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Towards the synthesis of new novel chromophores

Smith, Neil Adrian

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Towards The Synthesis of New Novel Chromophores

submitted by Neil Adrian Smith
for the degree of PhD
of the University of Bath
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Firstly, I would like to thank my supervisor, Professor Malcolm Sainsbury for his support, advice and encouragement during my time at Bath. I would also like to thank my industrial sponsors, Ciba-Geigy, for their financial support.

I would also like to thank the members of the MS and MMC groups past and present for making it an enjoyable three years. I would especially like to thank the members of the lab 4-12, Dr. Dave Brown, Dr. Ali Ninan, Dr. Deradji Boumrah, Max Liu and Virginia Wood for the friendly and relaxed atmosphere in which we all managed to work together.

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Finally, I would like to say thank you to Judith for her love, support, proof reading and patience during the writing-up period.

^tBoc	*tert*-Butoxycarbonyl
br	Broad
Bzl	Benzyl
CDI	Carbonyl diimidazole
CuTC	Copper thiophene-2-carboxylate
d	Doublet
DIC	2-Diisopropylaminoethyl chloride
DMAP	*N,N*-Dimethyl-4-aminopyridine
DME	Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DPP	1,4-Diketo-3,6-diarylpyrolo[3,4-c]pyrrole
dppf	Diphenylphosphinoferrocene
HOBT	1-Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
NBS	*N*-bromosuccinimide
NMP	*N*-Methylpyrrolidinone
ppm	Parts per million
s	Singlet
t	Triplet
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethyl silane

INTRODUCTION

ELECTRONIC TRANSITIONS

Absorption of light that gives rise to an excitation of an electron from a bonding π-molecular orbital to an anti-bonding π^*-molecular orbital is referred to as a π-π^* transition. 1,3-Butadiene has an intense absorption band at 217 nm, λ_{max}, that results from an excitation of an electron from π_2 having one node, to π_3 having two. 1,3,5-Hexatriene absorbs at a longer wavelength, $\lambda_{max} = 258$ nm, so it takes less energy to promote an electron from π_3, the highest occupied π-molecular orbital of hexatriene which has two nodes, to π_4 that has three nodes. The lowest energy transition of 1,3,5,7-octatetraene is at 320 nm, whereas ethylene has $\lambda_{max} = 175$ nm. It can be seen from this trend that the longer the chain of conjugation, the longer the wavelength of absorption. The highly conjugated hydrocarbon *trans*-β-carotene has eleven double bonds in conjugation. This should give rise to λ_{max} of a still longer wavelength if the above theorem holds true. Its ultraviolet spectrum in solution shows two intense absorptions at 483 nm and 453 nm. These absorptions are now in the visible region of the spectrum and correspond to blue to blue-green light. Since light of this colour is absorbed by the molecule, β-carotene appears yellow to orange in colour in solution, the complementary colour for the wavelength.

The main part of a molecule that absorbs light is normally referred to as a chromophore, and is usually unsaturated or aromatic in nature. Other groups attached to the chromophore containing non-bonded electrons that can overlap with the π-system of the chromophore are referred to as auxophores, and modify the position of λ_{max} through conjugation.

Extending the conjugation of a system usually leads to an absorption of light of a longer wavelength, for example ethylene has λ_{max} = 180 nm, and 1,3-butadiene has λ_{max} = 217 nm. This shift towards the red end of the spectrum is known as a bathochromic shift. This shift occurs as the molecular orbitals of the two chromophores mix to form a new set of molecular orbitals for the new molecule. In the new molecule, the energy gap between the HOMO and LUMO has been reduced, corresponding to a longer wavelength of light. In this example, the energy gap between the HOMO and LUMO in 1,3-butadiene is less than that found in ethylene. In opposition to bathochromic shifts are hypsochromic shifts. Here λ_{max} is shifted to a shorter wavelength of light, resulting from an increase in the energy gap between the HOMO and LUMO of the chromophore.

COLOUR

The visible spectrum is between 400-750 nm in the electromagnetic spectrum. When molecules absorb in this region, then we perceive the complementary colour as shown in Table 1.

Wavelength of light, nm	Colour	Complementary colour
400-430	Violet	Green-yellow
430-480	Blue	Yellow
480-490	Green-blue	Orange
490-510	Blue-green	Red
510-530	Green	Purple
530-570	Yellow-green	Violet
570-580	Yellow	Blue
580-600	Orange	Green-blue
600-680	Red	Blue-green
680-750	Purple	Green

Table 1

Most organic molecules tend to absorb light in the ultraviolet region (200-400 nm) of the spectrum and are colourless or white. Some compounds appear to be yellow even though their λ_{max} is in the ultraviolet region. In these cases a "tail" of an absorption band stretches into the visible region of the spectrum. The light absorbed by the molecule is violet or blue, so we see the complementary colour of yellow. In organic compounds, electronic absorptions are usually π-π* or n-π*, so therefore the colour of such systems is a property of the π-system of the molecule. If the absorption band of the molecule is sharp, then the colour is seen as bright and clean. If however the absorption band is broad, or more than one band is present, then the colour tends to be dull.

DYES AND PIGMENTS

Dyes are colouring matters that will bind in some way to a substrate, usually a fibre or cloth, and are fast to light and washing. Pigments are defined as substances being highly coloured, yet being particulate and practically insoluble in most solvents and also the media into which it is being incorporated. Dyes have found uses for thousands of years. Although the first dyes were of natural origin, today nearly all are synthetic. There are different methods of combining the dye with the fibre, some of the main methods are outlined below.

Indigo (1) is the most common form of a **vat** dye. It is the woad of ancient Britain, and is a highly insoluble blue coloured compound. A warm suspension of indigo with other materials is allowed to ferment for several days. This results in a reduced "leuco" form (2) which is soluble and colourless. The material to be treated is then immersed in the solution, and exposed to air to reoxidise the leuco base. Today indigo is treated with sodium hydrosulfite to reduce it to the leuco form, and can be reoxidised with a number of oxidising agents which act more quickly than exposing the material to air.


Indigo (1)   Leuco form (2)
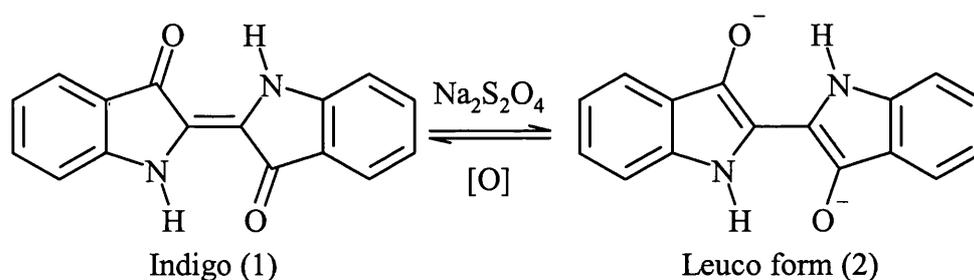
Mordant dyes, (L. *Mordere*, to bite), are used in conjunction with a metal salt that forms an insoluble complex with the dye. The dye is applied to a cloth that has been pretreated with a metal salt. An example from the ancient world was the extract of the madder root, which was mordanted with aluminium salts to produce a colour known as turkey red. Different metal salts produce different colours. The dye that co-ordinates to the metal is alizarin (3), which was first synthesised in 1869. This consequently led to a decrease in the production of natural alizarin.

Alizarin (3)
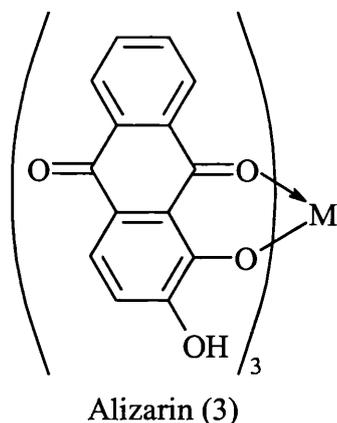
Direct dyes can be applied directly to the fibre from an aqueous solution. This process is especially applicable to wool and silk. Both of these fibres are proteins that incorporate both acidic and basic groups that can combine with basic and acid dyes respectively. One of the most well known dyes of this class is mauve (4), which started the modern synthetic dye industry.

Mauve was discovered by William Henry Perkin in 1856, whilst at the Royal College of Chemistry. He treated aniline sulfate with sodium dichromate and obtained a black coloured precipitate, from which he extracted a purple coloured compound. The

compound showed promise as a dye and he resigned his position to manufacture it. Not long after Perkin started to produce the dye, additional synthetic dyes emerged from German laboratories. Soon almost all synthetic dyes came from Germany. However, Perkin had found this compound by mistake. The aniline that he had used had come from nitration of benzene followed by reduction. Unbeknown to him, the benzene that he had used was contaminated with substantial amounts of toluene, giving rise to the unexpected product.
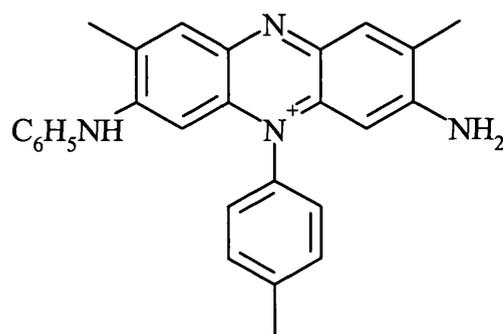
Mauve (4)

Mauve is an example of a basic dye that can ion-pair with acidic centres of the fibre.

Disperse dyes are used as aqueous dispersions of finely divided dyes or colloidal suspensions. These form solid solutions of the dye within the fibre. They are useful for synthetic polyester fibres, which do not contain acidic or basic groups and are also sensitive to hydrolysis under the strongly alkaline conditions of vat dyeing. The disadvantage of such dyes is that they tend to lack fastness to washing, tend to sublime on ironing and are prone to fading with nitrogen dioxide or ozone in the atmosphere, a condition known as gas fading.

Dyes can also be classified on the basis of their chemical nature. These usually contain a functional group that is principally involved in the n-π* and π-π* transitions. Examples of such groups is the azo group -N=N-, the carbonyl group in quinones and extended chains of conjugation.

Azo dyes form the largest class of dyes. They consist of a diazotised amine coupled to an amine or phenol and have one or more azo linkages. An example of a diazo dye is direct blue 2B (5), formed by coupling tetrazotised benzidine with H-acid (8-amino-1-naphthol-3,6-disulfonic acid) in alkaline solution. If H-acid is coupled with a diazonium ion in dilute acid solution, the coupling occurs *ortho-* to the amino group. This gives rise to the possibility of coupling either position to different diazonium salts.

Direct Blue 2B (5)
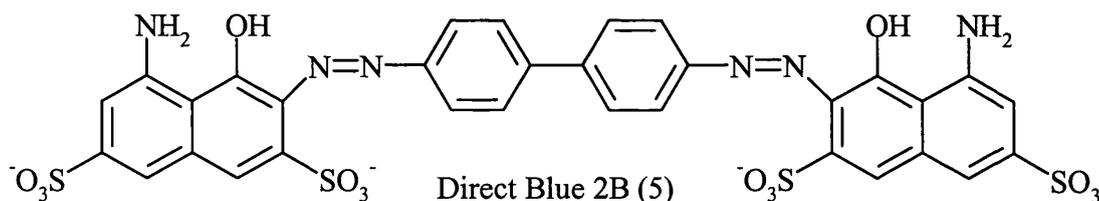
Triphenylmethane dyes are derived from the triphenylmethyl cation. They are basic dyes and suitable for silk and wool. Malachite green (7) is an example, prepared from condensing benzaldehyde with dimethylaniline and then oxidising the leuco base.
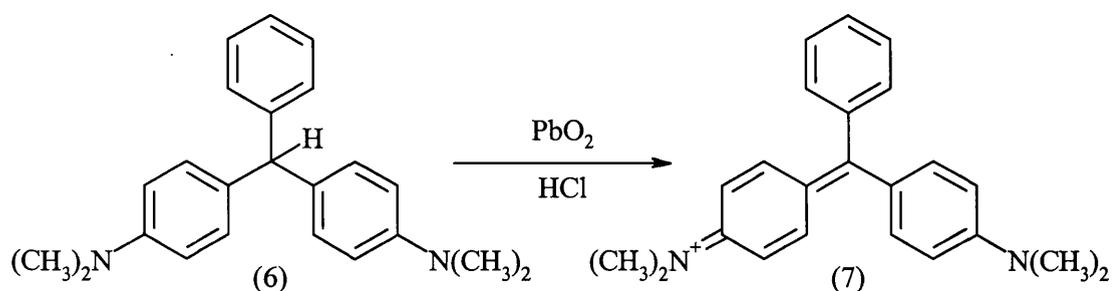
Anthraquinone dyes are generally vat dyes, as shown by alizarin. More complex dyes can be produced by dimerizing molecules containing the anthraquinone core, hence extending the conjugation of the system.
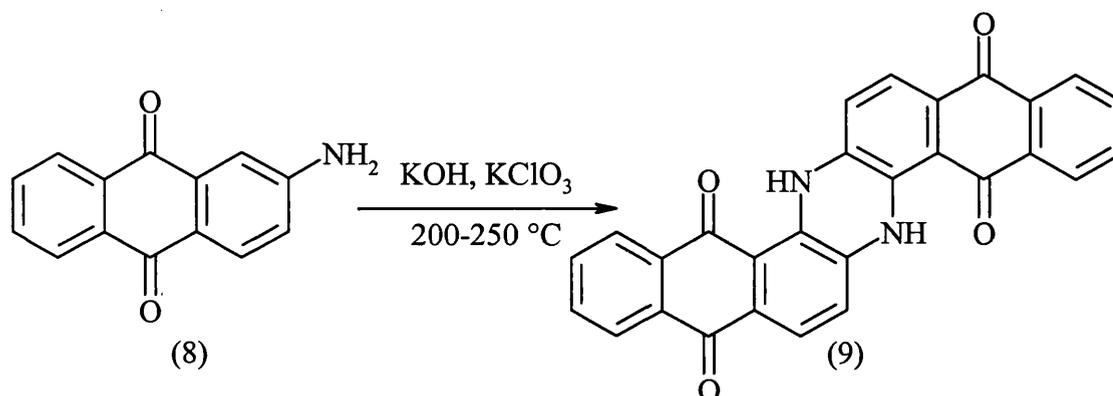
Indigoid dyes are also vat dyes based on the indigo skeleton. 6,6'-Dibromoindigo (10) was known as Tyrian purple in the ancient world. It was extracted from a family of molluscs, and hence was restricted to the wealthy.

Tyrian Purple (10)
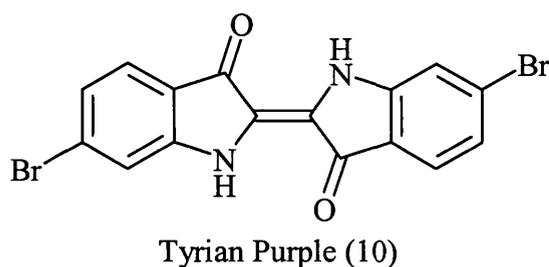
Azine dyes are derivatives of phenoxazine, phenothiazine or phenazine. Mauve is an example of a phenazine based dye. Methylene blue (11) is a thiazine derivative used as a bacteriological stain.
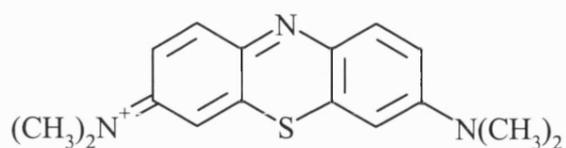
Methylene Blue (11)

Phthalocyanines are used as pigments rather than dyes. An important member of this group is copper phthalocyanine (12), a brilliant blue pigment used in writing ink. It can easily be prepared by heating phthalonitrile with copper.
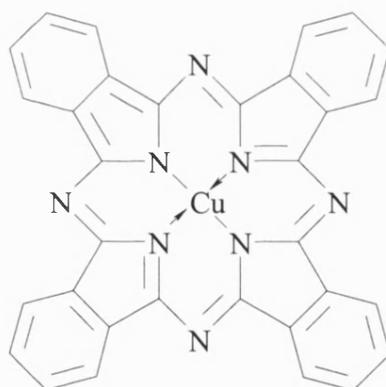
Copper Phthalocyanine (12)

A recent addition to the pigments are the 1,4-diketo-3,6-diarylpyrrolo[3,4-c]pyrroles. The underlying 1,4-diketo-3,6-diarylpyrrolo[3,4-c]pyrrole, DPP, chromophoric system in these pigments combine the elements of indigo-like cross-conjugated vinylogous amidic and vinylogous hydrazine units in a rigid planar structure (13).
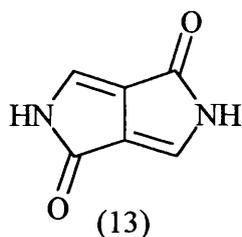
The first synthesis of a molecule incorporating the DPP skeleton was in 1974 by

Farnum[1], who, whilst attempting to synthesise 2-azetines, inadvertently isolated a

small amount of the diphenyl DPP derivative (16), scheme 1.
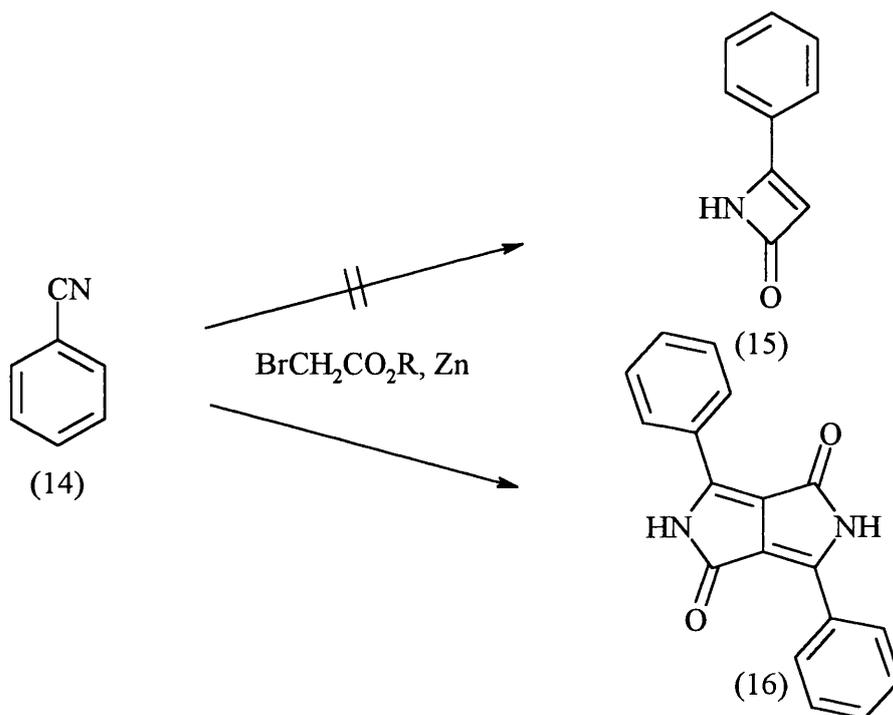
Scheme 1

Later investigations by Ciba-Geigy showed that the DPP structure could have potential

as a pigment. It was found that different substituents at the *meta-* and *para-* positions

of the phenyl ring attached to the DPP structure gave a broad spectrum of colours,

ranging from orange-yellow *via* blue-red to violet. Despite the low molecular masses

of the DPP pigments, they are highly insoluble and also highly resistant to chemicals

and heat[2]. Such properties may be attributed to strong intermolecular bonding forces

(e.g. H-bonding, Van der Waals contact, π-π interactions between molecular planes) in

the pigment crystal lattice.

