **(154)** was unstable and decomposed very quickly. The ^{1}H NMR spectrum of **(155)** showed evidence of the *N*-methyl group at δ 3.66 and the

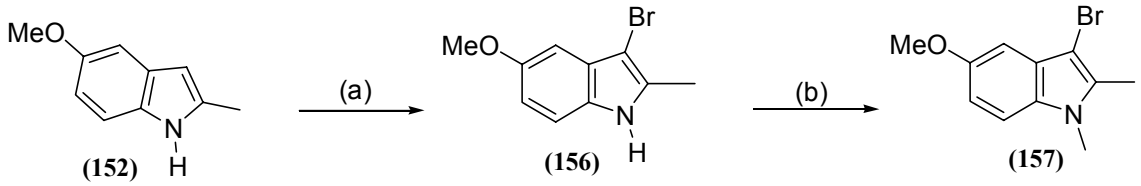
aromatic protons integrated for four protons. More evidence in support of the formation of **(155)** included the disappearance of the broad singlet for the N-H group.



(151) (154) (155)

Scheme 44: (a) Br_2, DMF; (b) NaH, THF, Me_2SO_4**.**

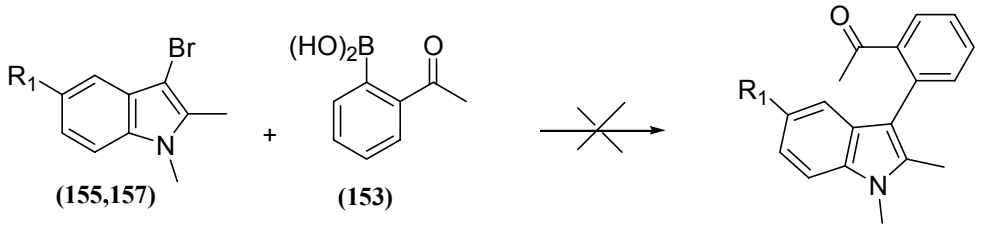
The use of molecular bromine to brominate 5-methoxyindole **(152)** resulted in simultaneous bromination of the electron-rich aromatic ring. Therefore, milder conditions for the bromination were used. Exposure of **(152)** to *N*-bromosuccinimide with a catalytic amount of silica gel in dichloromethane afforded the desired intermediate **(156)** in 99% yield as shown in **Scheme 45**. The protection of the indole nitrogen was also achieved by *N*-methylation, which was also done immediately to avoid decomposition to give **(157)** in 94% as shown in **Scheme 45**. As with **(155)**, spectroscopic evidence for the formation of **(157)** included the sharp singlet for the *N*-methyl protons at δ 3.61 and the disappearance of the broad singlet for the N-H group.



(152) (156) (157)

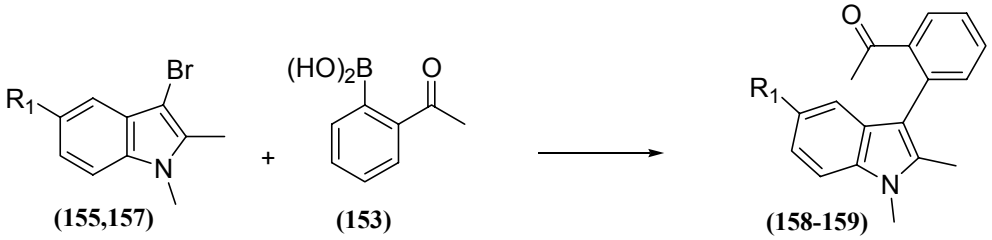
Scheme 45: (a) NBS, CH_2Cl_2, $SiO_{2(cat.)}$; (b) NaH, THF, Me_2SO_4.

At this point we were in position to attempt the Suzuki coupling methodology used in our laboratories for the synthesis of phenanthrenes,[11] benzo[*a*]-, pyrido[*a*]carbazoles[10,11] precursors and including the biaryl compounds **(139)** and **(140)**. As depicted in **Scheme 46**, the Suzuki coupling methodology under aqueous conditions applied to **(155)** and **(157)** was unsuccessful, resulting in the decomposition of our starting material and no identifiable product was formed.



Scheme 46: $Pd(PPh_3)_4$, DME/EtOH, aq. Na_2CO_3

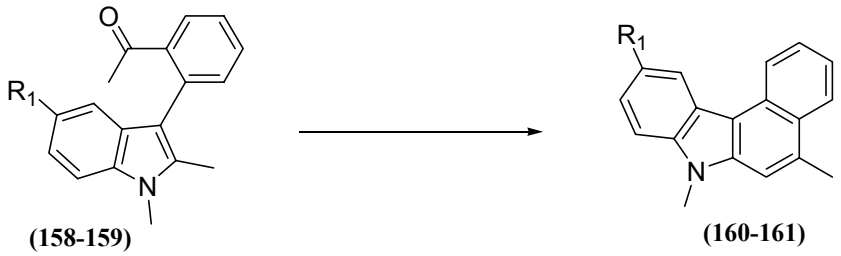
We thus decided to attempt the Suzuki coupling under non-aqueous conditions and to this effect, treatment of **(155)** and **(157)** with boronic acid **(153)** and potassium phosphate in DMF in the presence of tetrakis(triphenylphoshine)palladium(0) afforded the coupled products **(158)-(159)** in good yields as shown in **Scheme 47**. The ^1H NMR spectra showed methyl proton (acetyl) at δ 2.25 and δ 2.24 respectively. The ^{13}C NMR also showed the carbonyl carbons at δ 205.0 and δ 205.1 respectively for **(158)** and **(159)**. The high-resolution mass spectra provided further, irrefutable proof of formation of the biaryl compounds showing molecular ions at 263.1312 ($C_{18}H_{17}NO$ requires 263.1310) for **(158)** and at 293.1407 ($C_{19}H_{19}NO_2$ requires 293.1416) for **(159)**.



Product	Substituent	Yield
(158)	R_1= H	83%
(159)	R_1= OMe	80%

Scheme 47: $Pd(PPh_3)_4$, DMF, K_3PO_4, 100 ˚C.

Finally, we were ready to subject the biaryl precursors **(158)-(159)** to our novel cyclisation reaction. Treatment of **(158)-(159)** with potassium *t*-butoxide in DMF and with simultaneous irradiation from a mercury lamp afforded, to our delight, the desired benzo[*a*]carbazole **(160)-(161)** in good yields as shown in **Scheme 48**. It was clear from spectroscopic evidence that the desired products had formed. The ^{1}H NMR showed the disappearance of the protons of the acetyl substituent group and there was an increase in integration for aromatic protons [*i.e*. from 8 to 9 hydrogens for **(160)** and from 7 to 9 hydrogens for **(161)**] for both products. The high-resolution mass spectroscopy showed expected molecular ions at 245.1198 ($C_{18}H_{15}N$ requires 245.1204) for **(160)** and at 275.1308 ($C_{19}H_{17}NO$ requires 275.1310) for **(161)**.



(158-159) **(160-161)**

Product	Substituent	Yield
(160)	R_1= H	71%
(161)	R_1= OMe	70%

Scheme 48: ^{t}BuOK, DMF, hν, 70-80 ^{o}C.

A crystal structure (**Figure 3**) also provided further and conclusive evidence for the formation of benzo[*c*]carbazole **(160)**. The site of fusion of the aromatic ring (from the boronic acid) on the *c* face of the newly formed ring is clearly evident from the structure. All bond lengths in the aryl rings are equal and within the expected aromatic C=C range (please see the appended data). The target molecules, though still containing *N*-methyl groups whose removal are known to be a challenge, have been submitted for various biological testing and aspects of this work have been submitted for publication.[66]

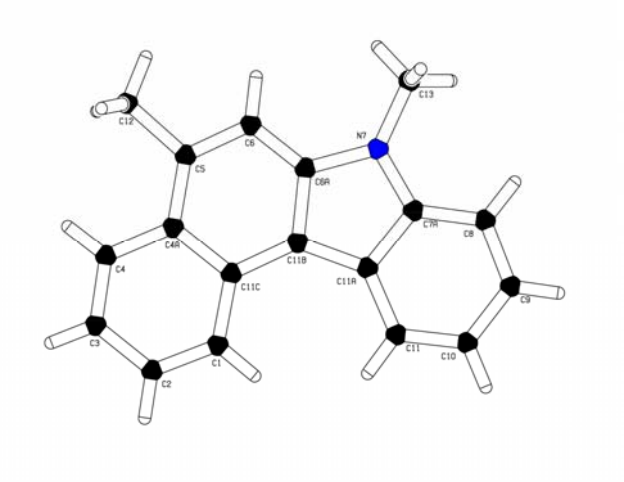


Figure 3 : The X-ray crystal structure of benzo[*c*]carbazole **(160)**.