The Reformatsky synthesis of DPP as detailed by Farnum was found to be too low

yielding to warrant commercial production of the process. A simple elaboration of the

process however gave a commercially viable alternative[3], scheme 2.
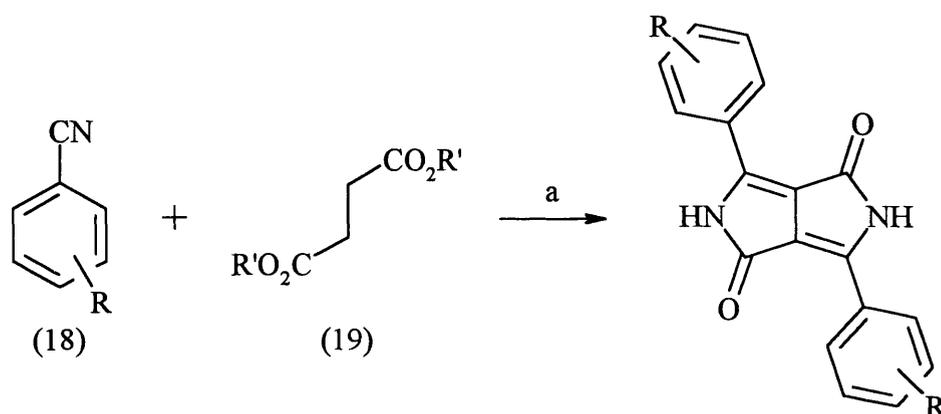
a) Base

Scheme 2

This method also enables a variety of compounds to be synthesised easily by varying

the nature of the R group in the starting cyanobenzene. The compound where R=Cl is

an important pigment known as Pigment Red 254 (20), which is highly stable to light,

heat and chemicals, and has found use as an automotive finish.
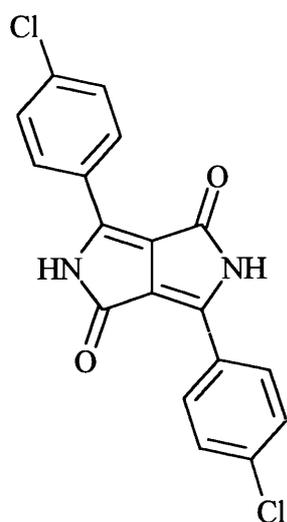
Pigment Red 254 (20)

The structural properties of the DPP pigments (extended conjugation, carbonyl and NH moieties) were considered important in the design of a new class of pigments. The design of the new class of pigments was to augment compounds such as the DPP family rather than to replace them. The class of compounds that we were to investigate was based on a central chromophoric unit (21) as was the case of the DPP pigments.
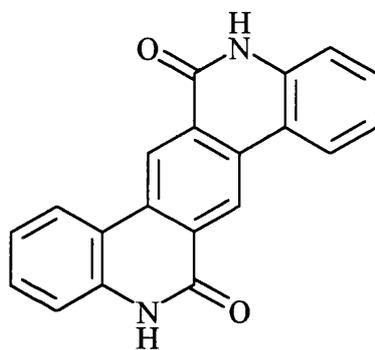
(21)

ARYL-ARYL COUPLING REACTIONS

All the early examples of dyes and pigments have a common element; they all contain an aromatic structure. This is because of the inherent conjugation associated with such systems. The structures we were interested in synthesising were also based on aromatic systems, but with aryl units directly bonded together. It was hoped that a carbon-carbon bond would be stronger than either a carbon-nitrogen or carbon-sulfur bond found in some of the examples. A stronger bond would be more stable to the conditions that would cause other pigments to break down and gradually lose their colour.

Average Bond Energies, kcal/mol

	C	N	S
C	348	305	272
N	305	163	
S	272		255

Bond Dissociation Energies, kcal/mol

	NH_2	CH_3	C_6H_5
CH_3	356	377	427
C_2H_5	343	360	410
C_6H_5	427	427	481

Conventional methods for synthesising aryl-aryl bonds are usually only suitable for the production of homo-coupled products[4,5]. The Ullmann coupling[6] is a well-known example where an aromatic halide is heated to a high temperature in the presence of copper, scheme 3.
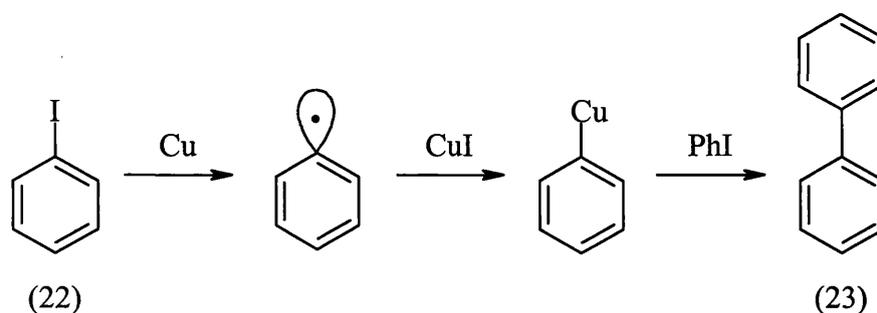
Scheme 3

The first stage of the reaction is thought to be the formation of an aryl cuprate, which reacts with another molecule of aryl halide to form the biaryl. The second stage is indiscriminate, so therefore is unsuitable for synthesising hetero-coupled products.

More modern techniques have been developed for the synthesis of cross coupled products and require more complicated starting materials than simple aryl halides. Three examples are described, the Suzuki coupling reaction, the Stille coupling reaction and oxazoline chemistry by Albert Meyers. Each different method has its advantages and disadvantages. The Suzuki and Stille coupling procedures both rely upon the use of palladium catalysts, whereas the oxazoline chemistry is independent of any catalyst.

THE SUZUKI COUPLING REACTION
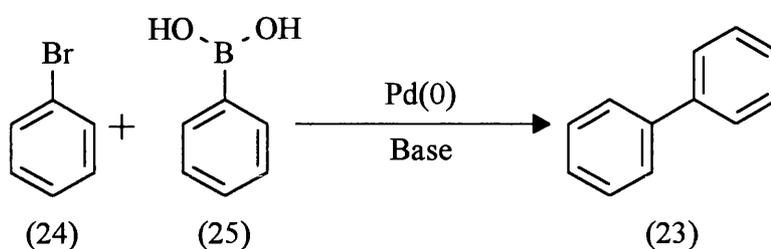
Scheme 4

Suzuki discovered that arylboronic acids undergo palladium catalysed cross couplings with aryl bromides in the presence of base[7], scheme 4. The advantage of this system is that the reagents are easy to handle compared to previous methods that involved the direct coupling of highly reactive organometallic reagents, Grignards for example. Boronic acids are air stable and are of low toxicity. The Stille coupling reaction is similar to the Suzuki reaction, but uses toxic organotin reagents, which would make the procedure less attractive to perform on a large scale. Also the Suzuki reaction can be performed in the presence of a variety of functional groups.

The original work by Suzuki used 3 mole % *tetrakis*-(triphenylphosphine) palladium(0) as the catalyst and 2 equivalents of aqueous sodium carbonate as the base.

A catalytic cycle for the reaction has been proposed by Martin and Yang[8], scheme 5.

Ar-Ar'   Ar'-X

Pd(0)

Ar-Pd-Ar'   Ar'-Pd-X

B(OH)$_3$ Na$^+$

Ar'PdOH

ArB(OH)$_2$ $\xrightarrow{\text{-OH}}$ ArB$^-$(OH)$_3$ NaX
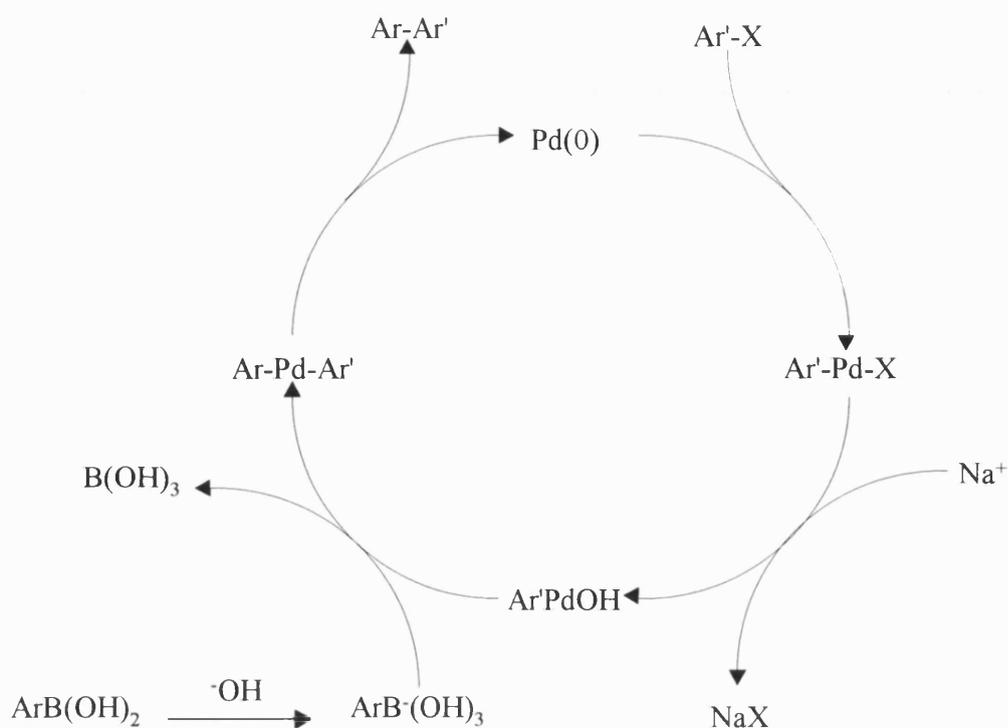
Scheme 5

The mechanism of the reaction has been studied in detail[9]. Aryl bromides are commonly used as the electrophilic species, but other halides have also been used in the reaction. Iodides are more reactive than the bromides and chlorides have been found to be less reactive. Triflates have also been used successfully, being slightly less reactive than iodides. Variations in the procedure also include varying the palladium catalyst and the choice of base. Other palladium sources include *bis*-(triphenylphosphine) palladium dichloride, *bis*-(acetonitrile) palladium dichloride and palladium acetate-tri(*o*-tolyl)phosphine. Alternative bases include potassium carbonate, sodium bicarbonate and triethylamine-DMF. Suzuki showed that the use of stronger bases such as ethoxide and hydroxide were less effective in the reaction and gave a lower yield.

An example of the Suzuki coupling reaction is in the synthesis of Hippadine (28)[10],

scheme 6.

(26)   (27)   (28)
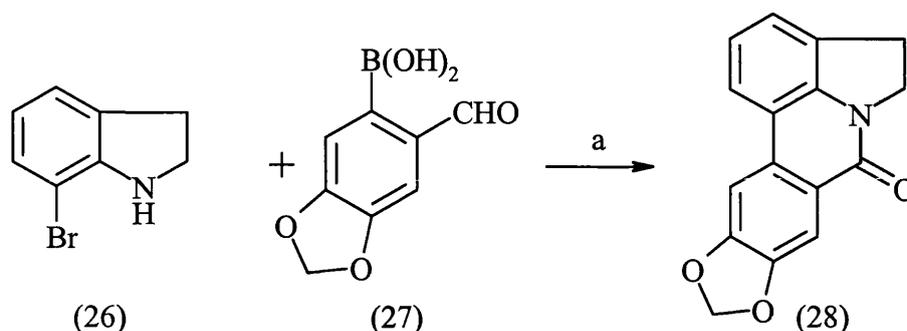
a) Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, DME, Δ

Scheme 6

The yield for coupling reaction is 45 % and the overall yield for Hippadine is 24 %.

The scope of the reaction has been reviewed recently[11], but the reaction is finding

newer applications. Combinatorial chemistry was originally a tool for the mass

production of peptide libraries. The trend is now towards using more traditional

chemistry in the high output robots that were designed by the combinatorial chemist.

Piettre and Baltzer published a method of attaching iodobenzoic acid to a solid

support and preparing a boronate *in situ*, scheme 7.

P—NH$_2$ a   b

(29)   (30)
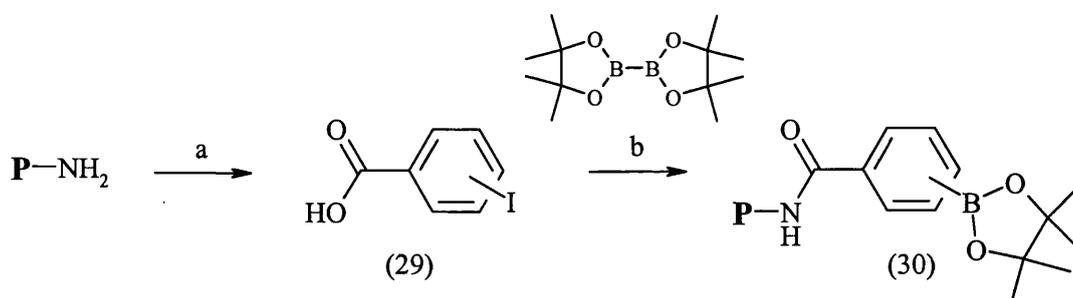
a) DIC, HOBT, DMF; b) PdCl$_2$(dppf), KOAc

Scheme 7

With the boronate made from the alkyldiboron *via* a palladium catalysed reaction, the

Suzuki coupling can now be performed followed by release from the resin, scheme 8.

a) $Pd(PPh_3)_4$, K_3PO_4, DMF, 80 °C; b) $TFA\text{-}CH_2Cl_2$ (1:4)
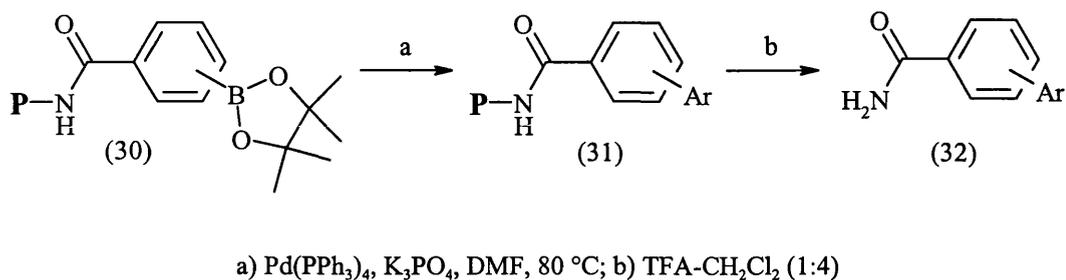
Scheme 8

The incorporation of boron into the molecule as the pinacol boronate ester has

previously been reported[12].

Other developments of the reaction for use in combinatorial systems include the use

of different linkers to join the aromatic unit to the resin. The use of silicon as a linker

extends the possibilities when cleaving the biaryl product from the resin. The use of

different electrophiles to give *ipso*-substitution means that a greater diversity of

products can be produced by using the combinatorial approach, scheme 9.
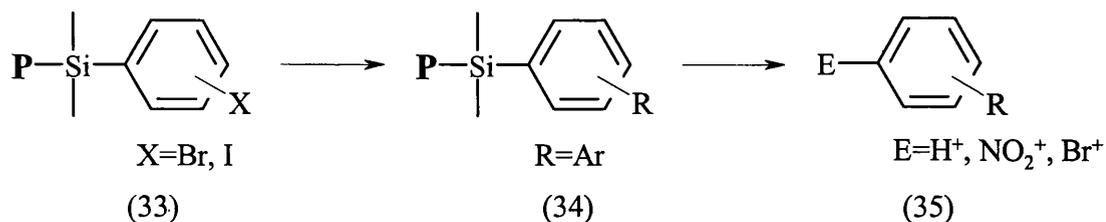
Scheme 9

An alternative way of performing the reaction is to use microwave radiation on the

tethered system, resulting in short reaction times and high yields[13], scheme 10.
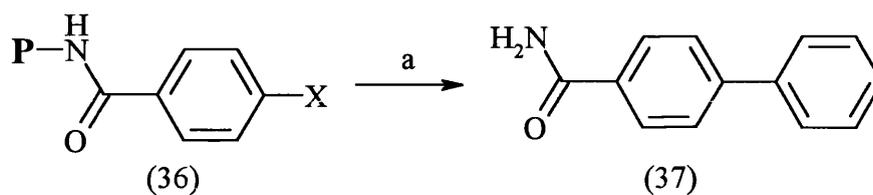
a) i) PhB(OH)$_2$, 3.8 min, 45 W; ii) TFA

Scheme 10

When X=I the yield is 98 % and where X=Br the yield is found to be 97 %. Methoxy-,

nitro- and halo- substituted aryl boronic acids have all been used successfully in the

system, all achieving comparable yields.

THE STILLE COUPLING REACTION
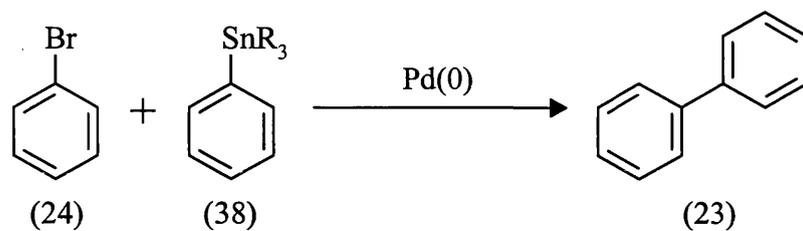
Scheme 11

In the Stille coupling reaction[14], an organo electrophile reacts with an organotin compound in the presence of a palladium catalyst to form a new carbon-carbon bond, scheme 11. A catalytic cycle can be proposed for the reaction, and is shown in scheme 12.
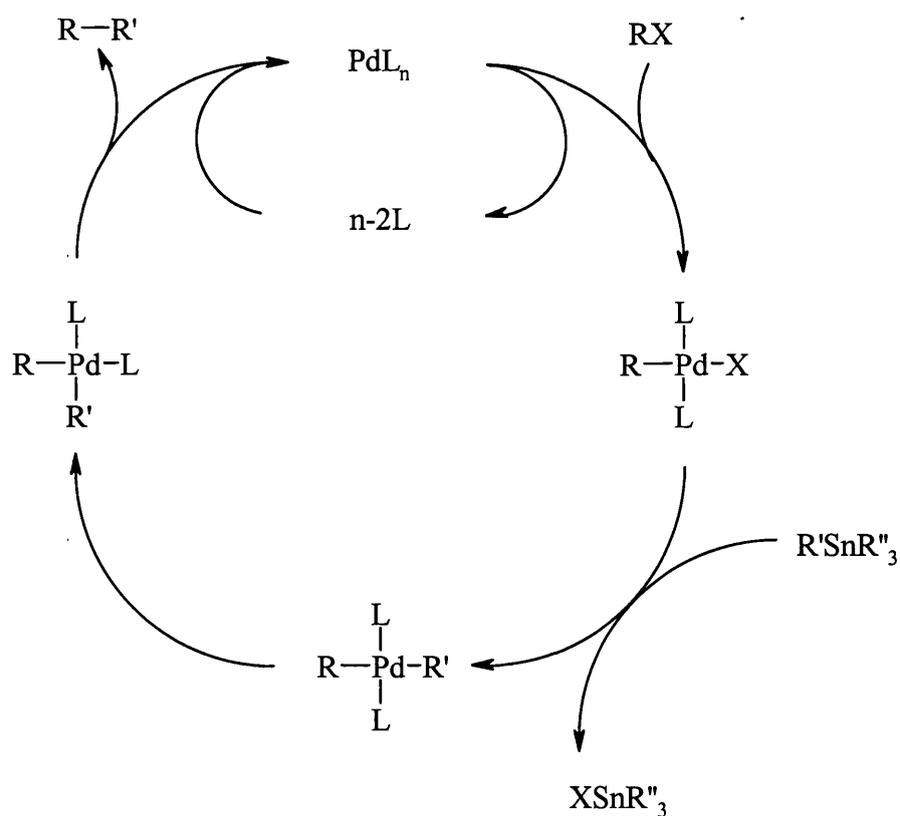
Scheme 12

In the palladium-catalysed coupling of organic electrophiles with organotin reagents, only one of the groups on tin enters into the coupling reaction.

This is not a problem if a relatively simple organic group, for example, methyl, is to be transferred, since tetramethyltin can be used. If the group is more expensive or difficult to synthesise, however, then the utilisation of only one of four identical groups would be a distinct disadvantage. Fortunately, different groups are transferred with different selectivities from tin, the simple alkyl group having the slowest transfer rate. Thus, an unsymmetrical organotin reagent containing three simple alkyl groups, such as methyl or butyl, is chosen; the fourth group that undergoes transfer, is usually an alkynyl, alkenyl, aryl, benzyl, or allyl group.

Hippadine (28) has also been synthesised *via* a Stille Coupling[15], in a similar reaction scheme to that shown for the Suzuki coupling, scheme 13.
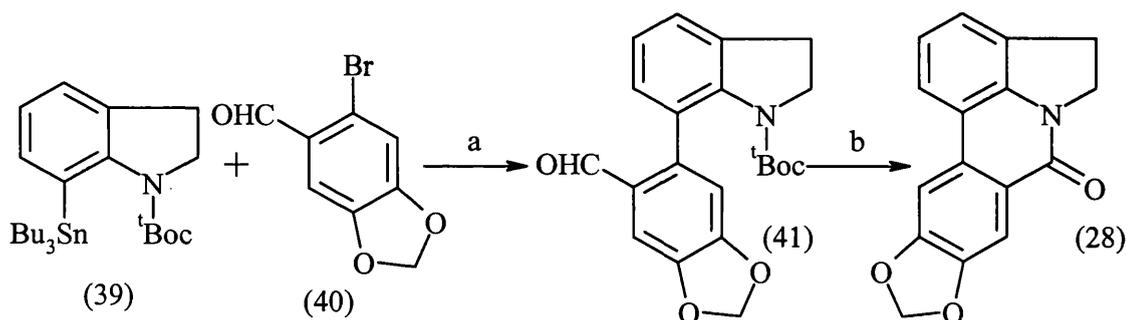
a) Pd(OAc)$_2$, P(*o*-Tol)$_3$, Et$_3$N, 63 %; b) i) conc. HCl; ii) Ag$_2$O, 80 %

Scheme 13

The yield for the Stille coupling reaction is 63 %, and for the deprotection and lactamisation 80 %, giving a yield for the two steps of 50 %. This yield is comparable with that of the corresponding Suzuki mediated transformation, as is the overall yield of 28 %.

MEYERS OXAZOLINE METHODS

(42)   (43)
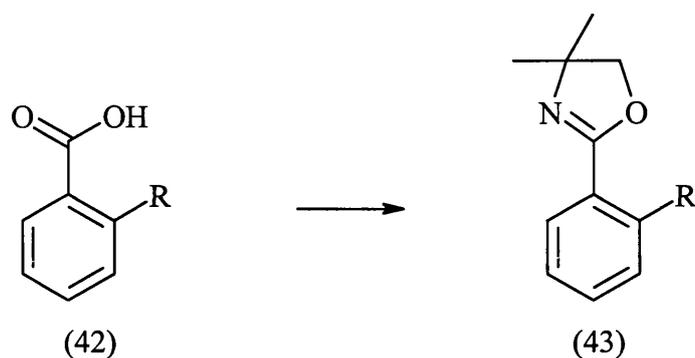
a) Thionyl chloride; b) 2-amino-2-methylpropan-1-ol; c) thionyl chloride, sodium hydroxide

Scheme 14

Scheme 14 shows the synthesis of the oxazoline group from the corresponding carboxylic acid. The nature of the R group present enables two transformations to be performed at the site. If a methoxy group is present in the *ortho-* position, nucleophilic substitution reactions can occur. If, however, there is no *ortho-*substituent present, then *ortho-*lithiation can occur at the position, which can be quenched with electrophiles. In both cases hydrolysis of the oxazoline group leads to 2-substituted benzoic acids.

NUCLEOPHILIC SUBSTITUTIONS

(44)   (45)
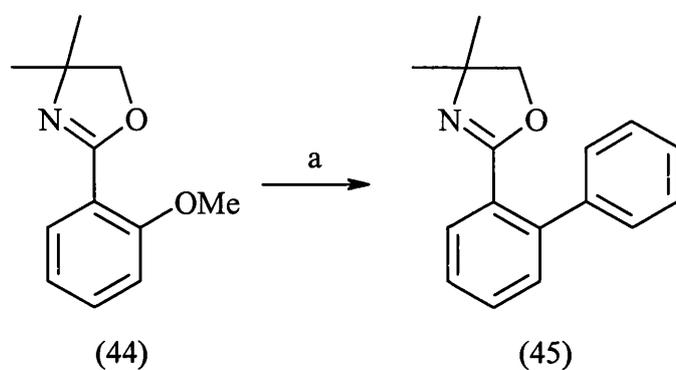
a) PhMgBr, THF

Scheme 15

Scheme 15 shows the simplest case of the nucleophilic substitution reaction, where the *ortho*-substituent is a methoxy group. Grignard reagents are commonly used as the nucleophile. The oxazoline group performs two functions in the transformation. It activates the reaction centre by making it more electrophilic and also acts as an additional directing complex for the incoming Grignard reagent, scheme 16.
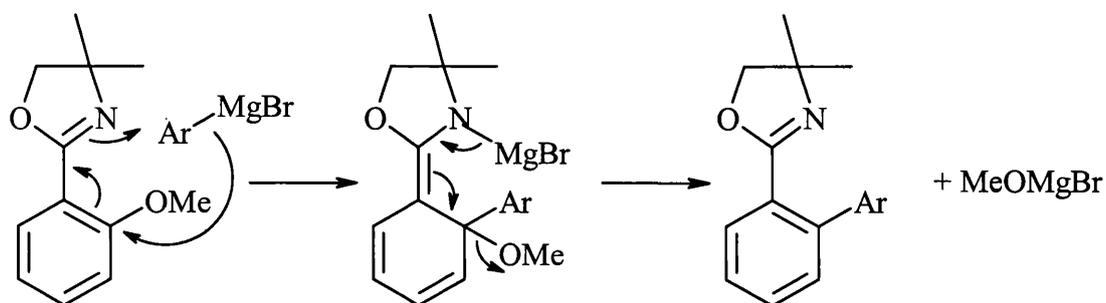
Scheme 16

METALLATION AND ELECTROPHILIC SUBSTITUTION

(46)   (47)
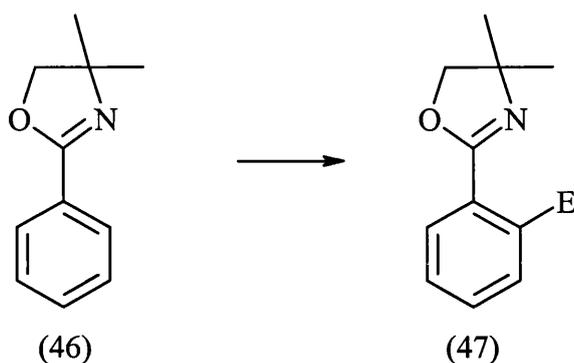
a) BuLi, E$^+$

Scheme 17

Scheme 17 shows the treatment of an unsubstituted oxazoline with butyllithium and subsequent quenching with an electrophile. The success of the *ortho*-lithiation procedure depends upon the ability of the oxazoline group to direct the lithiation. The use of the oxazoline as a directing group has been studied alongside the use of the benzamide group. The benzamide group has been found to be superior to the oxazoline group[16,17].
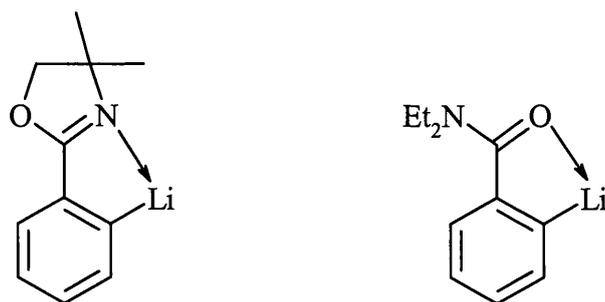
Scheme 18

It is believed that the slower rate of lithiation of the oxazoline may be due to the greater degree of strain in the lithiated products. In the o-lithiooxazoline, the lithiated species contains two five membered rings fused to benzene. This is not the case with diethyl benzamide, scheme 18.

Hippadine (28) has also been synthesised via Oxazoline mediated nucleophilic substitution chemistry[18], scheme 19.

a) Mg, THF, BrF$_2$CCF$_2$Br; b) i) H$_2$SO$_4$, EtOH; ii) Pd/C, H$_2$
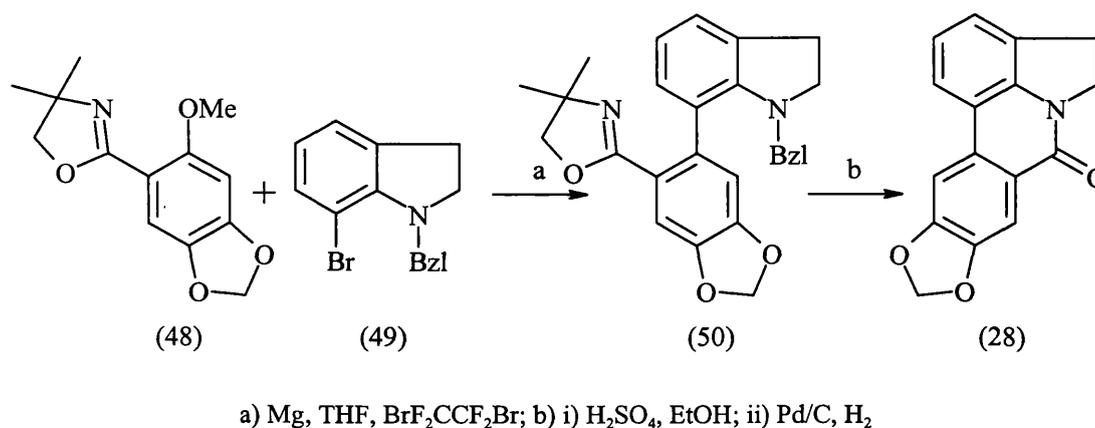
Scheme 19

The yield for the coupling reaction is 68 % and the deprotection and lactamisation 66 %, giving an overall yield for the transformation of 45 %. This is comparable with both the Suzuki (45 %) and the Stille (50 %) for the same transformation. The overall yield for the synthesis of Hippadine is 33 %, again comparable with the Suzuki (24 %) and the Stille (28 %) methodology.

CONCLUSIONS ON HETERO COUPLING REACTIONS

The syntheses of the reagents for the Suzuki and Stille couplings are usually similar and normally employ lithiation or Grignard chemistry to introduce the relevant functional groups necessary for the transformation. The Suzuki coupling employs aryl boronic acids and aryl halides in the presence of a palladium source. If the aryl boronic acid is to be synthesised, it is usually from an aryl halide by way of lithium-halogen exchange or treatment with magnesium to produce the corresponding Grignard reagent, followed by quenching with a boronic acid precursor. The nature of the boronic acid precursor is usually a trialkyl borate that is hydrolysed to the acid by aqueous acidic work up. An alternative is to use boron tribromide, which after hydrolysis also gives the boronic acid.

A similar approach is usually employed when synthesising reagents for the Stille coupling reaction. A trialkyl stannyl chloride is used to quench the lithio species, or Grignard reagent, to give the trialkyl stannyl derivative. Tributyl and trimethyl stannyl chloride are commonly used, but the butyl derivative is usually the preferred reagent as it is less volatile. The toxicity and volatility of tin compounds are an important consideration when contemplating the Stille coupling. The non-toxic nature of boronic acids makes the Suzuki coupling a more attractive proposition.

The oxazoline group can be used for protection of the carboxylic acid group, so it can be easily introduced and removed. Treatment of an acid chloride with an amino alcohol gives initially the amido alcohol and ring closure forms the oxazoline ring.

RESULTS AND DISCUSSION

The purpose of the investigations described in this thesis was to synthesise highly conjugated, light stable compounds which might act as pigments for automobile paints.

The targets selected were all polyaromatic compounds containing amide linkages of which the pentacycle (21) is the simplest example.
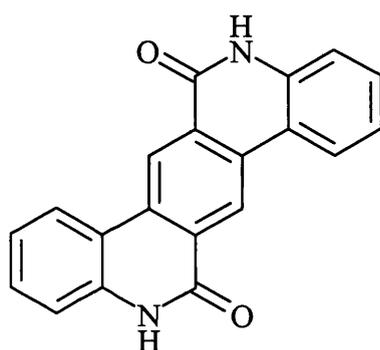
(21)

The pentacycle (21) was chosen because it is described in the literature as an insoluble yellow compound and simple quantum mechanical calculations indicate that substitution in the SW and NE rings by electron withdrawing groups would generate derivatives which have absorption maxima in the regions of the visible spectrum of interest to our industrial collaborators. Our work began with an attempted synthesis of (21) using the literature method[19].

This began an investigation into the synthesis of terphenyl systems, with a mind to produce a general methodology. We also looked at some syntheses of biaryl systems, some intentionally and others not. We hoped that some of the biaryl syntheses available could be extended to producing terphenyl systems as well.

THE ROUTE ACCORDING TO LAMBA AND TOUR

In the published method by Lamba and Tour[19], the construction of (21) is broken down into three operations. The first is the synthesis of methyl 2,5-dibromoterephthalate (54), then that of the boronic acid (57) and finally a coupling of (54) and (57) using Suzuki methodology.

STAGE 1

Scheme 20 shows the projected synthesis of methyl 2,5-dibromoterephthalate (54) from 2,5-dibromo-*p*-xylene, (51).
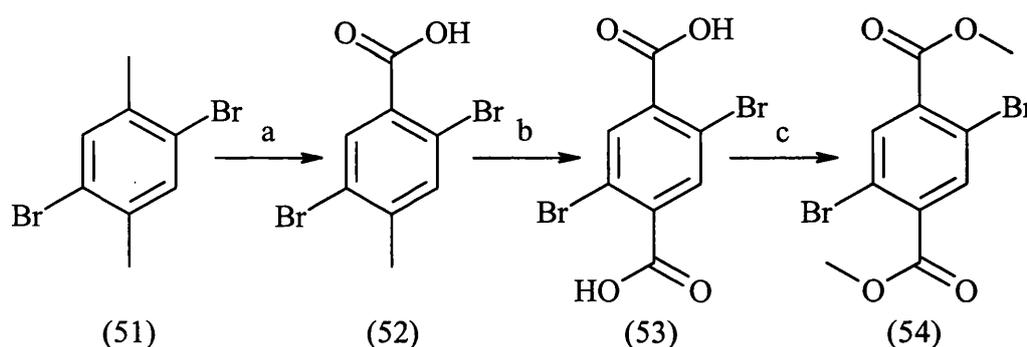
a) 30% HNO_3; b) $KMnO_4$; c) MeOH, H^+, 4Å Molecular sieves

Scheme 20

The key step is the oxidation of the methyl group of the starting bromoxylene. Lamba and Tour state that both methyl groups can be oxidised at once using potassium permanganate, but only in poor yield (3-19 %). Better results were obtained with

cobalt acetate/oxygen as reagents (53 %)[20], but surprisingly these authors settled for a two step operation using first 30% nitric acid to give the monoacid (52) in 35 % yield, and then potassium permanganate to complete the oxidation in a follow up yield of 75 %. In practice they claimed only a yield of 26 %. After these confusing remarks we found that by using the two step procedure we isolated the bromo acid (53) in only 16 % yield.