CHAPTER 4: CONCLUSIONS AND FUTURE WORK

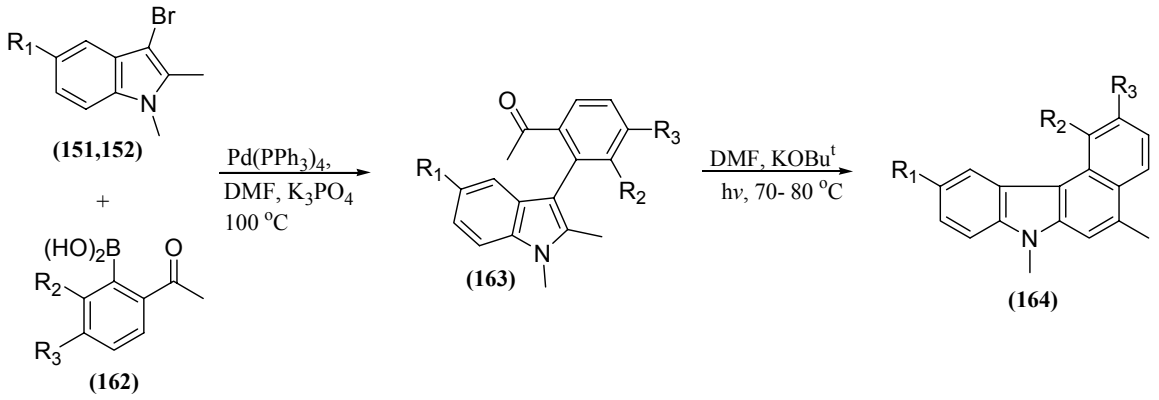
The Suzuki coupling methodology under both aqueous and non-aqueous reaction conditions used for the synthesis of polycyclic heteroaromatic compounds has been successfully used in our laboratories for the synthesis of biaryl compounds. Some of these biaryl compounds have been subjected our novel base/light mediated-cyclisation reaction to afford benzo[*c*]carbazoles.

The initial route towards the synthesis of benzo[*c*]carbazoles which hinged on cylisation of a coupled indole with the carbonyl group attached to the indole fragment, did not give the desired results. Applying the aqueous Suzuki coupling methodology compound **(139)** was synthesised from indole **(2)** in 99% over three steps and compound **(140)** also obtained in 99% over three steps from the precursor **(135)**. The formylated compounds **(145)-(146)**, which were synthesized with the objective of subjecting them to our cyclisation method were also synthesised in good yields of 95% and 88% in six steps respectively.

The second route proved to be successful; a number of biaryl compounds were synthesised in excellent yields by rearrangement of the substituents on the biaryl precursors, using acetophenone-derived boronic acids. The coupled indole compounds successfully underwent our novel cyclisation method. Specifically, 5,7-dimethyl-7*H*-benzo[*c*]carbazole **(160)** was synthesized from 2-methyl-1*H*-indole **(151)** in 79% over four steps and 10-methoxy-5,7-dimethyl-7*H*-benzo[*c*]carbazole **(161)** was synthesized from 5-methoxy-2methyl-1*H*-indole **(152)** in 75 % also over 4 steps. An investigation by a former PhD student at this university towards the mechanism of the cyclisation reaction has indicated the involvement of photochemically generated radical intermediates, although the exact mechanism could not be elucidated.

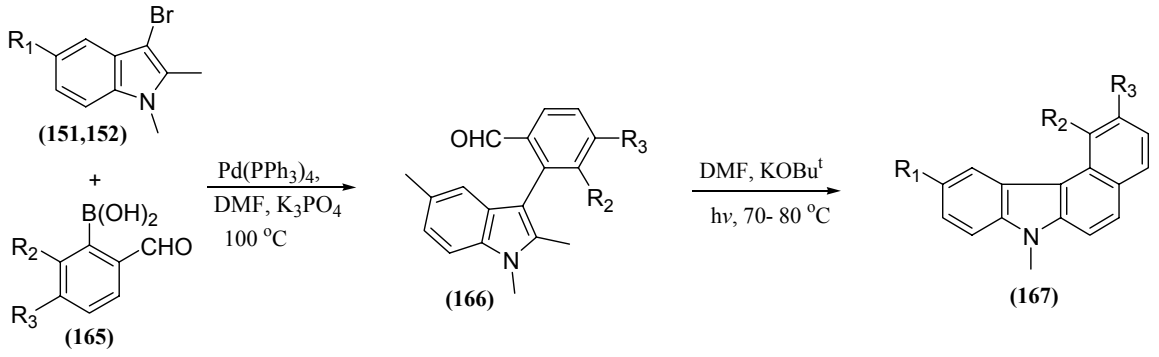
Future work in this area could include the synthesis of highly substituted benzo[*c*]carbazoles. This could be achieved by using highly substituted boronic acids as shown in **Scheme 49** below. The treatment of **(151)** and **(152)** with boronic acids **(162)**

and potassium phosphate in DMF in a catalytic amount of tetrakis(triphenylphoshine)palladium(0) should afford the substituted the biaryl compounds **(163)** and subjection of this compounds **(163)** to our cyclisation conditions should afford benzo[*c*]carbazoles **(164)**.



Scheme 49

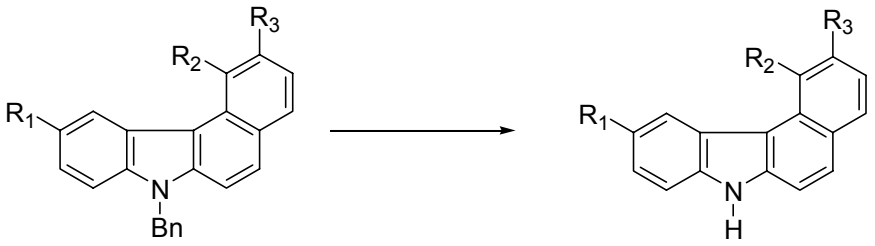
The functionality on the benzo[*c*]carbazoles could also be varied by using for an example as shown in **Scheme 50** a boronic acid substituted with an aldehyde **(165)** in place of a ketone.



Scheme 50

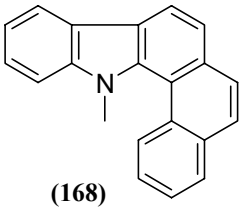
Furthermore, different protecting groups for the nitrogen could be used. In particular, protecting groups (*e.g.* benzyl, **Scheme 51**) that could be easily removed at the end of the

synthesis since the indole nitrogen of many naturally occurring and biologically active carbazoles is unprotected. Benzo[*c*]carbazoles synthesized this way would have added functionality, which could be exploited for further reactions and may exhibit good biological activity.

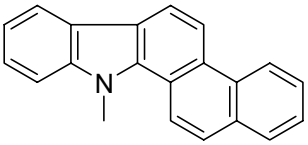


Scheme 51

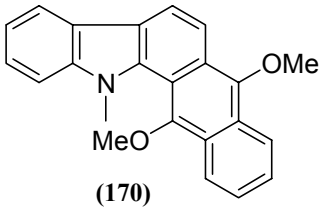
Suzuki coupling methodology and our novel cyclisation reaction has been further successfully applied in our laboratories in the synthesis of naphtho[*a*]carbazoles **(168)-(170)**.[94]



(168)

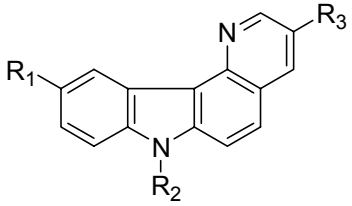


(169)



(170)

Also, the Suzuki coupling methodology and the novel cyclisation reaction can be applied for the synthesis of pyrido[*c*]carbazoles, below. However, there is a wide scope for the synthesis of other polycyclic aromatic compounds.



CHAPTER 5: EXPERIMENTAL PROCEDURES

5.1 GENERAL PROCEDURES

5.1.1 Reagents and Purification of Solvents

Reagents were obtained commercially and not purified before use unless stated otherwise. A stock solution of benzenesulfonyl chloride (M 176.6; mp 14.5 ^{o}C; bp 120 ^{o}C/10mm, d 1.384) was treated with 3 mol% each of toluene and aluminium trichloride, and allowed to stir at room temperature for 16 hours under nitrogen. The free benzenesulfonyl chloride was distilled under reduced pressure at 100 ^{o}C.

All solvents were distilled before use, unless otherwise stated. THF, toluene, dichloromethane and diethyl ether were pre-dried over 4Å molecular sieves for a minimum of 36 hours. The molecular sieves used for pre-drying were freed from water by constantly heating at 200^{o}C under vacuum for minimum of 12 hours. THF, toluene and diethyl ether were distilled from sodium wire with benzophenone. Hexane, ethyl acetate, dichloromethane and *N,N*-dimethylformamide were not pre-dried but distilled directly from calcium hydride. Carbon tetrachloride was dried by filtration through alumina and storage over 4Å molecular sieves. All distillation were carried out in flame-dried glassware under a static nitrogen (99.99%) atmosphere. The nitrogen was pre-dried by bubbling through sulphuric acid then through sodium hydroxide pellets.

5.1.2 Experimental Techniques

All reactions were carried out in pre-dried glassware under a constant flow of nitrogen. The reagents and solvents were transferred using appropriate size syringes or cannulas. Heating of the reaction mixtures was accomplished by heating the half-immersed glassware in liquid paraffin with continuous stirring using a magnetic heater/stirrer. Macherey-Nagel Kieselgel 60 (particle size 0.063- 0.0200 mm) was used for conventional silica gel column chromatography and Macherey-Nagel Kieselgel 60 (particle size 0.040- 0.63mm) was used for flash column chromatography. Thin layer chromatography was carried out on aluminium foil-backed Macherey-Nagel ALUGRAM Silica G/UV_{254} plates pre-coated with 0.25 mm silica gel 60.

5.1.3 Characterisation Procedures

^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) Spectroscopy

^{1}H and ^{13}C NMR spectra were recorded either on a Bruker AC 200 MHz connected to an Aspect 3000 data processing unit; or a Bruker DRX 400 MHz connected to a Silicon Graphics Indy workstation. All spectra were recorded in chloroform-d (99.8 atom %D) containing 0.03% v/v TMS as internal standard. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or b (broadened). Coupling constants, *J*, are reported in Hertz, Hz.

Infrared (IR) Spectroscopy

Infrared spectra were recorded on either a Bruker IFS 25 Fourier Transform Spectrometer or a Bruker Vector 22 Fourier Transform Spectrometer and selected absorption maxima are reported in wavenumbers, cm^{-1}.

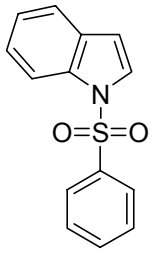
Mass Spectroscopy

Mass spectra were recorded on a Kratos MS 8/50, VG 70E MS or a VG 70 SEQ Mass spectrometer.

Crystal structure solution and refinement

Intensity data were collected on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50kV, 30mA). The collection method involved ω-scans of width 0.3^{o}. Data reduction was carried out using the program *SAINT+* (Bruker, 1999a) and the data further processed using the program *SADABS*. The crystal structure was solved by direct methods using *SHELXTL*. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using *SHELXTL*. Hydrogen atoms were first located from the difference map then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using SHELXTL and PLATON.

1-(Phenylsulfonyl)-1H-indole (24)



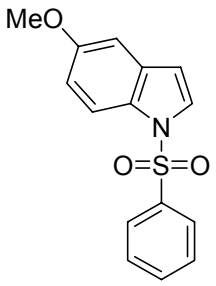
To an ice-cold mixture of powdered sodium hydroxide (3 mol equiv., 1.06 g, 26.5 mol) and tetra-*n*-butylammonium bromide (0.026 mol equiv., 0.072 g, 0.22 mmol) in dry dichloromethane (20 cm^3) under nitrogen, was added indole **(2)** (1.00 g, 8.54 mmol) in one portion followed by a slow addition of benzenesulfonyl chloride (1.25 mol equiv., 1.89 g, 1.40 cm^3, 10.7 mol). The light pink reaction mixture was then stirred at room temperature for 2 h. The resulting milky white reaction mixture was filtered and the filtrate evaporated under vacuum to produce thick orange oil. This oil was purified by recrystallisation from methanol to afford white crystals (**24**) (2.17 g, 99%); R_f 0.52 (20% ethyl acetate-hexane).

mp 76-78 °C. lit. (78-79 °C) [35,71]

δ_H (100 MHz, $CDCl_3$, Me_4Si)
6.65-6.66 (1H, m, 3-H), 7.41-7.88 (7H, m, 7 × ArH), 7.98-7.99 (2H, m, 2'-H and 6'-H) and 8.00-8.01 (1H, m, 4-H).

δ_C (50 MHz, $CDCl_3$)
109.2 (3-CH), 113.5 (7-CH), 121.4 (6-CH), 123.3 (4-CH), 124.6 (5-CH), 126.2 (2-CH), 126.7 (2'-CH and 6'-CH), 129.2 (3'-CH and 5'-CH), 130.7 (3a-C), 133.7 (4'-CH), 134.8 (7a-C) and 138.2 (1'-C)

5-Methoxy-1-(phenylsulfonyl)-1H-indole (138)



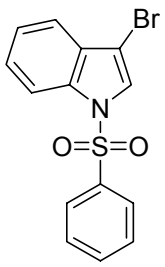
To an ice-cold mixture of powdered sodium hydroxide (3.00 mol equiv., 1.69 g, 42.1 mmol) and tetra-*n*-butylammonium bromide (0.026 mol equiv., 0.11 g, 0.35 mmol) in dry dichloromethane (40 cm^3) under nitrogen, was added 5-methoxy-1*H*-indole (2.00 g, 13.6 mmol) in one portion followed by a slow addition of benzenesulfonyl chloride (1.25 mol equiv., 3.00 g, 2.20 cm^3, 17.0 mmol). The light pink reaction mixture was then stirred at room temperature for 2 h. The resulting milky white reaction mixture was filtered and the filtrate evaporated under vacuum to produce thick orange oil. This oil was purified by recrystallisation from methanol to afford white crystals (**139**) (3.86 g, 99%); R_f 0.40 (10% ethyl acetate- hexane).

mp 98-99 ^oC. lit. (98-99 ^oC) [72]

δ_H (100 MHz, $CDCl_3$, Me_4Si)
3.79 (3H, s, OCH_3), 6.58-6.59 (1H, m, 3-H), 6.89-6.96 (2H, m, 3-H and 6-H) and 7.24-7.91 (7H, m, ArH).

δ_C (50 MHz, $CDCl_3$)
55.6 (OCH_3), 103.7 (3-CH), 109.3 (6-CH), 113.7 (4-CH), 114.3 (7-CH), 126.6 (2'-CH and 6'-CH), 127.0 (2-CH), 129.1 (3'-CH and 5'-CH), 129.5 (7a-C), 131.7 (3a-C), 133.6 (4'-CH), 138.2 (1'-C) and 156.4 (5-C).

3-Bromo-1-(phenylsulfonyl)-1H-indole (136)



1-(Phenylsulfonyl)-1*H*-indole **(24)** (2.00 g, 7.77 mmol) was dissolved in carbon tetrachloride (60 cm^3). To the resulting solution, bromine (1.10 mol equiv., 1.37 g, 0.440 cm^3, 8.55 mmol) was added drop-wise. The red reaction mixture was then stirred at room temperature for 4.5 h, and then poured into saturated solution of aqueous $NaHCO_3$ (80 cm^3). The resulting two layers were separated, and the organic layer successively washed with aqueous $Na_2S_2O_3$ (60 cm^3), water (60 cm^3), brine (60 cm^3) then dried with $MgSO_4$ mixed with charcoal. The solvent was removed under reduced pressure and the crude residue was purified by chromatography (20% ethyl acetate-hexane) to afford the product (**136**) (2.58 g, 99%) as orange crystals. R_f 0.61 (20% ethyl acetate-hexane).

mp 125-126 ^oC. lit. (125-127 ^oC)[26]

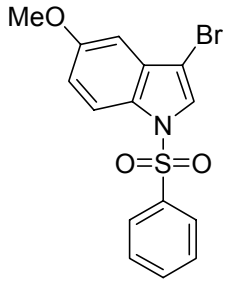
δ_H (200 MHz, CDCl_3, $MeSi_4$)

7.30-7.62 (7H, m, 7 x ArH), 7.87-7.91 (2H, m, 2'-H and 6'-H) and 7.98-8.02 (1H, m, 4-H).