Lamba and Tour reported that 2,5-dibromo-*p*-xylene sublimed in the condenser during the first oxidation step. In our hands this was a major problem becoming severe whenever we attempted to overcome the low yields by scaling up the original procedure. In such cases the condenser attached to the reaction flask became completely blocked within a short time. In view of this the method was considered unsuitable and an alternative was sought.

STAGE 2

In parallel with the reactions of stage 1 we also began to assemble the boronic acid (57) by the route outlined in scheme 21.
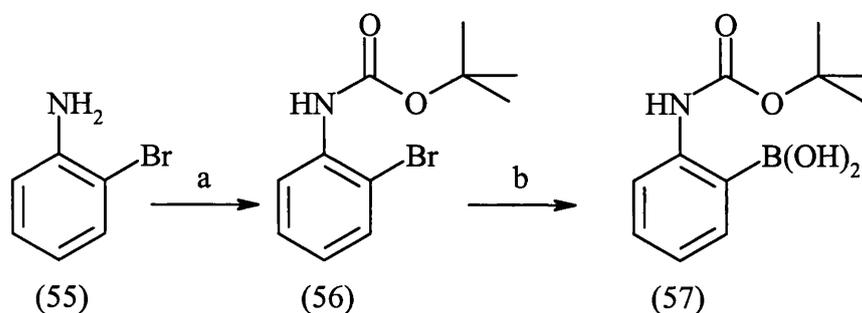
a) NaH, THF, ('BuOCO)$_2$O; b) MeLi, 'BuLi, THF, B(OMe)$_3$, H$_3$O$^+$

Scheme 21

The conversion of 2-bromoaniline (55) into the *ortho*-bromocarbamate (56) went well, although the yield obtained (73 %) was less than that reported (96 %) by Lamba and Tour. Deprotonation first with methyllithium followed by lithium-halogen exchange with 'butyllithium gave a golden yellow coloured solution that became colourless on treatment with trimethyl borate. The solution was then treated with aqueous hydrochloric acid (3 M) to release the boronic acid. However, attempts made to extract the boronic acid with diethyl ether failed. Even after adding sodium chloride in excess to the aqueous phase and further extraction all we obtained was a small amount of a yellow gummy material. Following Lamba and Tour's procedure again we attempted to refine this product by taking it up in 2M aqueous sodium hydroxide solution, reacidification with hydrochloric acid and re-extraction into diethyl ether. Removal of the organic solvent, however, simply afforded rather less than the same product that we had started with. Subsequently the impure material was used in the Suzuki coupling reaction just to see if this intractable substance contained any of the required boronic acid.

Clearly this procedure was very unsatisfactory and we subsequently learnt that workers at Ciba had experienced similar difficulties in attempting to repeat the published work. They too obtained a yellow gummy mixture that proved impossible to separate into pure compounds. The mass spectrum of this material did however exhibit a molecular ion peak at the mass expected for the boronic acid.

ATTEMPTS TO RESOLVE LAMBA AND TOUR'S WORK

It was now necessary to attempt to solve the problems inherent in both stages 1 and 2

of the above paper, since we felt that the basic approach was correct.

STAGE 1

2,5-Dibromo-*p*-xylene was still considered the best starting material to use, so initial

strategies were based upon it. Thus, bromination of the methyl groups followed by

hydrolysis and subsequent oxidation seemed a possible way of effecting access to the

dibromo-acid on a large scale, scheme 22.
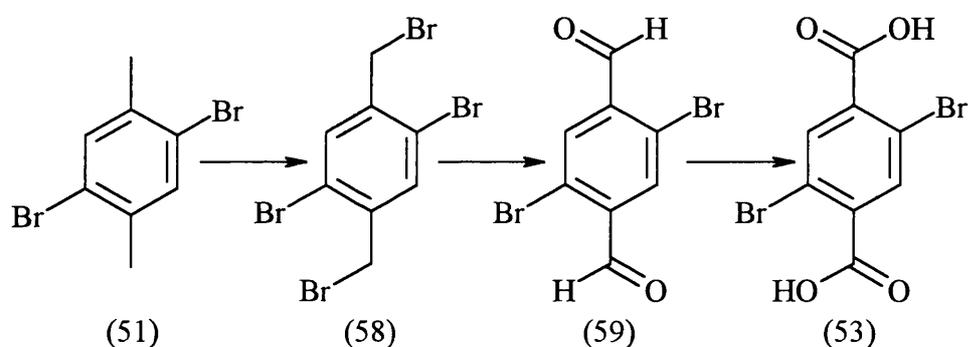
Scheme 22

The bromination of 2,5-dibromo-*p*-xylene with *N*-bromosuccinimide gave a mixture of

polybrominated compounds, which proved difficult to separate. We also noted that this

mixture was insoluble in either dichloromethane or ethanol, solvents in which we had

hoped to effect conversion of the 1,4-*bis*-(bromomethyl)benzene (58) into the aldehyde

(59) *en route* to the diacid[21,22].

As a result of this failure, direct oxidation of both methyl groups was re-evaluated. It

was reported that direct oxidation of (51) with potassium permanganate had worked

well but was low yielding (3-19 %). As a number of discrepancies in Lamba and Tour's

work had already been found we wondered if in this case a reappraisal of the oxidation

might yield in our favour.
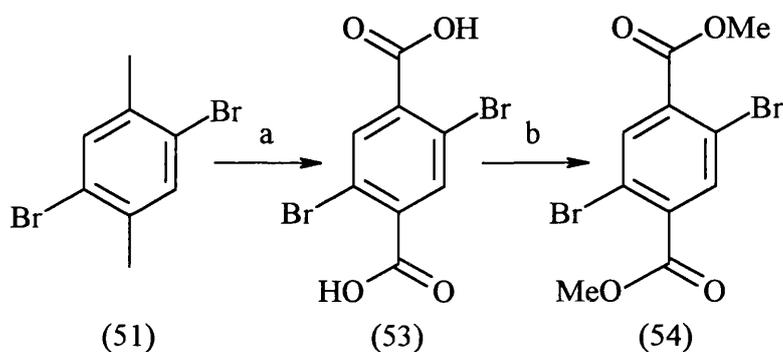
a) KMnO$_4$, NaHCO$_3$, 'BuOH, H$_2$O; b) MeOH, H$_2$SO$_4$

Scheme 23

In fact the oxidation of 2,5-dibromo-*p*-xylene with potassium permanganate gave a

mixture of the diacid (53), the monoacid (52) and starting material (51). From this

mixture the starting material could be recovered by dissolving the mixture in diethyl

ether and washing the solution with aqueous sodium bicarbonate. The mixture of

mono- and diacids was obtained from the ether layer and was esterified using methanol

and sulfuric acid prior to separation by flash chromatography. The diester was obtained

in 15 % yield from 2,5-dibromo-*p*-xylene (51), and methyl 2,5-dibromo-4-

4-methylbenzoate was obtained in 6 % yield from (51). Here at least Lamba and Tour were accurate!

Stage 2

We considered that a direct *ortho*-lithiation of *N*-butoxycarbonylaniline might avoid the problems we had experienced with the 2-bromo analogue.
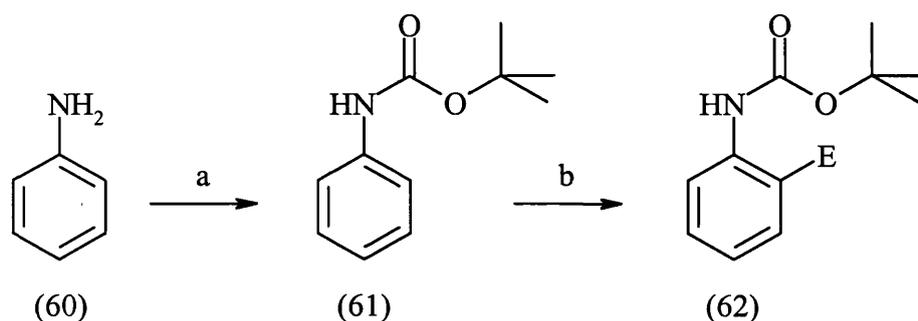
a) (BuOCO)$_2$O, dioxan/H$_2$O; b) BuLi, Et$_2$O, E$^+$

Scheme 24

N-butoxycarbonylaniline (61) was prepared by treating aniline with butoxy dicarbonate in water/dioxan in 76 % yield. This method was much more convenient than using sodium hydride according to Lamba and Tour. Additionally the carbamate is a highly crystalline material and is easier to purify than its 2-bromo derivative (56). Initially direct *ortho*-lithiation was attempted, and we attempted to quench the product with chlorotrimethyl silane. Once the optimum conditions for the lithiation[23] had been selected, we obtained the trimethylsilyl derivative (63) in 85 % yield, scheme 25.
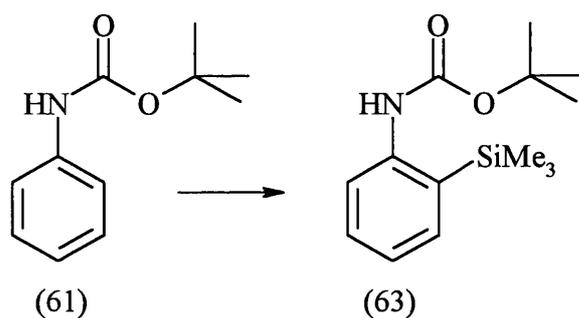
Scheme 25

With this result in hand, our attention turned to the synthesis of the desired boronic acid. Treatment of the lithiated species with trimethyl borate gave the dimethyl boronate ester (64), however, direct hydrolysis with dilute hydrochloric acid was unsatisfactory as the free boronic acid (57) was difficult to isolate. This was attributed to the solubility of the acid in water.
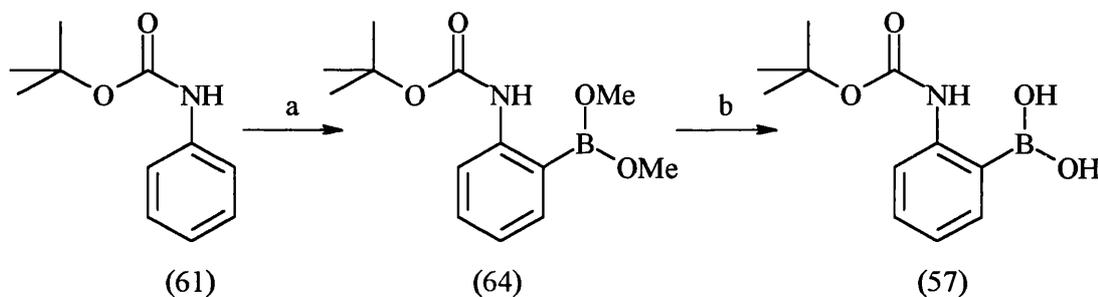
a) ^{t}BuLi, Et$_2$O, B(OMe)$_3$; b) H$_3$O$^+$

Scheme 26

Next we decided to avoid the acid altogether and to use boronate esters in the coupling reaction with the diester (54). We had some evidence to show that the dimethyl boronate (64) would be too unstable to purify so we considered other esters.

(57)   (65)
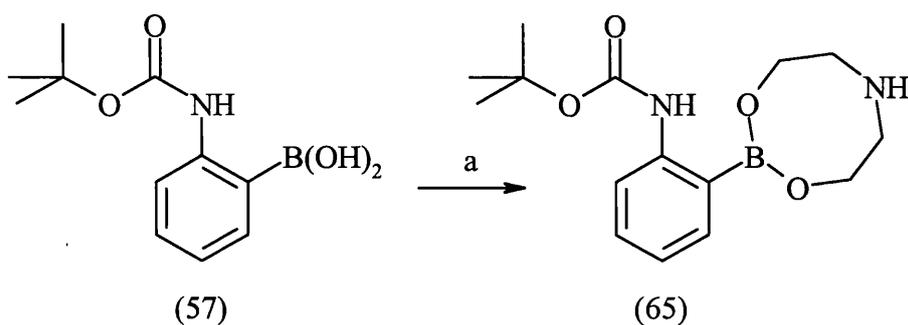
a) Diethanolamine, PhMe, Δ

Scheme 27

In a trial experiment we treated the crude dimethyl boronate with diethanolamine and

obtained the azodioxaboracyclooctyl derivative (65) as a very stable compound in

45 % yield. It is known that such boronates are of limited value in coupling reactions

and are mainly used as analytical tools[24]. We had clearly gone from one extreme to

the other and now selected the pinacol boronate ester (66) as a more suitable

intermediate.

(61)   (66)
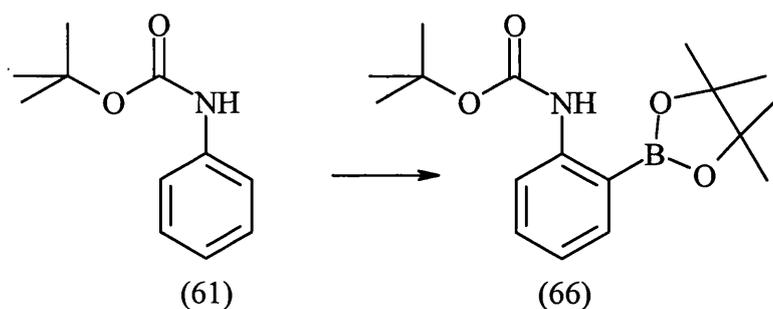
a) ᵗBuLi, Et₂O; b) B(OMe)₃; c) Pinacol, Et₂O

Scheme 28

The procedure outlined in scheme 28 was partially successful and after the excess

pinacol had been removed by suction filtration, the solvent was removed and the

residue was purified by column chromatography, to give the pinacol boronate ester

(66) in an overall yield of 39 %.

STAGE 3

We were now able to attempt Suzuki coupling reactions with a limited amount of the

impure boronic acid (57) and with the pure pinacol boronate ester (66) we had

prepared.

Neither of the two coupling attempts worked to produce an insoluble yellow coloured

compound as reported. The residue that was collected, an off-white/grey coloured

material, was examined spectroscopically in an attempt to determine its identity. Mass

spectrometry was performed on the isolated compound, and also on the residues left

after concentrating any solvent or aqueous fractions collected during the work-up

procedure. None of the samples tested showed a mass ion for the desired compound.

Spectra were also obtained of all of the starting materials used in the reaction. These

were compared with the spectra of the compound obtained from the reaction. The

spectra did not show any trace of the starting materials either.

CONCLUSIONS DRAWN FROM LAMBA AND TOUR'S SYNTHESIS

To make the amide bond last, the failings of the Lamba and Tour route had to be established. An obvious explanation is that the ᵗBoc- group and the ester functionality were too bulky to allow the methyl terephthalate access during the Suzuki procedure. This would be borne out if the first reaction in the Lamba and Tour sequence was Suzuki coupling, route 2, rather than amide formation, route 1, scheme 29.
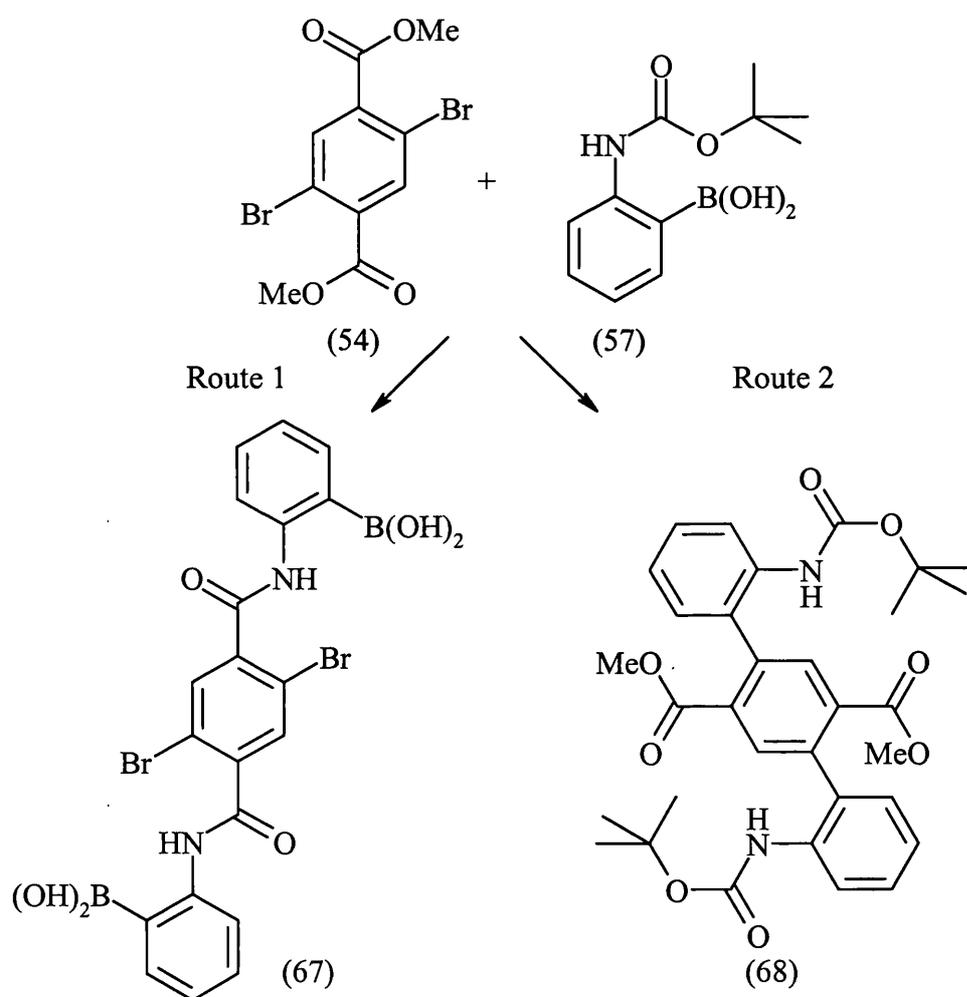
Route 1   Route 2

Scheme 29

If Suzuki coupling occurs first (route 2) in Lamba and Tour's route before amide

formation (route 1), see scheme 29, then the most probable explanation for the failure

of the reaction between methyl 2,5-dibromoterephthalate (54) and the pinacol

boronate ester (66) is the steric problem presented by the ^{t}butoxycarbonyl and the

ester groups. The fact that two arylations are needed as well as two amide bond

formations makes this a complex procedure with a high probability that a mixed

sequence of reactions occurs.