δ_C (100MHz, CDCl_3)

99.8 (3-C), 113.5 (7-CH), 120.1 (6-CH), 124.0 (4-CH), 124.7 (5-CH), 125.8 (2-CH), 126.8 (2'-CH and 6'-CH), 129.3 (3a-C), 129.4 (3'-CH and 5'-CH), 134.1 (4'-CH), 134.3 (7a-C) and 137.8 (1'-C)

3-Bromo-5-methoxy-1-(phenylsulfonyl)-1H-indole (137)



5-Methoxy-1-(phenylsulfonyl)-1*H*-indole (**139**) (2.00 g, 6.97 mmol) was dissolved in carbon tetrachloride (60 cm^3). To the resulting solution, bromine (1.10 mol equiv., 1.22 g, 0.40 cm^3, 7.67 mmol) was added drop-wise. The red reaction mixture was then stirred at room temperature for 4.5 hours, and then poured into saturated solution of aqueous $NaHCO_3$ (80 cm^3). The resulting two layers were separated, and the organic layer successively washed with aqueous $Na_2S_2O_3$ (60 cm^3), water (60 cm^3), brine (60 cm^3) then dried with $MgSO_4$ mixed with charcoal. The solvent was removed under reduced pressure and the crude residue was purified by chromatography (10% ethyl acetate-hexane) to afford the product (**137**) (2.53 g, 99%) as orange crystals. R_f 0.70 (20% ethyl acetate-hexane). Found (M^+ 364.9721. $C_{15}H_{12}Br^{79}NO_3S$ requires 364.9722).

mp 129°C

IR ν_{max}/cm^{-1}

1615 and 1583 (ArC=C), 1475, 1447, 1435 and 1375

δ_H (400 MHz, $CDCl_3$, Me_4Si)

3.91 (3H, s, OCH_3), 6.97-7.00 (1H, m, 6-H), 7.44-7.94 (8H, m, ArH).

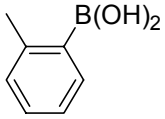
δ_C (100 MHz, $CDCl_3$)

54.5 (OCH_3), 101.7 (3-CH), 111.2 (6-CH), 114.3 (4-CH), 115.2 (7-CH), 127.5 (2'-CH and 6'-CH), 128.2 (2-CH), 130.3 (3'-CH and 5'-CH), 130.9 (7a-C), 131.9 (3a-C), 134.1 (4'-CH), 138.9 (1'-C) and 156.9 (5-C).

m/z(%)

367 (M^+, 64%), 365 (64) 226 (98), 224 (100), 211 (14), 209 (14), 183 (21), 181 (16), 178 (25), 124 (21), 102 (16), 81 (15), 77 (51), and 69 (36).

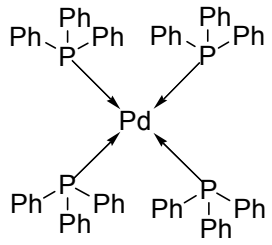
2-Bromophenylboronic acid (133)



1-Bromo-2-methylbenzene (5.00 g, 3.50 cm^3, 29.3 mmol) was dissolved in THF (30 cm^3) and cooled to –78 ^oC. *n*-Butyllithium (1.100 mol equiv., 25.12 cm^3, 32.16 mmol) was added drop-wise and the resulting white suspension was stirred at –78 ^oC under an atmosphere of nitrogen for 30 mins. After this time trimethyl borate (3.00 mol equiv., 9.11 g, 9.83 cm^3, 37.7 mmol) was added drop-wise and the reaction mixture stirred for a further 30 mins at –78 ^oC. The reaction mixture was then gradually warmed to room temperature and acidified with 10% aqueous $HC\ell$ and extracted with dichloromethane (3 × 60 cm^3) and the combined organic extracts were dried with $MgSO_4$. The inorganic solids were filtered off and the solvent removed under reduced pressure to afford white

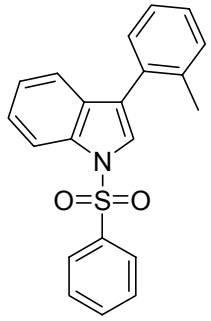
crystalline material (**133**) in quantitative yield. The product was then used without any further purification or characterisation.

Tetrakis(triphenylphosphine)palladium(0)



Palladium dichloride (0.50 g, 2.8 mmol), triphenylphoshine (5 mol equiv., 3.70 g, 14.1 mmol) and dimethyl sulfoxide (40 cm^3) were placed in a Schlenk tube and stirred under a nitrogen atmosphere at 140 ^oC until complete solution occurred. The solution was then removed from heat and the solution further stirred for 15 min. Hydrazine hydrate (4 mol equiv., 0.62 g, 0.60 cm^3, 11 mmol) was rapidly added to the solution and the reaction mixture cooled in a water bath until crystallisation occurred. When the reaction mixture was completely cooled and crystallization complete the mixture was filtered under a constant flow of nitrogen. The filtrate was washed successively with dry ethanol (2 × 50 cm^3) and dry ether (2 × 50 cm^3) still under a flow of nitrogen. The product, bright yellow shiny crystals, was dried by passing through it a slow stream of nitrogen for 18 h. The product was obtained in a quantitative yield with no further purification or characterisation.

3-(2-Methylphenyl)-1-(phenylsulfonyl)-1H-indole (139)



A solution of 3-bromo-1-(phenylsulfonyl)-1*H*-indole **(136)** (0.25 g, 0.74 mmol) in DME (6 cm^3) was deoxygenated by passing through it a fast stream of nitrogen for 5 mins. This deoxygenated solution was added to $Pd(PPh_3)_4$ (10%, 86.00 mg, 0.074 mmol) and stirred under an atmosphere of nitrogen at room temperature for 10 mins. A solution of 2-bromophenylboronic acid (1.5 mol equiv., 0.15 g, 1.1 mmol) in 96% ethanol (2 cm^3) was also deoxygenated and added to mixture. The mixture was stirred for another 10 mins followed by the addition of deoxygenated sodium carbonate solution (8.5 mol equiv., 3.2 cm^3, 6.3 mmol, 2M). The resulting mixture was further stirred at room temperature under nitrogen for 10 min. The mixture was then heated at reflux for 18 h under nitrogen. The mixture was cooled to room temperature and quenched with water (20 cm^3). The organic material was extracted into dichloromethane (3 × 30 cm^3), the combined organic extracts dried with magnesium sulfate and the solvent evaporated under reduced pressure. The crude residue was purified with column chromatography (20% ethyl acetate-hexane) to afford the product **(139)** (0.26 g, 100%) as an orange oil; R_f 0.55 (20% ethyl acetate-hexane). Found (M^+ 347.0980. $C_{21}H_{17}NO_2S$ requires 347.0980).

IR ν_{max}/cm^{-1}

3020s (=CH), 1523m (C=C) and 1216s (C-N).

δ_H (400 MHz, $CDCl_3$, Me_4Si)

2.19 (3H, s, $ArCH_3$), 7.19-7.45 (7H, m, ArH, overlapping with indole-H), 7.50-7.51 (2H, m, ArH), 7.51-7.52 (2H, m, ArH), 7.91-7.92 (2H, m, ArH), 8.05-8.08 (1H, m, ArH).

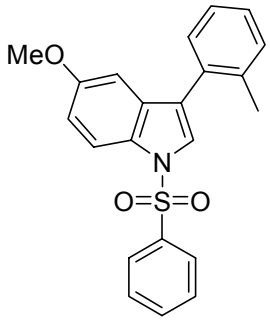
δ_C (100 MHz, $CDCl_3$)

20.3 ($ArCH_3$), 113.8 (7-C), 120.7 (2-C), 123.5 (Ar-CH), 123.7 (Ar-C), 124.0 (Ar-CH), 124.(Ar-CH), 125.78 (Ar-CH), 126.7 (each 2'-CH and 6'-CH)[a], 127.9 (Ar-CH), 129.2 (each 3'-CH and 5'-CH)[a] 130.4 (Ar-CH), 130.5 (Ar-CH), 130.7 (Ar-C), 131.8 (Ar-C), 133.8 (Ar-C), 134.9 (Ar-C), 136.8 (Ar-C), 138.1 (1'-C).

m/z(%)

347 (M^+, 61), 206 (100), 178 (31), 103 (4) and 77 (10).

5-Methoxy-3-(2-methylphenyl)-1-(phenylsulfonyl)-1H-indole (140)



A solution of 3-bromo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole **(137)** (2.21 g, 6.04 mmol) in DME (48 cm^3) was deoxygenated by passing through it a fast stream of

nitrogen for 5 min. This deoxygenated solution was added to $Pd(PPh_3)_4$ (10%, 0.70 g, 0.60 mmol) and stirred under an atmosphere of nitrogen at room temperature for 10 min. A solution of 2-bromophenylboronic acid (1.50 mol equiv., 1.23 g, 9.07 mmol) in 96% ethanol (16 cm^3) was also deoxygenated and added to mixture. The mixture was stirred for another 10 min followed by the addition of deoxygenated 2M sodium carbonate (8.5 mol equiv., 26 cm^3, 51.3 mmol). The resulting mixture was further stirred at room temperature under nitrogen for 10 mins. The mixture was then heated at reflux for 18 h under nitrogen. The mixture was cooled to room temperature and quenched with water (80 cm^3). The organic material was extracted into dichloromethane (3 × 80 cm^3), the combined organic extracts dried with magnesium sulfate and the solvent evaporated under reduced pressure. The crude residue was purified with column chromatography (20% ethyl acetate-hexane) to afford the product **(140)** (0.26 g, 100%) as white crystals; R_f 0.61 (20% ethyl acetate-hexane). Found (M^+ 377.1078. $C_{22}H_{19}NO_3S$ requires 377.1086).

mp 128 ^oC (MeOH).

IR ν_{max}/cm^{-1}

2360s (C-H), 1616w (C=C), 1365s (C-O) and (1215s (C-N).

δ_H (400 MHz, $CDCl_3$, Me_4Si)

2.18 (3H, s, $ArCH_3$), 3.73 (3H, s, OCH_3), 6.72-6.73 (1H, d, *J* 2.5, 4-H), 6.95-6.97 (1H, dd, *J* 2.5 and 8.7, 6-H), 7.25-7.32 (4H, m, Ar-H), 7.43-7.47 (3H, m, Ar-H), 7.51-7.53 (1H, m, 2-H), 7.88-7.90 (2H, m, Ar-H), 7.94-7.97 (1H, dd, *J* 0.3 and 9.0, 7-H).

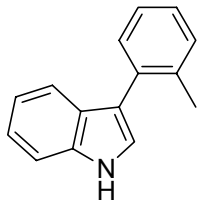
δ_C (50 MHz, $CDCl_3$)

20.3 ($ArCH_3$), 55.7 ($ArOCH_3$), 102.9 (Ar-CH), 114. 0 (Ar-CH), 114.8 (Ar-CH), 124.0 (Ar-CH), 124.9 (Ar-CH), 125.8 (Ar-CH), 126.7 (2'-CH and 6'-CH), 128.0 (Ar-CH), 129.2 (3'-CH and 5'-CH), 129.7 (Ar-C), 130.4 (Ar-CH), 130.5 (Ar-CH), 131.8 (Ar-C), 131.9 (Ar-C), 133.7 (Ar-CH), 136.9 (Ar-C), 138.1 (Ar-C), 156.8 (1'-C).

m/z(%)

377 (M^+, 100), (236 (80), 220 (7), 204 (19), 192 (9), 165 (10) and 77 (10).

3-(2-Methylphenyl)-1H-indole (141)



The 3-(2-methylphenyl)-1-(phenylsulfonyl)-1*H*-indole **(139)** (0.028 g, 0.080 mmol) was dissolved in methanol (20 cm^3) at room temperature under nitrogen. Potassium carbonate (16 mol equiv., 1.78 g, 12.9 mmol) was added to the solution and the reaction mixture heated to reflux under an atmosphere of nitrogen for 18 h. The mixture was allowed to cool to room temperature, filtered and the filtrate concentrated under reduced pressure. Water (15 cm^3) was added to the crude material and slowly acidified to pH 2-4 with 10% HC*l*. The aqueous portion was saturated with solid sodium chloride and extracted with dichloromethane (3 × 20 cm^3). The combined organic extracts were washed with water (2 × 20 cm^3), brine (2 × 20cm^3), dried with magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography (20% ethyl acetate-hexane) to afford product **(141)** (0.16 g, 93%) as a light yellow oil. R_f 0.47 (20% ethyl acetate-hexane). Found (M^+ 207.1050. $C_{15}H_{13}N$ requires 207.1048).

IR ν_{max}/cm^{-1}

3487w (N-H), 3019s (=CH), 1523w (C=C) and 1211s (C-N).

δ_H (200 MHz, CDC*l*$_3$, MeSi$_4$)

2.31 (3H, s, Ar-H), 7.12-7.33 (6H, m, Ar-H), 7.37-7.44 (2H, m, Ar-H), 7.50-7.54 (1H, dd, *J* 1.1 and 7.9, 7H) and 8.09 (1H, br. s, N-H).

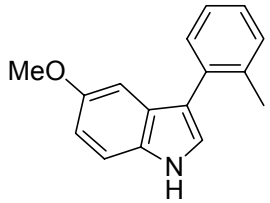
δ_C (100 MHz, CDC*l*$_3$)

20.7 (ArCH$_3$), 111.2 (2-CH), 117.4 (7a-C), 119.9 (Ar-CH), 120.1 (Ar-CH), 122.1 (Ar-CH), 122.7 (Ar-CH), 125.6 (Ar-CH), 126.7 (Ar-CH), 127.1 (3a-C), 130.3 (Ar-CH), 130.9 (Ar-CH), 134.4 (3-C), 135.8 (6'-C), 136,8 (1'-C).

m/z(%)

207 (M^+, 100), 206 (63), 178 (15), 102 (10), 90 (4) and 77 (4).

5-Methoxy-3-(2-methylphenyl)-1H-indole (142)



The 5-methoxy-3-(2-methylphenyl)-1-(phenylsulfonyl)-1*H*-indole **(140)** (0.30 mg, 0.80 mmol) was dissolved in methanol (30 cm^3) at room temperature under nitrogen. Potassium carbonate (16 mol equiv., 1.76 g, 12.7 mmol) was added to the solution and the reaction mixture heated to reflux under an atmosphere of nitrogen for 18 h. The mixture was allowed to cool to room temperature, filtered and the filtrate concentrated under reduced pressure. Water (30 cm^3) was added to the crude material and slowly

acidified to pH 2-4 with 10% HC*l*. The aqueous portion was saturated with solid sodium chloride and extracted with dichloromethane (3 × 30 cm^3). The combined organic extracts were washed with water (2 × 30 cm^3), brine (2 × 30cm^3), dried with magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography (20% ethyl acetate-hexane) to afford product **(142)** (0.18 g, 96%) as a light yellow oil. R_f 0.45 (20% ethyl acetate-hexane). Found (M^+ 237.1164. $C_{16}H_{15}NO$ requires 237.1154).

IR ν_{max}/cm^{-1}

3417br (N-H), 3058m (=CH), 2928s (C-H), 1624m (C=C), 1296s (C-O) and 1212s (C-N).

δ_H (400 MHz, CDC*l*$_3$, Me_4Si)

2.32 (3H, s, Ar-CH_3), 3.78 (3H, s, OCH_3), 6.89-6.94 (2H, m, Ar-H), 7.11-7.12 (1H, d, 2.5, 4-H), 7.25-7.41 (5H, m, Ar-H, overlapping with 2-H), 8.09 (1H, br. s, N-H).

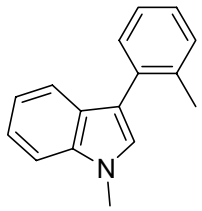
δ_C (100 MHz, CDC*l*$_3$)

20.7 ($ArCH_3$), 55.9 ($ArOCH_3$), 101.6 (6-CH)[a], 111.9 (4-CH)[a], 112.6 (Ar-CH), 117.3 (3-C), 123.5 (Ar-CH), 125.6 (Ar-CH), 126.7 (Ar-CH), 127.5 (2'-C), 130.3 (Ar-CH), 130.8 (Ar-CH), 131.0 (1'-CH), 134.6 (3a-C), 136.9 (7a-C), 154.2 (5-C)

m/z(%)

237 (100), 222 (51), 206 (12), 194 (17), 165 (11) and 115 (4).

1-Methyl-3-(2-methylphenyl)-1H-indole (143)



To a solution of 3-(2-methylphenyl)-1*H*-indole **(141)** (0.45 g, 2.18 mmol) in THF (10 cm^3) was added dimethyl sulfate (1.8 mol equiv., 0.50 g, 0.37 cm^3, 3.9 mmol) followed by sodium hydride (50% in oil, 2.4 mol equiv., 0.12 g, 5.2 mmol). The resulting mixture was stirred at room temperature under a constant flow of nitrogen for 18 h. The reaction was quenched with water (20 cm^3), extracted with diethyl ether (3 × 50 cm^3), combined organic layers dried with magnesium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (20% ethyl acetate- hexane) to afford **(143)** (481 mg, 99%); R_f 0.60 (20% ethyl acetate-hexane). Found (M^+ 221.1199. $C_{16}H_{15}N$ requires 221.1204).

IR ν_{max}/cm^{-1}

3057w (=CH), 2925 (C-H), 1616w (C=C) and 1223s (C-N).