(51)   (53)
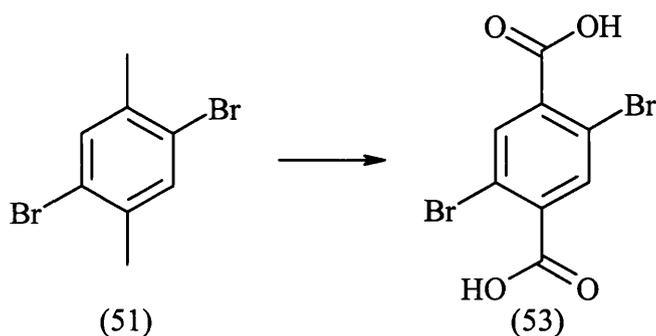
Scheme 30

Another major problem is in the oxidation of 2,5-dibromo-p-xylene, scheme 30.

Again this may reflect the steric bulk of the bromine atoms, and certainly the

oxidation of p-xylene to terephthalic acid works extremely efficiently.

IDEAS FROM LAMBA AND TOUR

From the results of work by Lamba and Tour, several suggestions were made for

novel routes to the terphenyl backbone. Scheme 31 shows the two potential

compounds.

(69)   (70)
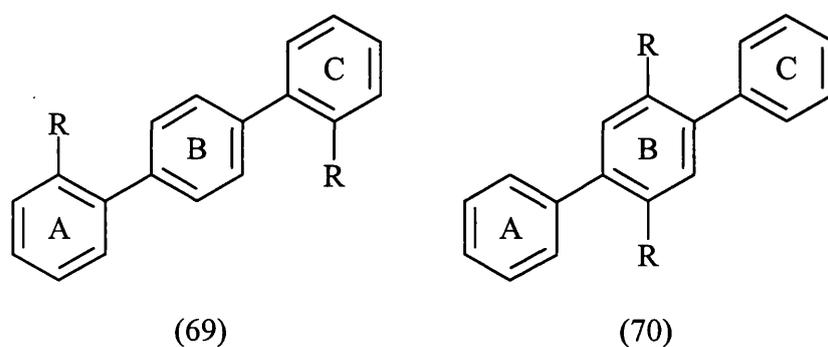
Scheme 31

We believed that the steric hindrance on the system that Lamba and Tour proposed

was the reason for its failure. The two compounds alleviate this problem by either

having functionality present in rings A and C, or solely on ring B.

TO INTRODUCE FUNCTIONALITY ON RINGS A AND C

(69)
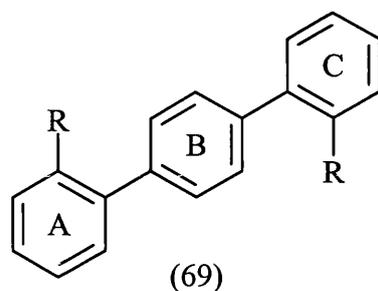
The first suggestion for the synthesis of such a molecule was to use a double Suzuki

coupling, as suggested from the work by Lamba and Tour.

A retrosynthetic analysis provided two possible synthetic pathways for producing

such a molecule, scheme 32.
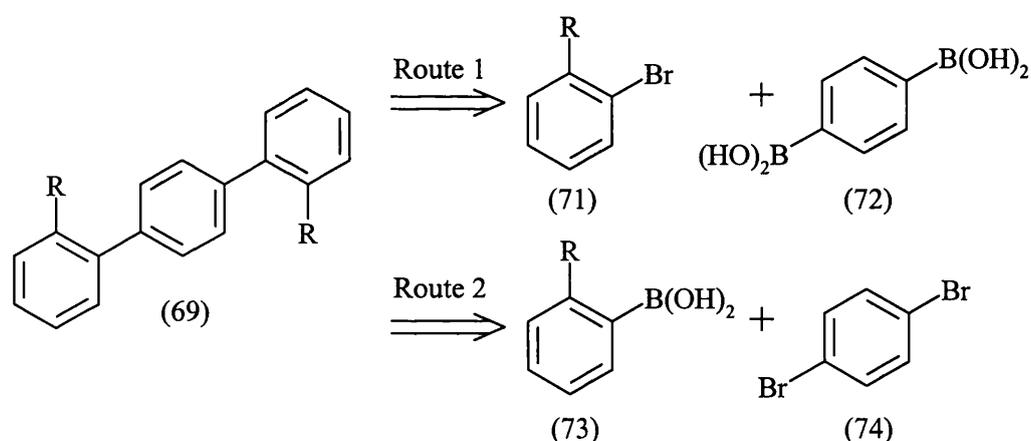
Scheme 32

Route 1 requires a diboronic acid and a 2-substituted bromobenzene, whereas route 2

requires a 2-substituted boronic acid and 1,4-dibromobenzene. The choice of starting

materials available meant that the diboronic acid, which is not readily available, was disfavoured.

With route 2 chosen as the more viable, a suitable boronic acid had to be selected.

(75)   (76)
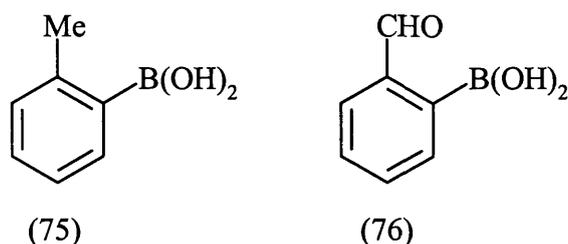
Scheme 33

Commercially available 2-substituted boronic acids were investigated. The methyl and formyl derivatives were the best candidates, scheme 33, and the 2-formyl derivative was chosen for the synthesis. Also the use of 1,4-diiodobenzene was considered to be superior to 1,4-dibrombenzene as reports in the literature had shown iodo- compounds to be higher yielding in the Suzuki coupling.

The first attempts used toluene as the solvent, 2M sodium carbonate as the base and *tetrakis*-(triphenylphosphine)palladium as the catalyst. These were the conditions outlined in the Lamba and Tour paper.
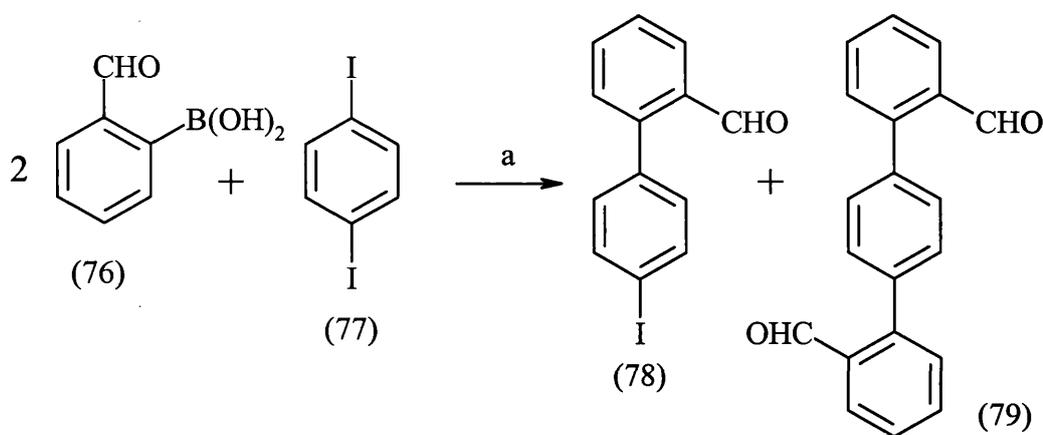
a) 2M Na$_2$CO$_3$, Pd(PPh$_3$)$_4$, degassed PhMe

Scheme 34

The reaction mixture was left for 24 hours, following its progress by TLC analysis. A new product was observed to form gradually as the starting material disappeared. The reaction mixture was purified by column chromatography, and the new product was identified as the monosubstituted product (78) in an overall yield of 17 %.

We did note that the reagents were only sparingly soluble in toluene and attributed the low yields to this fact. Once we changed to more polar solvent systems we were able to increase the yield and produce the disubstituted product (79).

Some of our best results are summarised in table 2.

Base	Solvent	Monosubstituted product %	Disubstituted product %
Na$_2$CO$_3$	PhMe	17	-
Na$_2$CO$_3$	PhMe/MeOH	35	22
Na$_2$CO$_3$	DME	14	25

Table 2

Other examples of using 2-formylbenzeneboronic acid in a double Suzuki coupling

are in the literature[25,26], although in these examples the two equivalents of boronic

acid are not coupling to the same aromatic ring. It is also known that the presence of

the 2-formyl group can accelerate the rate of hydrolytic deboronation[27], scheme 35.

(76)   (80)   (81)   (82)

                                                                 54 %   39 %
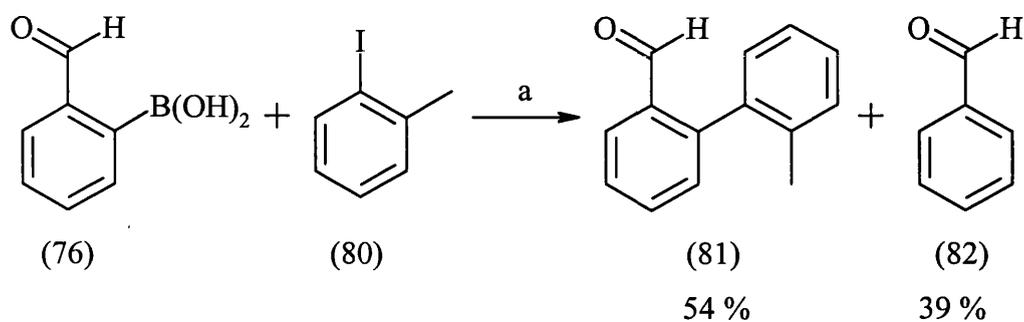
a) Na$_2$CO$_3$, DME, H$_2$O

Scheme 35

The poor yield of the disubstituted product suggested that the synthesis of (70),

having substituents on the central B ring, should be examined.

To Introduce Functionality on Ring B

R
C
B
A
R

(70)

Route 1

Br

(24)

+

B(OH)$_2$

(HO)$_2$B

(83)

Route 2

B(OH)$_2$

(25)

+

Br

Br

(51)

R

R

(70)
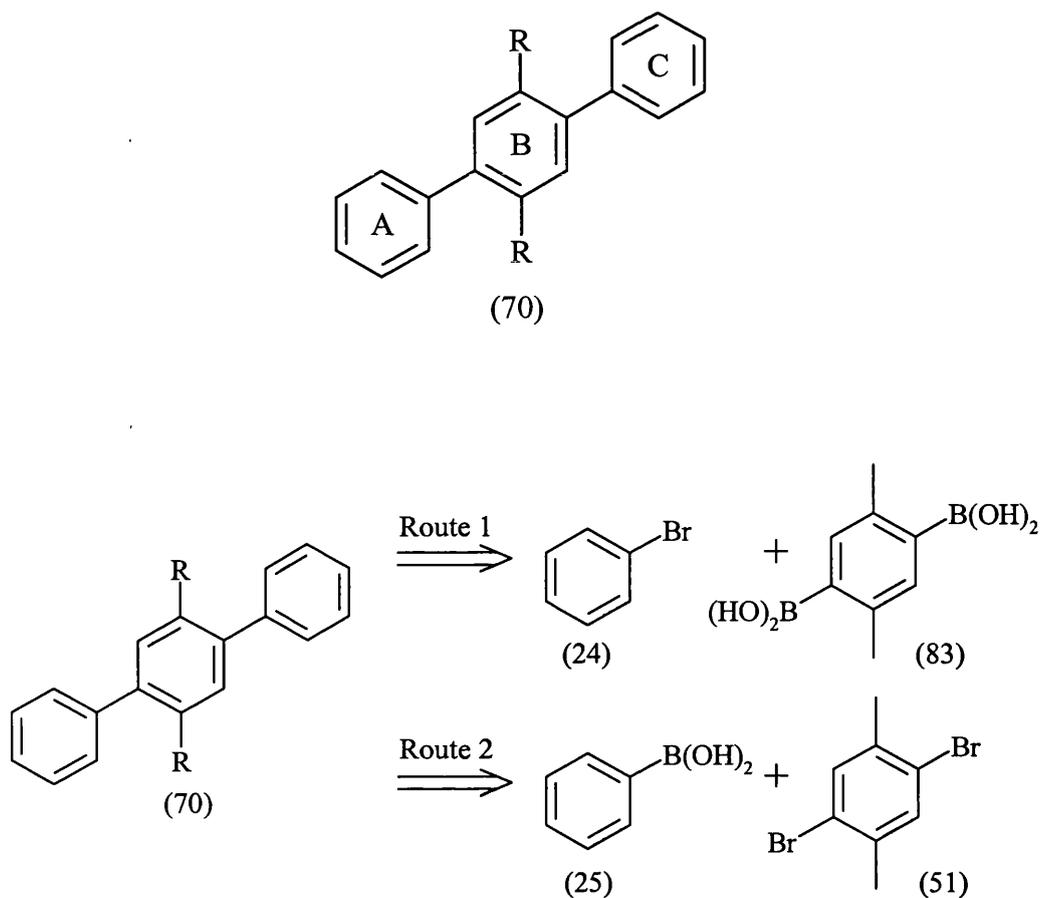
Scheme 36

Scheme 36 shows the retrosynthetic pathways for the system, again following a double Suzuki reaction. Route 1 involves reacting bromobenzene with a dimethyl bis-boronic acid. The boronic acid would need to be synthesised prior to the reaction. Route 2 was favoured as phenylboronic acid was readily available and 2,5-dibromo-p-xylene was already available, having been the starting material in the Lamba and Tour evaluation. This choice of starting materials meant that the methyl groups of the xylene would have to be developed later in the synthesis.
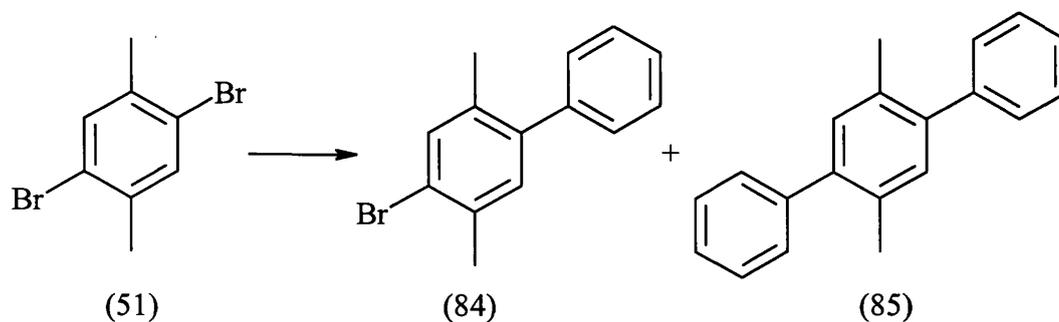
Scheme 37

In the first attempt at the reaction DME was chosen as the solvent, as this had been found to be the most successful solvent for producing the disubstituted product in the previous experiments. This did indeed produce the disubstituted product (85) in a greater yield than the monosubstituted product (84), 25 % opposed to 7 %. As the yield of this reaction was slightly lower than previous results it was decided that changing the solvent to a less polar system might enhance the reaction. The choice of base in the reaction was also changed at this point.

The decision to alter the base came after colleagues in Switzerland were visited by Professor Victor Snieckus. He reported that in his research caesium carbonate was proving to be a more efficient base for the Suzuki reaction than sodium carbonate. After consultation, the recommendation of using barium hydroxide was also given. They had found this reagent to be very efficient in the Suzuki reaction. A literature search also suggested that potassium carbonate and potassium phosphate were efficient bases for the reaction.

Following the previous procedure, the aryl bromide was dissolved in degassed toluene before adding the catalyst. The mixture was stirred at room temperature for 30 minutes. Again, a colour change from yellow to red was observed, and a solution of

the boronic acid in degassed toluene was added, followed by the base. The reactions were followed by TLC analysis and the reaction mixtures were purified by column chromatography. The results are shown in table 3.

Base	Solvent	Monosubstituted product %	Disubstituted product %
Na_2CO_3	DME	7	25
Cs_2CO_3	PhMe	24	42
K_3PO_4	PhMe	43	23
$Ba(OH)_2.8H_2O$	PhMe	34	9

Table 3

The results show that the efficiency of the reaction can be altered dramatically by using a different base. Caesium carbonate was found to be the best base for the reaction. It is interesting to note that the corresponding yields for mono- and disubstituted products when using caesium carbonate and potassium phosphate are reversed. A possible explanation for this is that potassium phosphate is not acting purely as a base in the reaction. Indeed, when potassium phosphate was used in other Suzuki coupling reactions where a protected functional group was present, the protecting group was removed instead of the Suzuki reaction occurring. The most disappointing result came from using barium hydroxide as the base. Although it was reported as being a superior base in the reaction, the outcome was poor in comparison to the result from caesium carbonate[28].