δ_H (200 MHz, $CDCl_3$, $MeSi_4$)

2.32 (3H, s, $ArCH_3$), 3.78 (3H, s, $N\text{-}CH_3$), 7.0 (1H, s, 2-H), 7.10-7.41 (7H, m, Ar-H), 7.49-7.54 (1H, m, Ar-H)

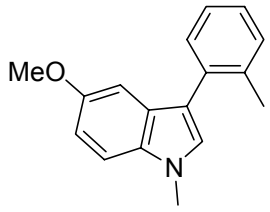
δ_C (200MHz, $CDCl_3$)

20.3 ($Ar\text{-}CH_3$), 32.7 ($N\text{-}CH_3$), 109.3 (Ar-CH), 119.4 (Ar-CH), 120.2 (Ar-CH), 121.7 (Ar-CH), 125.6 (Ar-CH), 126.5 (Ar-CH), 126.9 (Ar-C), 127.5 (Ar-CH), 130.3 (Ar-CH), 130.8 (Ar-CH), 131.8 (Ar-C), 132.0 (Ar-CH), 132.2 (Ar-C), 136.7 (Ar-C).

m/z(%)

221 (100), 220 (57), 204 (13), 178 (9), 110 (4) and 102 (3).

5-Methoxy-1-methyl-3-(2-methylphenyl)-1H-indole (144)



To a solution of 5-methoxy-3-(2-methylphenyl)-1*H*-indole **(142)** (175 mg, 0.74 mmol) in THF (10 cm^3) was added dimethyl sulfate (1.5 mol equiv., 0.14 g, 0.10 cm^3, 1.11 mmol) followed by sodium hydride (50% in oil, 2.4 mol equiv., 0.043 g, 1.8 mmol). The resulting mixture was stirred at room temperature under a constant flow of nitrogen for 18 h. The reaction was quenched with water (15 cm^3), extracted with diethyl ether (3 × 30 cm^3), combined organic layers dried with magnesium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (20% ethyl acetate- hexane) to afford **(144)** (183 mg, 99%); R_f 0.66 (20% ethyl acetate-hexane).

IR ν_{max}/cm^{-1}

3057w (=CH), 2944m (C-H), 1618w (C=C), 1271s (C-O) and 1213s (C-N).

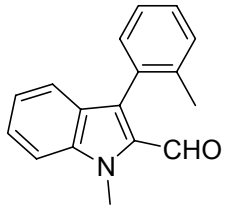
δ_H (400 MHz, $CDCl_3$, $MeSi_4$)

2.33 (3H, s, Ph-CH_3), 3.78 (3H, s, N-CH_3), 3.79 (3H, s, OCH_3), 6.90-6.94 (2H, m, Ar-H), 6.99 (1H, s, 2-H), 7.22-7.25 (3H, m, Ar-H), 7.30 (1H, m, Ar-H) and 7.39-7.41 (1H, m, Ar-H).

δ_C (100 MHz, CDC*l*$_3$)

20.7 (Ph-CH_3), 32.9 (N-CH_3), 55.9 (OCH_3), 101.7 (6-C), 110.1 (4-C), 112.1 (Ar-CH), 115.5 (Ar-C), 125.6 (Ar-CH), 126.5 (Ar-CH), 127.8 (Ar-C), 128.1 (Ar-CH), 130.4 (Ar-CH), 130.7 (Ar-CH), 132.1 (Ar-C), 134.6 (Ar-C), 136.7 (7a-C) and 154.3 (5-C).

1-Methyl-3-(2-methylphenyl)-1H-indole-2-carbaldehyde (145)



DMF (3 mol equiv., 0.30 g, 0.30 cm^3, 4.07 mmol) was added to $POCl_3$ (2 mol equiv., 0.42 g, 0.25 cm^3, 2.71 mmol) at 0 ^oC under an atmosphere of nitrogen. The resulting salt was treated with a solution of 1-methyl-3-(2-methylphenyl)-1*H*-indole **(143)** (300 mg, 1.36 mmol) in toluene (6 cm^3). The resulting reaction mixture was heated to reflux for 42 h under nitrogen atmosphere. The reaction mixture was then cooled to room temperature, quenched with water and excess $POCl_3$ neutralised with sodium carbonate. The crude product was extracted into dichloromethane (3 × 50 cm^3), the combined organic extracts dried with magnesium sulfate, and evaporated under reduced pressure. The crude material was purified by column chromatography (20% ethyl acetate-hexane) to afford product **(145)** (201.5 mg, 60%) as a brown oil; R_f 0.64 (20% ethyl acetate-hexane). Found (M^+ 249.1158. $C_{17}H_{15}NO$ requires 249.1154).

IR ν_{max}/cm^{-1}

2952w (C-H), 1709s (C=O), 1608w (C=C) and 1244m (C-N)

δ_H (200 MHz, $CDCl_3$, $MeSi_4$)

2.18 (3H, s, Ph-CH_3), 4.16 (3H, s, N-CH_3), 7.12 (1H, m, Ar-H), 7.23-7.44 (7H, m, Ar-H) and 9.66 (1H, s, CHO).

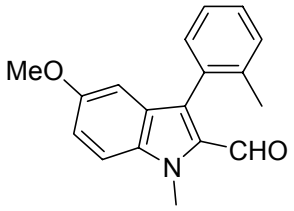
δ_C (100 MHz, $CDCl_3$)

20.9 (Ph-CH_3), 33.1 (N-CH_3), 56.01 (OCH_3), 101.5 (6-C), 110.8 (Ar-CH), 121.3 (Ar-CH), 122.9 (ArC-H), 125.9 (Ar-CH), 126.7 (Ar-C), 127.7 (Ar-CH), 128.7 (Ar-CH), 130.7 (ArCH), 131.7 (Ar-C), 131.8 (Ar-C), 131.9 (Ar-C), 132.5 (Ar-CH), 138.2 (7a-C), 140.0 (2-C) and 184.2 (CHO).

m/z(%)

249 (M^+, 100), 234 (32), 232 (69), 217 (24), 204 (18), 178 (8), 116 (4) and 102 (5).

5-Methoxy-1-methyl-3-(2-methylphenyl)-1H-indole-2-carbaldehyde (146)



DMF (3 mol equiv., 0.124 g, 0.13 cm^{-3}, 1.67 mmol) was added to $POCl_3$ (2 mol equiv., 0.17 g, 0.10 cm^3, 1.12 mmol) at 0 ^oC under an atmosphere of nitrogen. The resulting salt was treated with a solution of 5-methoxy-1-methyl-3-(2-methylphenyl)-1*H*-indole **(144)** (140 mg, 0.56 mmol) in toluene (4 cm^3). The reaction mixture was then heated to reflux for 42 h under nitrogen atmosphere. The reaction mixture was then cooled to room temperature, quenched with water and excess $POCl_3$ neutralised with sodium carbonate. The crude product was extracted into dichloromethane (3 × 30 cm^3), the combined organic extracts dried with magnesium sulfate, and evaporated under reduced pressure. The crude material was purified by column chromatography (20% ethyl acetate-hexane) to afford product **(146)** (155.6 mg, 27%) as a brown oil; R_f 0.38 (20% ethyl acetate-hexane). Found (M^+ 279.1259, $C_{18}H_{17}NO$ requires 279.1259).

IR ν_{max}/cm^{-1}

2952w (C-H), 1716s (C=O), 1617w (C=C), 1261s (C-O) and 1242m (C-N).

δ_H (200 MHz, $CDCl_3$, $MeSi_4$)

2.32 (3H, s, $ArCH_3$), 3.78 (3H, s, N-CH_3), 7.0 (1H, s, 2-H), 7.10-7.41 (7H, m, Ar-H), 7.49-7.54 (1H, m, Ar-H)

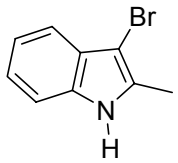
δ_C (100MHz, $CDCl_3$)

20.3 (Ar-CH_3), 32.7 (N-CH_3), 109.3 (Ar-CH), 119.4 (Ar-CH), 120.2 (Ar-CH), 121.7 (Ar-CH), 125.6 (Ar-CH), 126.5 (Ar-CH), 126.9 (Ar-C), 127.5 (Ar-CH), 130.3 (Ar-CH), 130.8 (Ar-CH), 131.8 (Ar-C), 132.0 (Ar-CH), 132.2 (Ar-C), 136.7 (Ar-C).

m/z(%)

279 (M^+, 100), 264 (19), 262 (38), 247 (16), 218 (9), 206 (10), 204 (9), 192 (6), 165 (9) and 152 (6).

3-Bromo-2-methyl-1H-indole (154)



2-methyl-1*H*-indole **(151)** (1.00 g, 7.62 mmol) was dissolved in DMF (7.5 cm^3). A solution of bromine (1 mol equiv., 1.22 g, 0.390 cm^3, 7.62 mmol) in DMF (7.5 cm^3) was added to the reaction mixture and the resulting mixture stirred at room temperature under nitrogen atmosphere for 4hours. After this time the reaction mixture was poured into an ice-cold mixture of water (10 cm^3), 25 % ammonia solution (10 cm^3) and a solution of sodium bisulphate (10 cm^3). The resulting precipitate was then dissolved in dichloromethane (20 cm^3). The organic layer was sequentially washed with water (20 cm^3), aqueous sodium chloride (20 cm^3), dried with magnesium sulphate and concentrated *in vacuo*. The residue was then loaded on a silica gel column and eluted with 20% ethyl acetate- hexane to afford the desired product **(154)** (1.61 g, 100%) as an off-white solid; R_f 0.47 (20 % ethyl acetate- hexane).

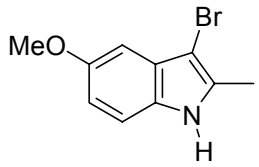
δ_H (200 MHz, CDC*l*$_3$, MeSi$_4$)

2.40 (3H, s, 2-CH_3), 7.13-7.23 (3H, m, 3 × Ar-H), 7.45-7.47 (1H, m, 7-H) and 8.0 (1H, br. s, N-H).

δ_C (50 MHz, CDC*l*$_3$)

12.2 (2-CH_3), 100.3 (3-C), 112.0 (7-CH), 121.5 (Ar-CH), 121.9 (Ar-CH), 122.3 (Ar-CH), 128.2 (3a-C), 130.3 (7a-C) and 136.7 (2-C)

3-Bromo-5-methoxy-2-methyl-1H-indole (156)



5-Methoxy-2-methyl-1*H*-indole **(152)** (200 mg, 1.24 mmol) was dissolved in dichloromethane (4 cm^3). To the resulting solution was added small spatula of silica gel followed by *N*-bromosuccinimide (1 mol equiv., 1.24 mmol, 220 mg). The resulting mixture was stirred at room temperature for 30 mins under an atmosphere of nitrogen. The reaction was quenched with water (15 cm^3), extracted with dichloromethane (3 × 20 cm^3), the combined organic extracts were dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (20% ethyl acetate-hexane) to afford **(156)** (290mg, 99%); R_f 0.39 (20% ethyl acetate-hexane)

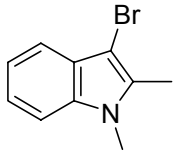
δ_H (400 MHz, CDC*l*$_3$, $MeSi_4$)

2.38 (3H, s, 2-CH_3), 3.87 (3H, s, OCH_3), 6.79-6.82 (1H, dd, *J* 2.12 and 8.7 Hz, 6-H), 6.91-6.92 (1H, d, *J* 1.5, 4-H), 7.10-7.13 (1H, d, J 8.7, 7-H) and 7.89 (1H, br. s, N-H)

δ_C (100 MHz, CDC*l*$_3$)

12.4 (2-CH_3), 55.80 (OCH_3), 90.0 (3-C), 100.0 (6-CH), 111.5 (4-CH), 112.3 (7-CH), 128.1 (3a-C), 129.60 (7a-C), 133.1 (2-C) and 154.7 (5-C).

3-Bromo-1,2-dimethyl-1H-indole (155)



To a solution of 3-bromo-2-methyl-1*H*-indole **(154)** (1.60 g, 7.60 mmol) in THF (50 cm^3) was added dimethyl sulfate (1.50 mol equiv., 1.44 g, 1.08 cm^3, 11.4 mmol) followed by sodium hydride (50% in oil, 2.4 mol equiv., 0.44 g, 18 mmol). The resulting mixture was stirred at room temperature under a constant flow of nitrogen for 18 h. The reaction was quenched with water (35 cm^3), extracted with diethyl ether (3 × 40 cm^3), combined organic layers dried with magnesium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (20% ethyl acetate-hexane) to afford **(155)** (1.68 g, 99%); R_f 0.67 (20% ethyl acetate-hexane).

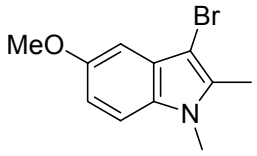
δ_H (200 MHz, CDC*l*$_3$, MeSi$_4$)

2.36 (3H, s, 2-CH_3), 3.59 (3H, s, N-CH_3), 7.12-7.20 (3H, m, 3 × Ar-H) and 7.45-7.49 (1H, m, 7-H)

δ_C (50 MHz, CDC*l*$_3$)

12.4 (2-CH_3), 33.5 (N-CH3), 102.4 (3-C), 112.9 (7-CH), 121.9 (Ar-CH), 122.3 (Ar-CH), 123.2 (Ar-CH), 128.7 (3a-C), 130.8 (7a-C) and 137.2 (2-C)

3-Bromo-5-methoxy-1,2-dimethyl-1H-indole (157)



To a solution of 3-bromo-5-methoxy-2-methyl-1*H*-indole **(156)** (0.35 g, 1.5 mmol) in THF (10 cm^3) was added dimethyl sulfate (1.5 mol equiv., 0.28 g, 0.21 cm^3, 2.2 mmol) followed by sodium hydride (50% in oil, 2.4 mol equiv., 0.084 g, 2.2 mmol). The resulting mixture was stirred at room temperature under a constant flow of nitrogen for 18 h. The reaction was quenched with water (20 cm^3), extracted with diethyl ether (3 × 20 cm^3), combined organic layers dried with magnesium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (20% ethyl acetate- hexane) to afford **(157)** (0.35 g, 94%); R_f 0.54 (20% ethyl acetate-hexane).

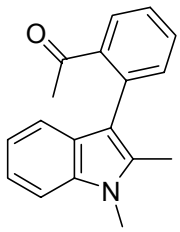
δ_H (400 MHz, CDC*l*$_3$, MeSi$_4$)

2.38 (3H, s, 2-CH_3), 3.61 (3H, s, N-CH_3), 3.87 (3H, s, OCH_3), 6.81-6.84 (1H, dd, *J* 2.4 and 8.8 6-H), 6.91-6.92 (1H, d, *J* 2.2, 4-H) and 7.09-7.12 (1H, d, *J* 8.8, 7-H).

δ_C (100 MHz, CDC*l*$_3$)

11.5 (2-CH_3), 30.3 (N-CH_3), 55.8 (OCH_3), 88.5 (3-C), 100.3 (4-CH), 109.8 (6-CH), 11.8 (7-CH), 127.1 (C-3a), 131.2 (7a-C), 134.5 (2-C) and 154.5 (5-C)

1-[2-(1,2-dimethyl-1H-indol-3-yl)phenyl]ethanone (158)



Boronic acid **(153)** (2 mol equiv. 0.29 g, 1.78 mmol) was dissolved in DMF (1.5 cm^3) and oxygen removed from the solution by three freeze-thaw cycles. The flask was transferred to an argon tent and 3-bromo-1,2-dimethyl-1*H*-indole **(155)** (0.2 g, 0.89 mmol), tribasic potassium phosphate (K_3PO_4) (3 mol equiv. 0.57g, 2.67 mmol) and

tetrakis(triphenylphoshine)palladium(0) (20 mol %, 0.21 g, 0.18 mmol) were added sequentially under an argon atmosphere. The reaction flask was sealed tightly and heated at 100 ^{o}C, for 65 h. After this time the reaction mixture was cooled followed by the addition of saturated solution of brine (10 cm^3). The reaction mixture was extracted with diethyl ether (4 × 15 cm^3), the organic extracts were combined and concentrated under reduced pressure. Purification of the residue by column chromatography (20% ethyl acetate-hexane) afforded the biaryl compound **(158)** as a yellow-brown oil (0.19 g, 83%), R_f 0.38 (20% ethyl acetate-hexane). Found (M^+ 263.1312, $C_{18}H_{17}NO$ requires 263.1310).

IR ν_{max}/cm^{-1}

3058w (=CH), 2890w (C-H), 1683s (C=O), 1614w (C=C) and 1238s (C-N).

δ_H (100 MHz, CDC*l*$_3$, $MeSi_4$)

1.88 (3H, s, 2-CH_3), 2.26 (3H, s, CH_3CO), 3.74 (3H, s, N-CH_3), 7.07-7.12 (1H, m, Ar-H), 7.18-7.24 (1H, m, Ar-H), 7.25-7.31 (1H, m, Ar-H), 7.37-7.44 (3H, m, Ar-H) and 7.50-7.64 (2H, m, Ar-H).

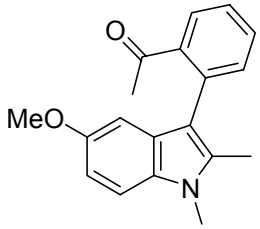
δ_C (400 MHz, CDC*l*$_3$)

10.9 (2-CH_3), 29.3 (N-CH_3), 29.8 ($\underline{C}H_3CO$), 108.8 (Ar-CH), 112.9 (Ar-C), 118.6 (Ar-CH), 120.0 (Ar-CH), 121.5 (Ar-CH), 126.8 (Ar-C), 127.4 (Ar-C), 128.0 (Ar-CH), 130.8 (Ar-CH), 132.1 (Ar-CH), 133.8 (Ar-CH), 134.6 (Ar-C), 136.7 (Ar-C), 142.2 (2-C) and 205.0 ($CH_3\underline{C}O$), (one quaternary not observed).

m/z(%)

263 (M^+, 100), 262 (11), 249 (14), 248 (68), 245 (16), 234 (10), 233 (21), 220 (9), 218 (14), 204 (16), 178 (9), 144 (10) and 102 (5).