An alternative to the Suzuki reaction was found during this investigation, again using palladium catalysis[29].
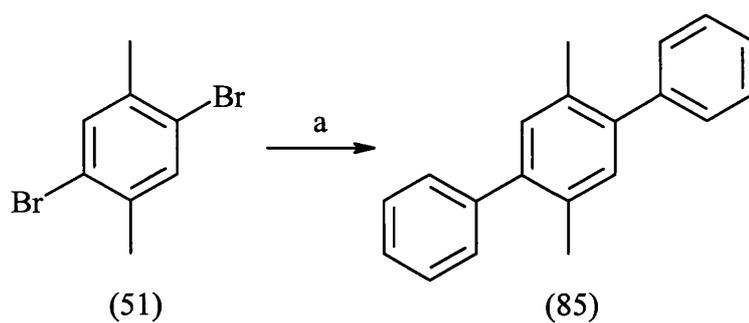
a) Phenylmagnesium bromide, PdCl$_2$(dppf), THF, Δ

Scheme 38

Using the same dibromide (51) and this time phenylmagnesium bromide, the same

terphenyl product (85) was afforded in 80 % yield and with a minimal formation of

the monosubstituted product (9%).

Next we wanted to see if we could develop dimethyl-*p*-terphenyl by oxidation of the

methyl groups. As we had experienced problems whilst trying to oxidise the methyl

groups of 2,5-dibromo-*p*-xylene, we believed that this may not be a straightforward

affair.
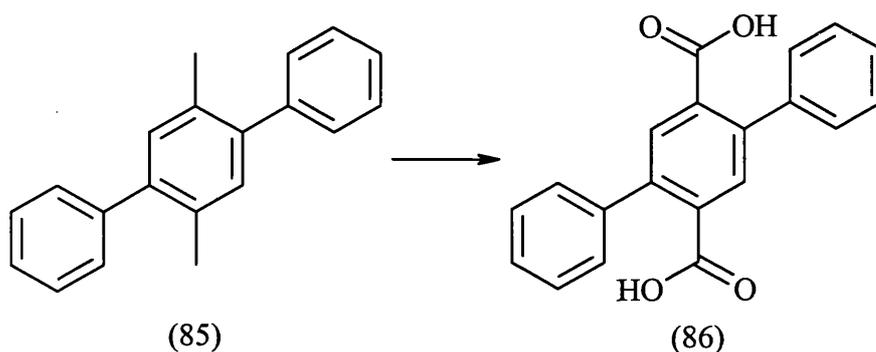
Scheme 39

With the starting material now available an attempt was made to oxidise the two

methyl groups to give the diacid. In fact this has been described previously, the

reagents being potassium permanganate in pyridine:water $(9:1)^{30}$. In our hands this procedure was difficult to monitor and it was also difficult to remove the pyridine at the end of the reaction. Recollecting the problems we had encountered when trying to oxidise 2,5-dibromo-*p*-xylene, we replaced the pyridine with 'butanol and added sodium bicarbonate to the aqueous potassium permanganate. A repeat oxidation now produced the diacid (86) in 24 % yield, scheme 39.

We now had several options available. One consideration was to cyclise the diacid to the diketone (87) and to use the Beckmann rearrangement to introduce the amide functionality. A disadvantage would be the lack of regiocontrol and a mixture of two products would be expected, scheme 40.

(86)   (87)

a) H⁺
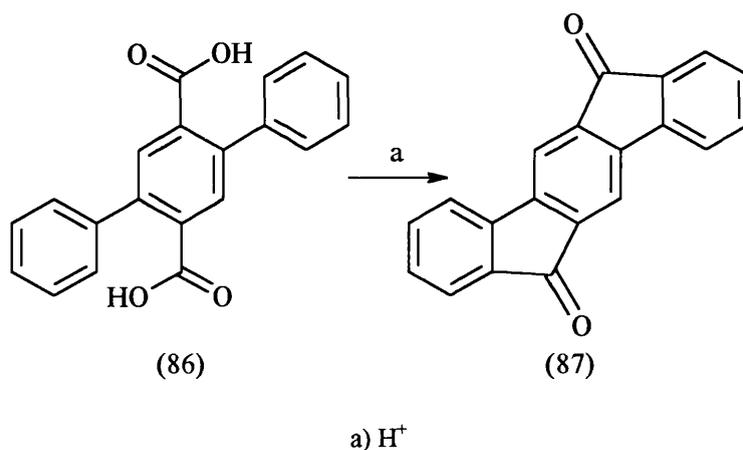
Scheme 40

Cyclisation to the diketone was to be an acid catalysed process, but several attempts to achieve this using methanesulfonic acid and sulfuric acid all resulted in complex mixtures of products.

An alternative method might involve a Curtius rearrangement of the diazide (90). This

could be prepared from the diester (89) and would lead to the diisocyanate (91) and

hence to the pentacyclic diamide (92).

a) NaN₃; b) PhMe, Δ; c) AlCl₃
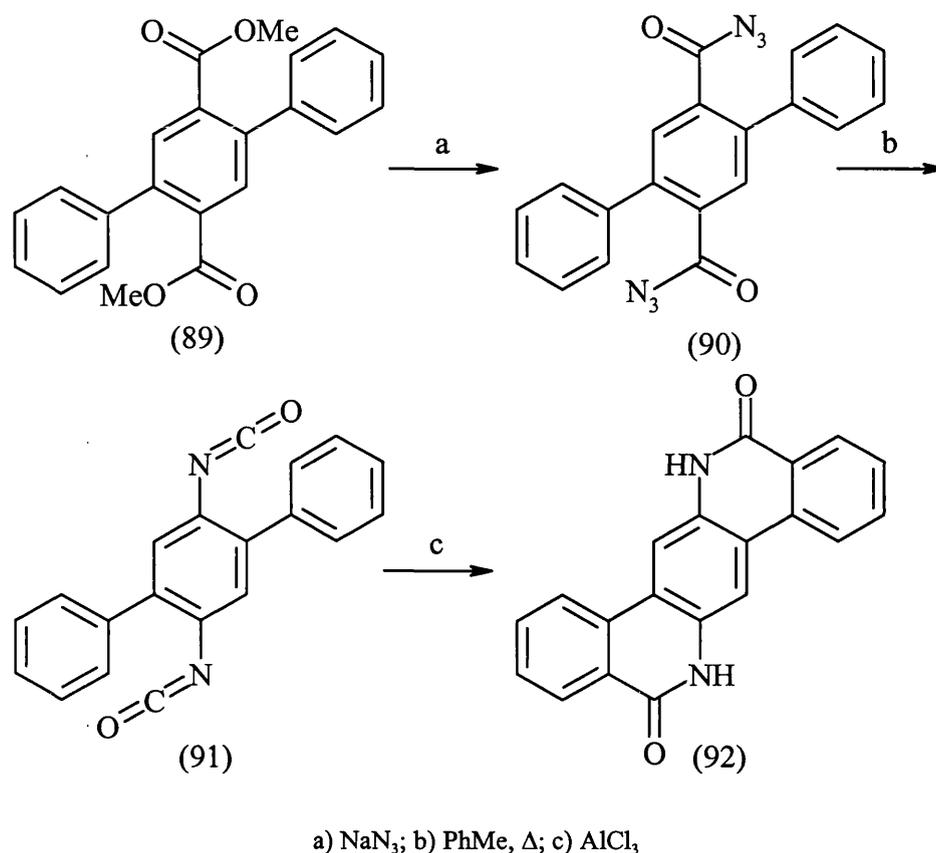
Scheme 41

Of course, this reaction sequence would produce a structural isomer of the desired

compound (21), but a calculation showed that this compound should be highly

coloured so this was not considered to be a major disadvantage. An advantage of the

route was that the isocyanate could only react in one position on the aromatic ring,

eliminating the possibility of multiple products as was the case with the Beckmann

rearrangement.
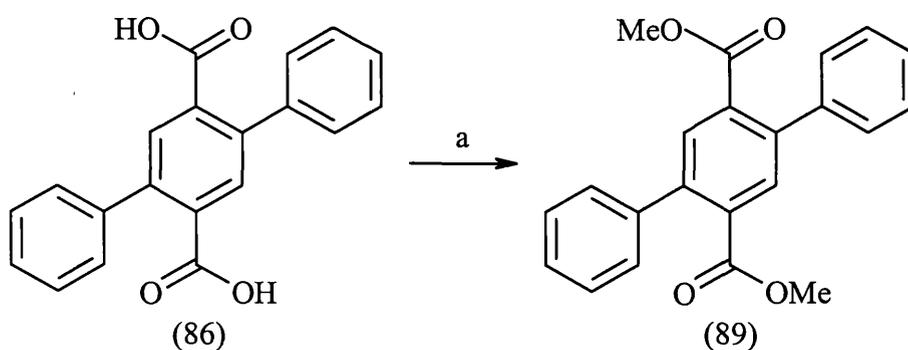
a) MeOH, c. H_2SO_4

Scheme 42 '

In practice, the diacid (86) was found to be highly unreactive. The dimethyl ester (89) was synthesised by treatment of the diacid with methanol and sulfuric acid, but the yield was only 5 %.

This was a minor disaster since most other procedures we had in mind would involve manipulations of the acid functions. Thus we had to accept that the methyl groups should be in a modified form. Alternatively the isomer (94) containing the methyl groups on the terminal phenyl rings could be synthesised. This would leave the methyl groups in a more accessible position to react with an oxidising reagent leading this time to the desired isomer of the pentacyclic amide, scheme 43.
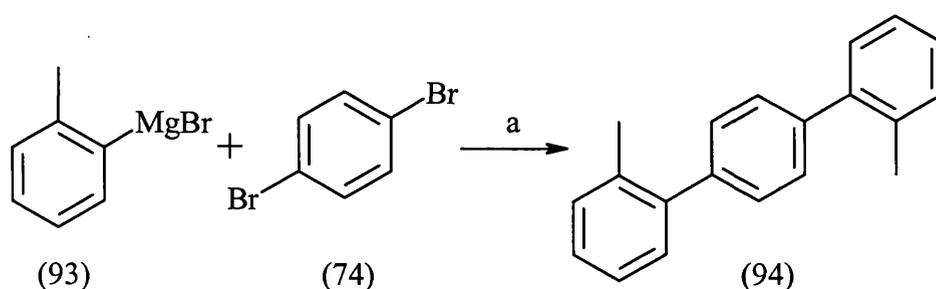
a) $PdCl_2(dppf)$, THF, Δ

Scheme 43

Before we attempted this synthesis however we sought to modify the original

approach to generate the dialdehyde via bromination of the methyl groups followed by

oxidative hydrolysis. This transformation has been reported previously[31].
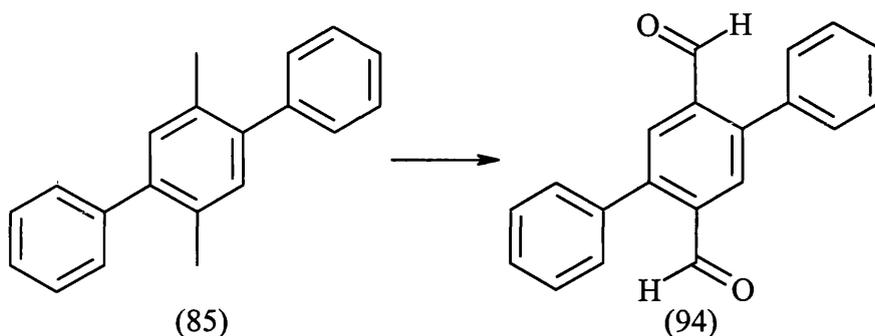
Scheme 44

The bromination step used NBS in carbon tetrachloride with benzoyl peroxide as the

initiator, scheme 45. When following this procedure we obtained a mixture of

products, but it was possible to isolate the major component as the bis(bromomethyl)

compound (96), and a small amount of the benzalbromide (97). Several

crystallisations were required to furnish (96) in a pure form.
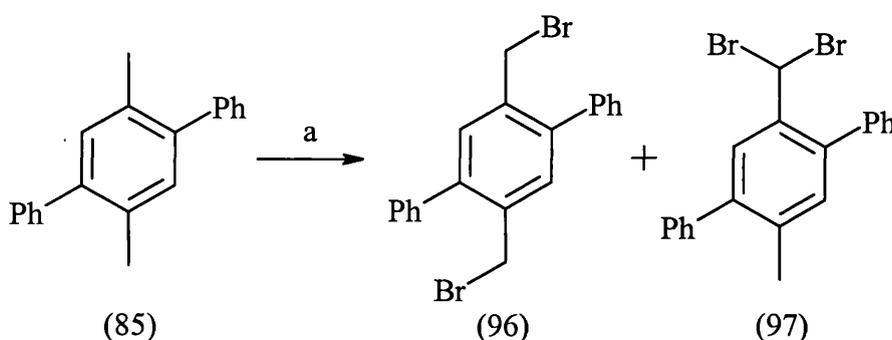
a) NBS, Benzoyl peroxide, CCl_4

Scheme 45

A Sommelet reaction with the bis(bromomethyl) compound (96) is the literature direct

route to the dialdehyde[31], but even so the product yields are variable and usually low

and again we consider this to be a reflection of adverse steric effects.

Considering this, we investigated a three step transformation rather than a direct

Sommelet reaction, scheme 46.
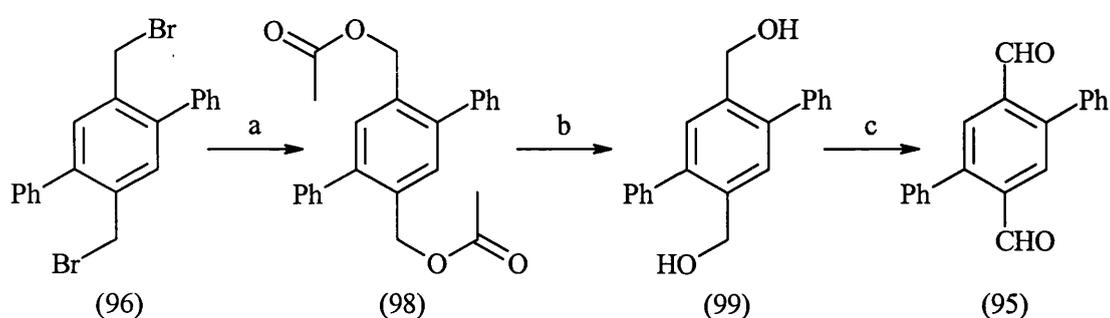
a) NaOAc, AcOH; b) 15 % (w/v) NaOH, MeOH; c) PCC, DCM

Scheme 46

Treatment of the crude mixture of brominated xylenes with anhydrous sodium acetate

gave mainly the diacetoxy compound (98). Two by-products, (100) and (101), were

also isolated, which arose from impurities in the starting material, scheme 47.
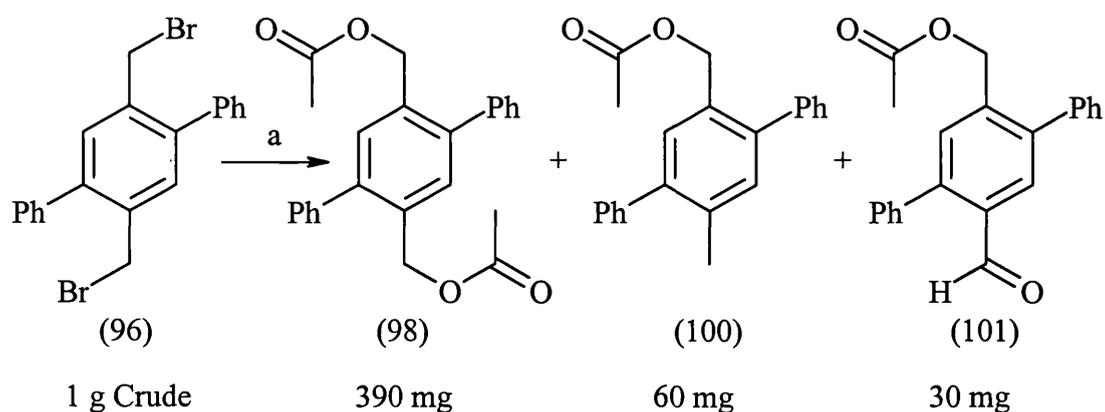
a) NaOAc, AcOH

Scheme 47

It was interesting to note that the aldehyde group was present in one of these by-products. This we assumed came from a benzalbromide, however, this was only present in small amounts. The major product from the bromination was the *bis*-(bromomethyl)xylene even though the brominating agent was already present in a large excess, extended reaction times however did not result in the *bis*-(dibromomethyl) compound stifling an approach to the dialdehyde directly through subsequent hydrolysis.
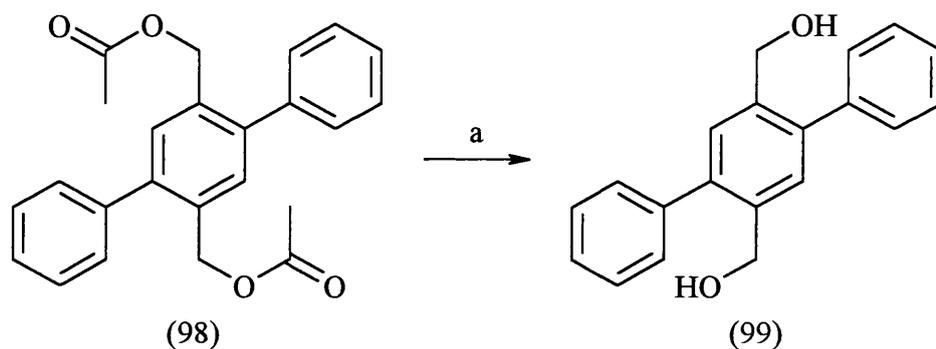
a) 15 % (w/v) NaOH, MeOH

Scheme 48

The next step was to remove the acetoxy groups from the diacetate (98) to furnish the dialcohol (99). This was achieved using aqueous sodium hydroxide solution in methanol. This reaction proceeded smoothly and the pure product (99) was isolated in 81 % yield after crystallisation.

At this stage one of the objectives had been achieved, in that the oxidation state of the methyl groups had been raised. Two possibilities now presented themselves. One was the oxidation to the aldehyde level, the other to attempt to form the acid. We decided

to follow the former objective using pyridinium chlorochromate in dichloromethane as the oxidant following the literature protocol, scheme 49.
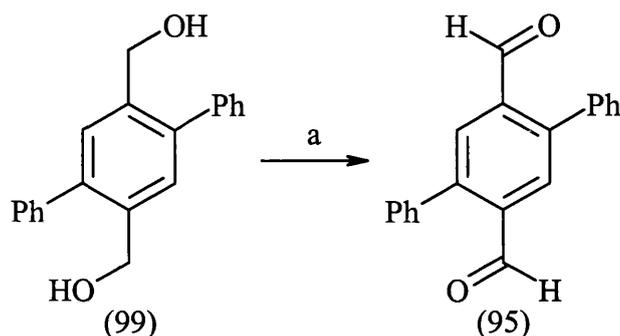
a) PCC, DCM

Scheme 49

The yield of dialdehyde was a rather disappointing 49 %, comparable with the literature value. More strenuous oxidation with potassium permanganate simply destroyed the compound.

This alternative method to the oxidation of methyl groups prompted more chemistry similar to the original Lamba and Tour route.

Following a literature precedent for this type of conversion we reacted 2,5-dibromo-*p*-xylene (51) with chromium trioxide, acetic anhydride and acetic acid in sulfuric acid. This gave the desired tetraacetyl product in only 23 % yield, scheme 50.
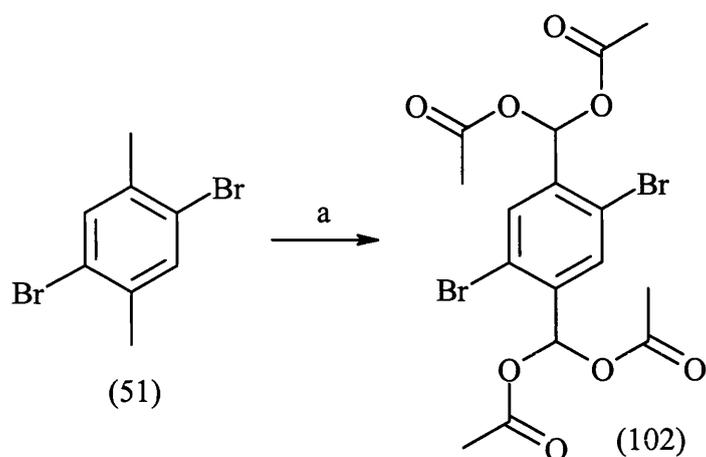
a) CrO₃, AcOH, Ac₂O, H₂SO₄

Scheme 50

Undeterred by this result, attempts were now made to remove the acetoxy groups to

furnish the dialdehyde (59), scheme 51.
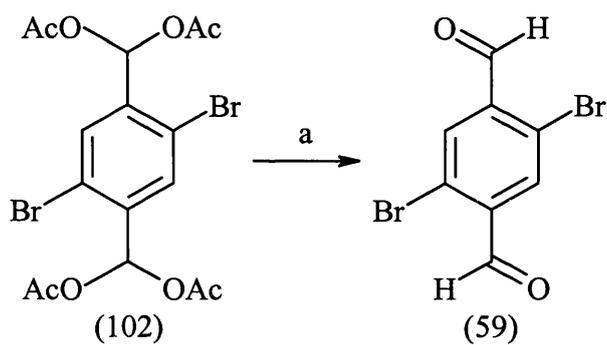
a) c. H₂SO₄, EtOH

Scheme 51

Our product was treated with sulfuric acid in ethanol to afford a new compound that at

first was thought to be the dialdehyde (59) in near quantitative yield. ¹H-NMR

Spectroscopy of this compound gave the first indication that something was amiss.

Signals from the proton resonances of an ethyl group were present in the spectrum. High resolution NMR spectroscopy revealed that the nature of the multiplets of the ethyl group were not straight forward. The expected highfield triplet was as to be expected, but the corresponding lowerfield quartet was more complex, figure 1.
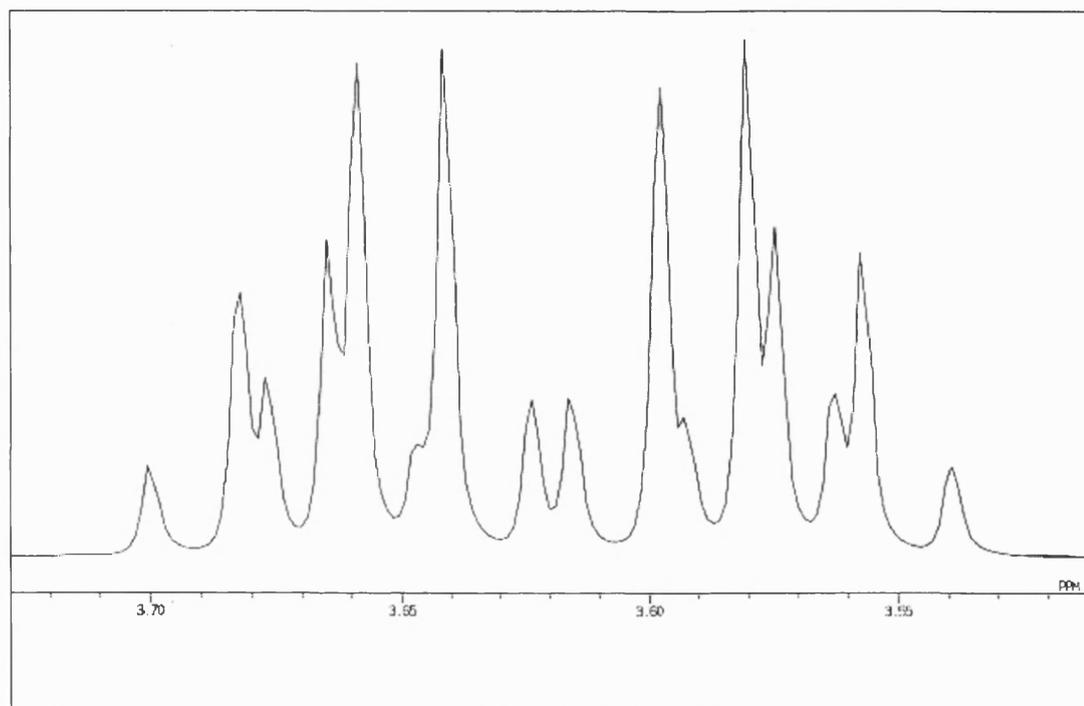
Figure 1

Four sets of quartets can be seen in the expansion, indicating that the methylene protons were non-equivalent. At this point it was presumed that the product was the ethyl acetal (103) and not the aldehyde (59).

(103)
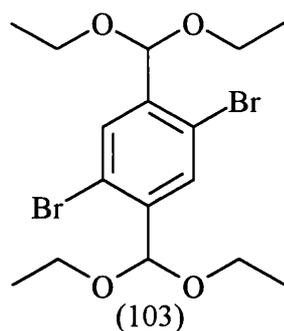
Elemental analysis was consistent with the ethyl acetal (103) and FAB mass

spectrometry also gave a mass ion of $[M-C_2H_5O]^+$ for the ethyl acetal. Notably the

intact mass ion did not survive as is commonly the case with acetals.

In an attempt to explain the complex methylene resonances observed in the proton

NMR spectrum, the conformation of the molecule was examined. The large *ortho*-

bromine atoms restrict the free rotation of the bond between the ring and the acetal

unit allowing three extreme rotamers.
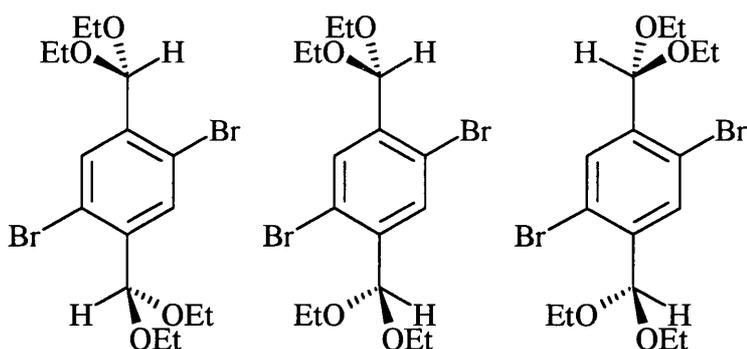
Scheme 52

In reality, the hydrogen and bromine atoms are more likely to be eclipsed than

overlapping as drawn, but this shows an average representation of the system. A

crystal structure determination would confirm the steric influence of the bromine atoms on the topology of the compound and the result of such an analysis follows.
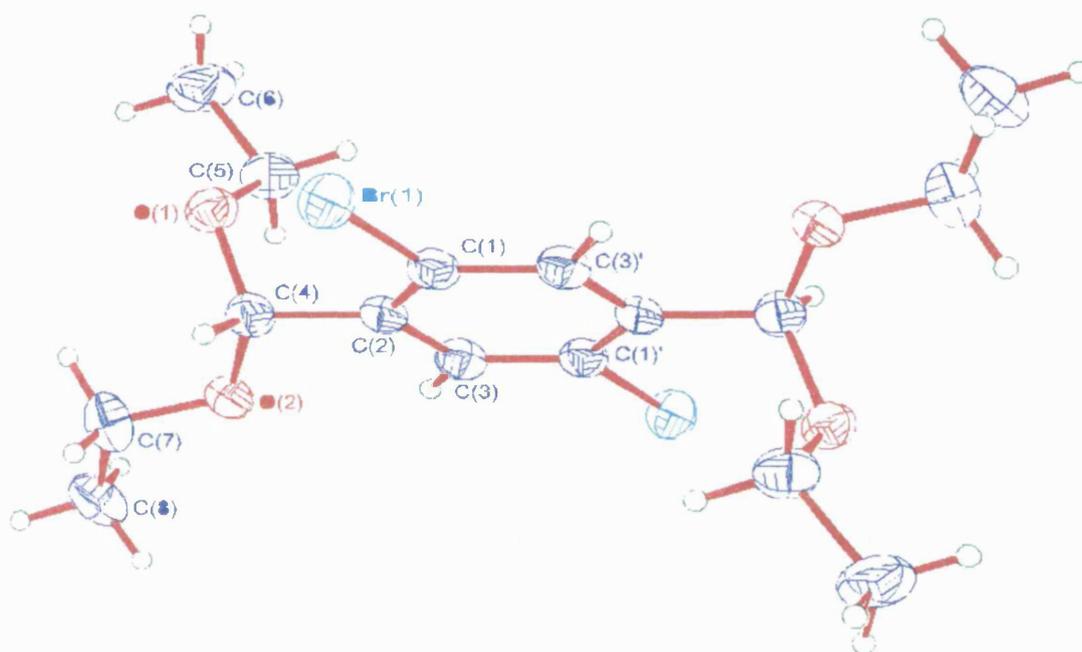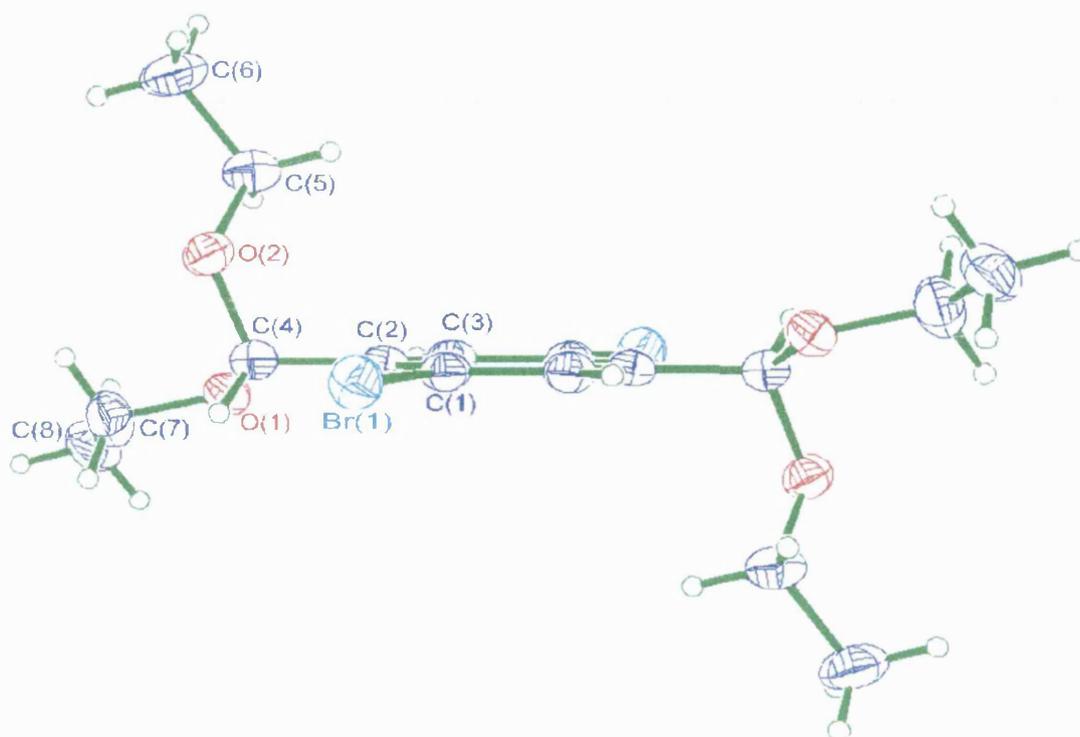
The crystal structure shows that in the solid state at least, the compound is non-planar and also demonstrates that the two methylene protons are in a different environment and therefore non-equivalent. This non-equivalence gives rise to the observed splitting pattern.

Each methylene proton signal is split by the other methylene proton and also the methyl protons, giving a doublet of quartets. Each methylene proton will give the same splitting pattern, so four quartets are observed. The signals are overlapped and the outer signals are diminished and the inner signals are enhanced, which is typical behaviour of AB systems.

DIFFERENT BORONIC ACIDS

The decision to look at alternatives to the nature of the boronic acid was reached after the problems associated with isolating boronic acids were encountered. This was particularly true when trying to isolate the 'Boc-aniline derivative by the method described by Lamba and Tour[19].

(57)
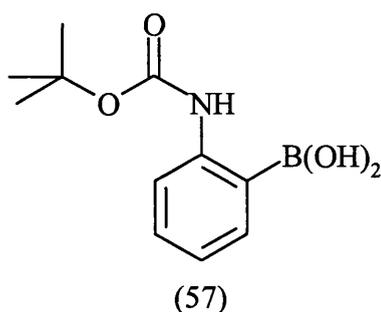
The presence of the amide proton was considered a problem when trying to synthesise the material. The method as outlined by Lamba and Tour used methyllithium to remove the amide proton before butyllithium was used to perform a lithium halogen exchange. We felt the absence of the amide proton would mean that less lithium alkyl would be needed in the reaction and it would make the product easier to isolate. A *bis*-protected aniline would be ideal for this, and likely candidates were evaluated, scheme 53.

R=H (104), Br (105)   R=H (106), Br (107)

R=H (60), Br (55)   R=H (108), Br (109)   R=H (110), Br (111)

R=H (112), Br (113)   R=H (114), Br (115)
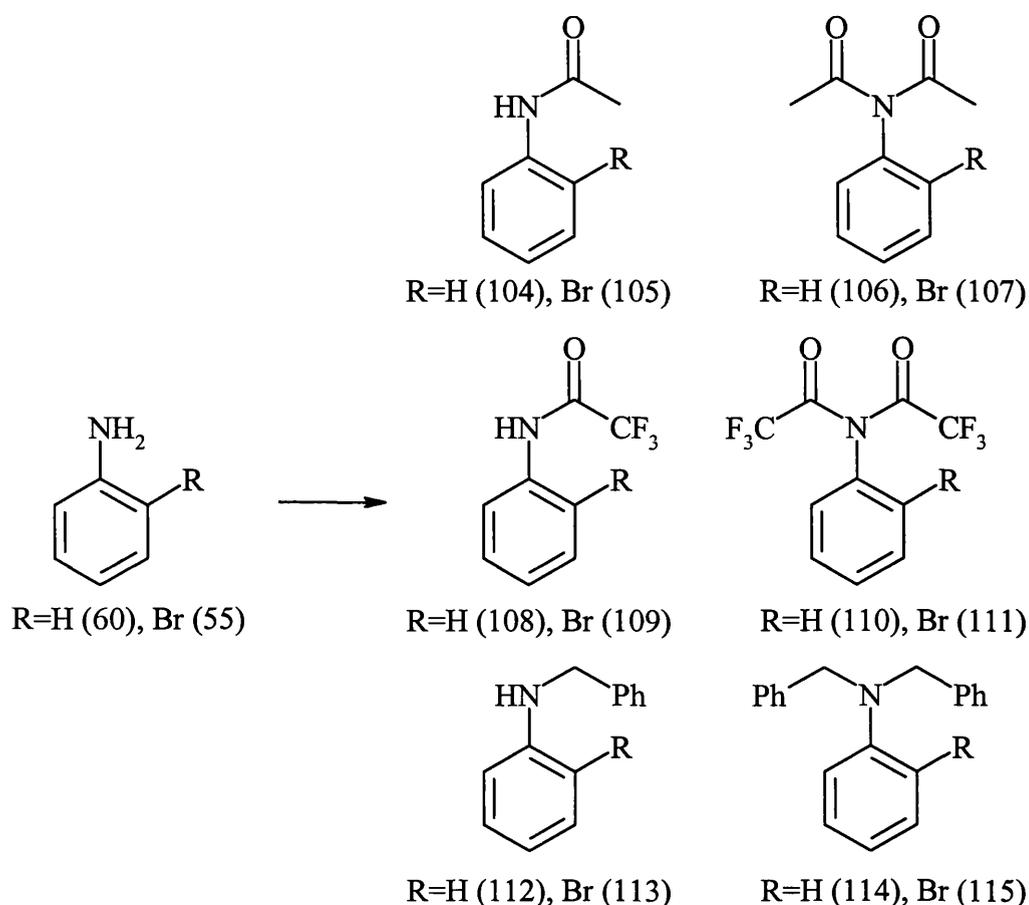
Scheme 53

The mono- protected products were also considered as they were normally synthesised

first before a second protection step introduced the second protecting group. Aniline

and 2-bromoaniline were used as the starting material in all cases, as this gave us

some variation in the procedure for introducing functionality in the 2- position. We

envisaged that either lithium-halogen exchange or directed *ortho*-lithiation would be

suitable for this.