1-[2-(5-methoxy-1,2-dimethyl-1H-indol-3yl)phenyl]ethanone (159)



Boronic acid **(153)** (2.0 mol equiv. 0.26 g, 1.6 mmol) was dissolved in DMF (2 cm^3) and oxygen removed from the solution by three freeze-thaw cycles. The flask was transferred to an argon tent and 3-bromo-5-methoxy-1,2-dimethyl-1*H*-indole **(157)** (0.20 g, 0.79 mmol), tribasic potassium phosphate (K_3PO_4) (3.0 mol equiv. 0.50 g, 2.4 mmol) and tetrakis(triphenylphoshine)palladium (0) (20 mol %, 0.18 g, 0.16 mmol) were added sequentially under an argon atmosphere. The reaction flask was sealed tightly and heated at 100 ^oC, for 65 h. After this time the reaction mixture was cooled followed by the addition of saturated solution of brine (15 cm^3). The reaction mixture was extracted with diethyl ether (4 × 20 cm^3), the organic extracts were combined and concentrated under reduced pressure. Purification of the residue by column chromatography (20% ethyl acetate-hexane) afforded the biaryl compound **(159)** as a yellow-brown oil (0.19 g, 80%), R_f 0.38 (20% ethyl acetate-hexane). Found (M^+ 293.1407, $C_{19}H_{19}NO$ requires 293.1416).

IR ν_{max}/cm^{-1}

3001w (=CH), 2940 (C-H), 1684s (C=O), 1617w (C=C), 1265 (C-O) and 1159 (C-N).

δ_H (400 MHz, $CDCl_3$, $MeSi_4$)

1.89 (3H, s, 2-CH_3), 2.24 (3H, s, CH_3CO), 3.71 (3H, s, N-CH_3), 3.78 (3H, s, OCH_3), 6.48-6.88 (2H, m, Ar-H), 7.20 (1H, d, *J* 9.5, 7-H), 7.25-7.48 (2H, m, Ar-H) and 7.52-7.65 (2H, m, Ar-H).

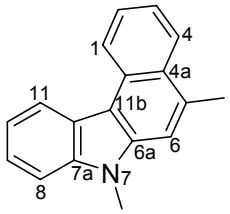
δ_C (100 MHz, CDCl_3)

10.9 (2-CH_3), 29.7 ($\underline{C}H_3CO$), 29.8 (N-CH_3), 55.8 (OCH_3) 100.4 (6-C), 109.5 (4-C), 111.4 (Ar-CH), 112.6 (Ar-C), 126.6 (ArCH), 127.6 (Ar-C), 128.0 (Ar-CH), 130.8 (Ar-CH), 131.9 (Ar-CH), 133.8 (Ar-C), 135.0 (7a-C), 142.1 (2-C), 154.6 (5-C) and 205.1 ($CH_3\underline{C}O$).

m/z(%)

293 (M^+, 100), 278 (35), 263 (8), 247 (5), 206 (8), 165 (5) and 117 (3).

5,7-Dimethyl-7H-benzo[c]carbazole (160)



1-[2-(1,2-dimethyl-1*H*-indol-3-yl)phenyl]ethanone **(158)** (96 mg, 0.36 mmol) was dissolved in DMF (4 cm^3) at 80 ^oC. To the resulting solution was added ^{t}BuOK (4 mol equiv., 0.164 mg, 1.46 mmol). The resulting reaction mixture was stirred at 80 ^oC and irradiated with a high pressure mercury lamp through a quartz filter for 10 mins. After this time, the reaction was quenched with water (15 cm^3), extracted with ether (3 × 20 cm^3) and the organic fractions were combined. The fractions were dried with magnesium sulfate, concentrated under reduced pressure and the residue purified by column chromatography (20% ethyl acetate-hexane) to afford **(160)** as yellow crystals (63 mg, 71%), R_f 0.5 (20% ethyl acetate-hexane) Found (M^+ 245.1198, $C_{18}H_{15}N$, requires 245.1204).

m.p 112 ^{o}C

IR ν_{max}/cm^{-1}

2932s (=CH), 2854s (C-H), 1616 m (C=C) and 1256m (C-N).

δ_H (400 MHz, CDCl_3, MeSi$_4$)

2.79 (3H, s, Ar-CH$_3$), 3.79 (3H, s, N-CH$_3$), 7.31-7.40 (2H, m, 2×ArH), 7.40-7.48 (3H, m, 3×Ar-H), 7.65-7.69 (1H, m, Ar-H), 8.08 (1H, d, *J* 8.4, Ar-H), 8.50 (1H, d, *J* 8.0, Ar-H) and 8.77 (1H, d, *J* 8.2, Ar-H).

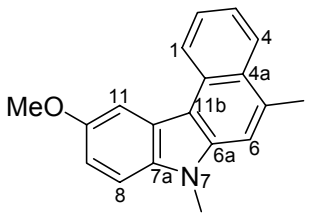
δ_C (100 MHz, CDCl_3)

20.6 (Ar-CH$_3$), 29.0 (N-CH$_3$), 108.9 (9-C), 111.2 (11-C), 113.4 (Ar-C), 119.6 (Ar-C), 121.6 (Ar-CH), 122.5 (Ar-CH), 123.5 (Ar-CH), 123.5 (Ar-CH), 123.6 (Ar-CH), 125.2 (Ar-CH), 126.5 (Ar-CH), 128.2 (Ar-CH), 130.2 (Ar-C), 133.4 (Ar-CH), 138.2 (Ar-C) and 139.6 (Ar-C).

m/z (%)

245 (M$^+$, 100), 244 (26), 230 (7), 202 (5), 122 (9), 115 (3) and 108 (3).

10-Methoxy-5,7-dimethyl-7H-benzo[c]carbazole (161)



1-[2-(5-Methoxy-1,2-dimethyl-1*H*-indol-3-yl)phenyl]ethanone **(159)** (114 mg, 0.48 mmol) was dissolved in DMF (4 cm^3) at 80 ^oC. To the resulting solution was added ^{t}BuOK (4 mol equiv., 0.21 g, 1.9 mmol). The resulting reaction mixture was stirred at 80 ^oC and irradiated with a high pressure mercury lamp through a quartz filter for 10 mins. After this time, the reaction was quenched with water (15 cm^3), extracted with ether (3 × 20 cm^3) and the organic fractions were combined. The fractions were dried with magnesium sulfate, concentrated under reduced pressure and the residue purified by column chromatography (20% ethyl acetate-hexane) to afford **(161)** as yellow crystals (92 mg, 70%), R_f 0.5 (20% ethyl acetate-hexane) Found (M^+ 275.1308, $C_{19}H_{17}NO$, requires 275.1310).

m.p 120 ^oC

IR ν_{max}/cm^{-1}

3016s (=CH), 2953s (C-H), 1608m (C=C), 1374m (C-N) and 1262s (C-O).

δ_H (400 MHz, CDCl_3, MeSi$_4$)

2.84 (3H, s, Ar-CH_3), 3.88 (3H, s, N-CH_3), 4.01 (3H, s, OCH_3), 7.11 (1H, dd, *J* 8.8 and 2.3, 9-H), 7.37-7.51 (3H, m, 3×Ar-H), 7.68-7.72 (1H, m, Ar-H), 8.00 (1H, d, *J* 2.2, Ar-H), 8.11 (1H, d, *J* 8.3, Ar-H) and 8.71 (1H, d, *J* 8.2, Ar-H).

δ_C (100 MHz, CDCl_3)

20.7 (Ar-CH_3), 28.9 (N-CH_3), 56.3 (OCH_3), 105.1 (9-C), 109.4 (11-C), 111.4 (Ar-CH), 112.5 (Ar-C), 113.1 (Ar-C), 122.4 (Ar-CH), 123.3 (Ar-CH), 123.7 (Ar-C), 125.3 (Ar-CH), 126.5 (Ar-CH), 128.1 (Ar-C), 128.8 (Ar-C), 133.4 (Ar-C), 134.9 (Ar-C), 138.8 (Ar-C) and 154.1 (10-C).

m/z(%)

275 (M^+, 100), 261 (10), 260 (39), 232 (30), 217 (9), 137 (12), 116 (8) and 115 (7).

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