The acetyl derivative was considered first, and the mono- protected species were

synthesised first. Problems were met when trying to introduce the second group

because of the presence of an α-proton and this could be overcome with the trifluoromethyl derivative.

We settled for the *N*-benzyl derivative that was found to be easier to synthesise, as either the mono- or *bis*- protected product could be made from the starting material in a single reaction, rather than a two step reaction. We also believed that we could remove the protecting group at a later stage by hydrogenation that we could keep at neutral pH, hopefully eliminating any isolation problems.

(113)   (115)
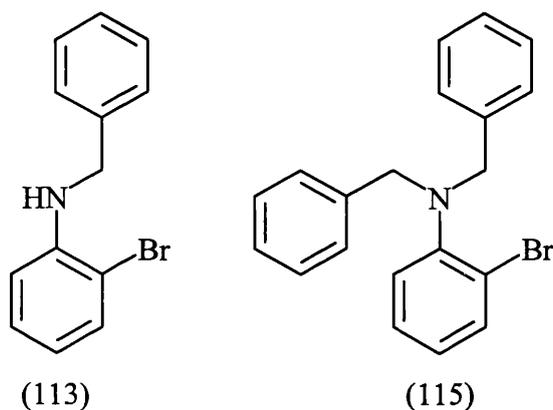
2-Bromoaniline was converted into the mono- and diprotected products in 81 and 77 % yield respectively. The directed *ortho*-lithiation and lithium-halogen exchange were performed and quenched with chlorotrimethyl silane to see which method was superior. The lithium-halogen exchange chemistry was found to be higher yielding than the *ortho*-lithiation chemistry, although the yield was still inferior to that found when using the ᵗBoc directing group. For this reason we continued our investigations and looked at the use of benzamides in both lithium-halogen exchange and *ortho*-lithiation chemistry.

(116)
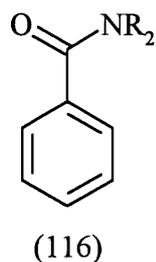
The use of benzamides was also considered for precursors to boronic acids. This would provide access to boronic acids with an acid functionality in the 2- position rather than an amino group. Various benzamides have already been used as directing groups for the *ortho*-lithiation reaction[32], so we knew that it would be unnecessary to attempt any lithium-halogen exchange chemistry as we had with the amino compounds.

(117)   (118)   (119)
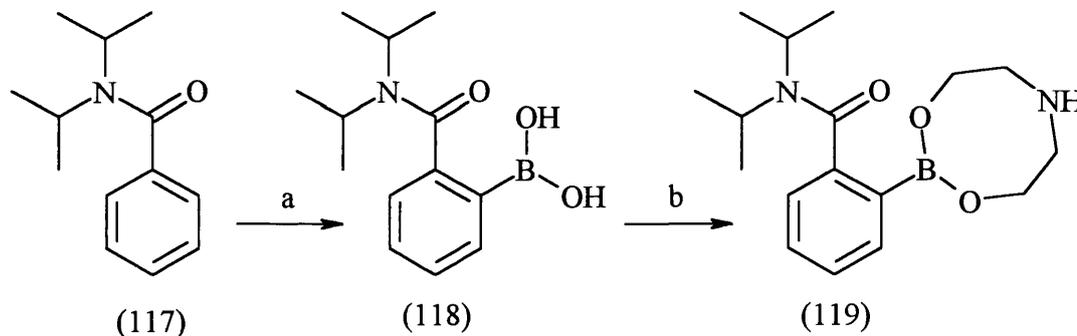
a) ^{n}BuLi, THF; B(OMe)$_3$; H$_3$O$^+$; b) diethanolamine, PhMe

Scheme 54

We started with the isopropyl derivative, R=^{i}Pr, a compound that has been used extensively in the literature. The *ortho*-lithiation was performed and the lithio intermediate was quenched with trimethyl borate before acidic aqueous work-up gave the boronic acid (118). We found that the product was easier to isolate than the ^{t}Boc-

aniline boronic acid had been. This was presumed to be due to the different nature of the directing group. We reacted the crude boronic acid with diethanolamine to produce the boronate ester (119) for analysis. From this we found that the isopropyl groups were non-equivalent due to the double bond nature of the amide linkage. This meant that the isopropyl signals in the ^{1}H-NMR were more complex than had been expected. We felt that in the later stages of a synthesis the NMR should be kept simple, so we also synthesised the ethyl derivative, R=Et, to alleviate this problem although we found this to be less effective.

(120)   (121)
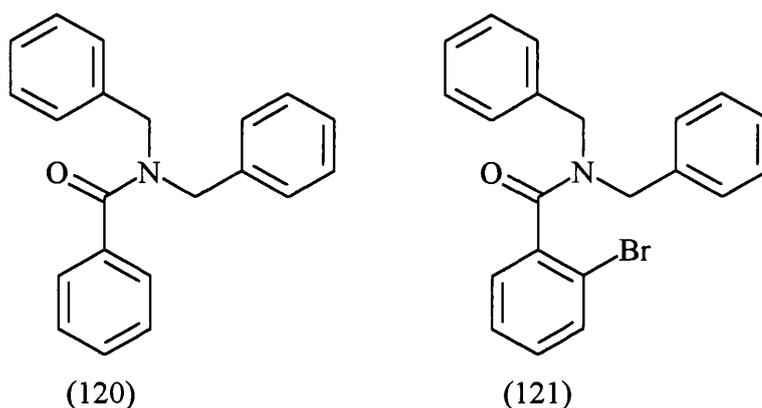
The use of N,N-dibenzylbenzamides was considered as another alternative to the isopropyl derivatives. The derivatives (120) and (121) were synthesised by reacting the corresponding ethyl or methyl ester with dibenzylamine to give the products in 78 and 42 % yield respectively. When we attempted the ortho-lithiation or lithium-halogen exchange chemistry, we found that the lithium halogen-exchange worked better. This can be attributed to the N,N-dibenzylamide group being a poor directing group.

The nature of the 2-bromo derivative also gave us more investigations. The presence

of the bromine atom in the *ortho-* position meant that there was some restricted

rotation about the C_{aryl}-N bond. Variable temperature ^{1}H-NMR studies showed that the

benzyl proton signals converged at higher temperatures. We considered this

information to be important when the bromine atom was substituted for an aryl group

later on in any possible synthesis. The spectra are shown in appendix A.

The isopropyl derivative was used in a Suzuki coupling with 1,4-dibromobenzene,

and the outcome will be discussed in the next section.

BIARYL SYNTHESIS

Whilst attempting to make terphenyl systems with the Suzuki coupling methods, biaryl

systems were commonly encountered. The reactions between phenylboronic acid and

1,4-dibromobenzene and between 2-formylbenzene boronic acid and 1,4-

diiodobenzene always gave a mixture of mono- and disubstituted products.

(118)
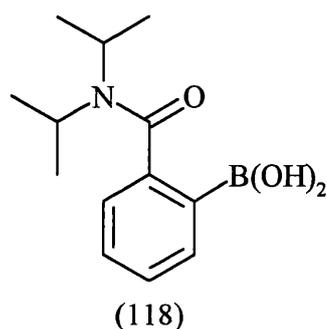
After we had studied other potential boronic acids for use in the reaction, the

diisopropylbenzamide (118) was chosen for further investigation. Its choice was made

due to several considerations. The boronic acid was found to be much easier to isolate

than the aniline based derivatives, and also it possessed an acid functionality. This was

thought to be important as we had already found that it was difficult to introduce this

functionality later in the synthesis by oxidation of alkyl sidechains[33].

When the boronic acid was reacted with 1,4-dibromobenzene under the same

conditions used previously a single product was formed. We presumed that the

product was a coupled product, and that it was either the mono- (122) or disubstituted

product (123).
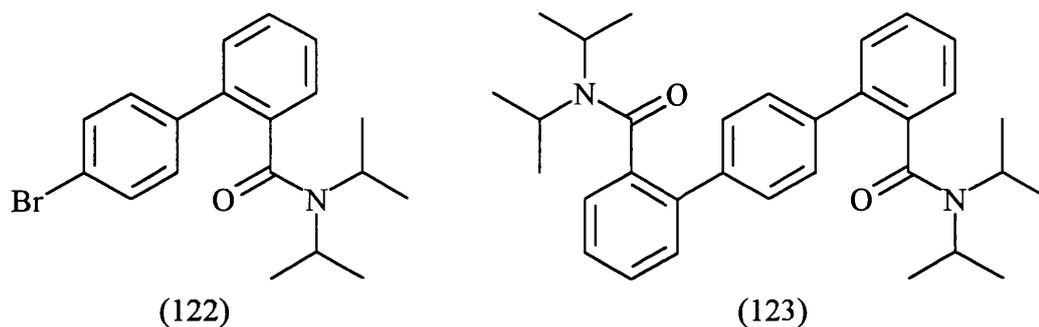
Scheme 55

The ^{1}H-NMR for each compound was assumed to be quite similar and the spectrum obtained bore this out. The integral trace for the aromatic and isopropyl protons was vague making it difficult to distinguish between the two compounds. Mass spectrometry gave a mass ion for the monosubstituted product giving a yield of 18 %. This result was disappointing as it meant that the disubstituted product was not obtainable by this method.

We tried using Stille couplings to access a terphenyl structure, but we found that all that was obtained was an intractable mixture of products[34]. We also tried using triflates in place of aryl halides for the reaction. This was especially useful when trying to synthesise naphthyl derivatives as the hydroxyl precursors are widely available[34,35]. However, we achieved the same result as that with the aryl halides. We did however discover in the literature more recent work on the reaction and moreover new methods for performing the transformation.

The use of copper(I) thiophenecarboxylate (CuTC) (125) is a new reagent for the Stille

reaction[36] and it is claimed that this reagent can replace the more expensive palladium

catalyst altogether. There is also an example where CuTC has been used in a double

Stille coupling reaction[37]. The reagent itself is prepared from copper(I) oxide and

2-thiophenecarboxylic acid, scheme 56.
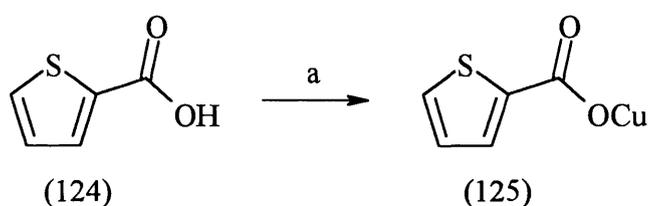
a) Cu_2O, PhMe, Δ

Scheme 56

We now attempted a CuTC catalysed reaction, scheme 57, as a comparison against the

more conventional Stille coupling.
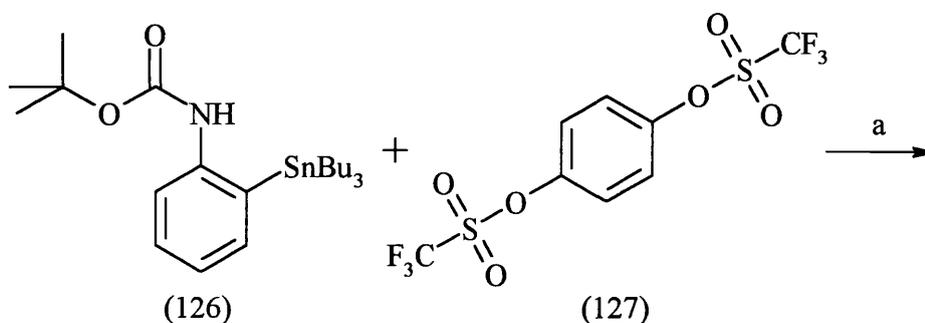
a) CuTC, PhMe

Scheme 57

The surprising result was the formation of the biaryl (128) in 42 % yield.

(128)
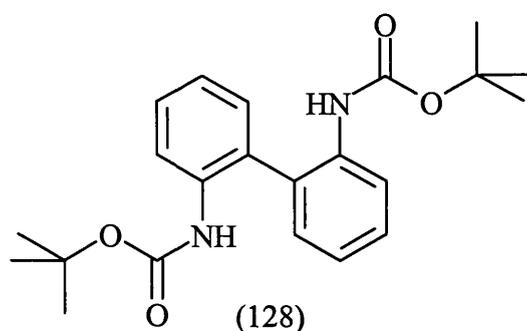
This biaryl compound had obviously been formed from a dimerisation of the stannyl

starting material. We considered that the presence of the copper catalyst could induce

a radical reaction and provide a pathway similar to that of the Ullmann coupling

reaction[38]. We tried a crossed Ullmann reaction to see if a terphenyl system could be

assembled from 2-iodonitrobenzene and 1,4-dibromobenzene.

(129)   (74)   (130)
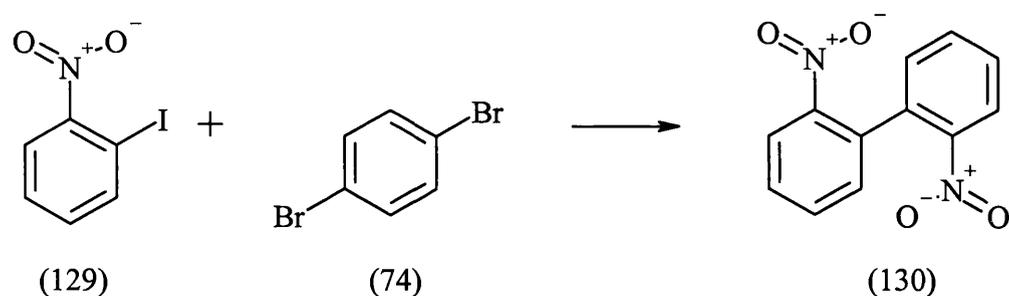
Scheme 58

This however resulted in only the homo-coupled product in a 41 % yield.

Other attempts were made to produce the phenanthridinone skeleton, which we hoped

would be suitable for producing the pentacycle (21). Whilst we were investigating the

possibility of synthesising acyl azides and isocyanates such as (90) and (91), we

investigated other routes to the isocyanate by using 2-aminobiphenyl as a model

system.

(131)   (132)
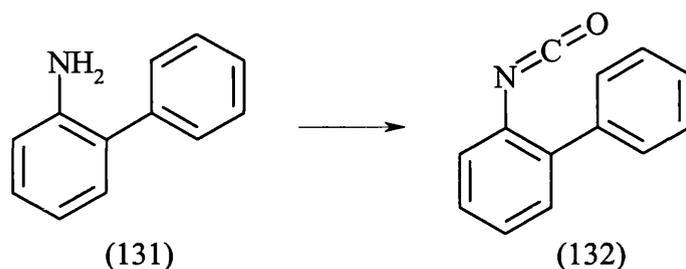
Scheme 59

The usual method of producing an isocyanate from an amine is to use phosgene. We

felt that as there are several alternatives to using phosgene that we should try to

implement one of them. We chose to use carbonyl diimidazole (CDI) as it is an easy

to handle solid and is less toxic than either diphosgene or triphosgene. Whilst using

CDI we obtained a single crystalline product. As the isocyanate product we were after

(132) was known to be an oil we knew that the product that we had obtained was not

the desired one. A strong carbonyl absorption in the IR suggested that a carbonyl

group had been transferred from the CDI into the new product. NMR and MS

suggested that instead of the isocyanate the product was the urea in a 6 % yield.

(133)
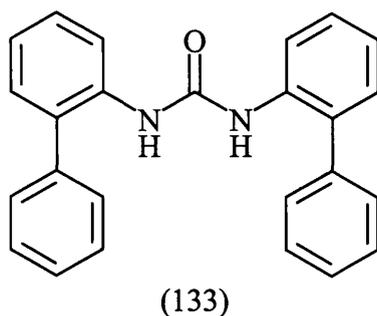
We found that when using CDI we only produced the urea product, even after altering the reaction conditions such as the order and rate of addition of the reagents. When we resorted to using phosgene, we were able to produce the desired isocyanate in 32 % yield.

In an attempt to construct the phenanthridine structure, the pinacol boronate ester (66) was reacted with 2'-bromoacetophenone (134) in a Suzuki coupling reaction, scheme 60.

(134)   (66)   (135)
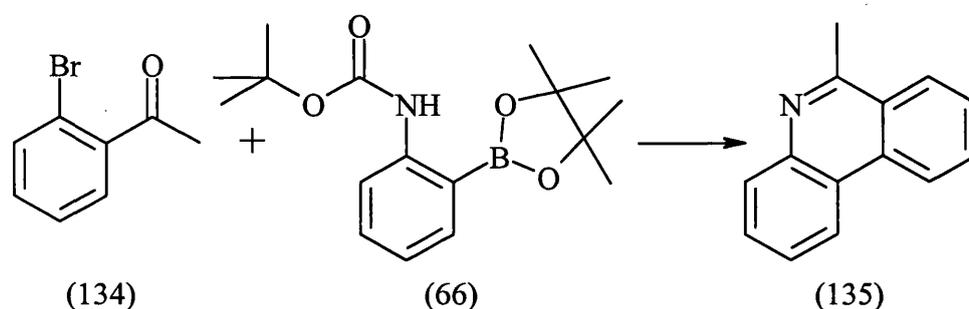
Scheme 60

We observed that after the Suzuki reaction had occurred, the amino group attacked the carbonyl centre. This was the same order of events as stated in the Lamba and Tour method, but which we had seen fail when using the methyl ester. The result of this reaction showed that the methodology was valid, but the ester was too sterically hindered to enable either the Suzuki coupling, or the subsequent amide formation to take place. We also found the same result when reacting the pinacol boronate ester with 2-bromobenzaldehyde to give phenanthridine.

OXAZOLINE CHEMISTRY

We looked at oxazoline chemistry initially with the intention of producing biaryl systems, and we hoped that the methodology could later be used to produce terphenyl systems as well. Oxazoline chemistry initially provided two possible routes, either the substitution chemistry as developed by Meyers, or to use *ortho*-lithiation chemistry. In either scenario, the oxazoline had to be synthesised first.

The simplest example of an aryl oxazoline, 2-phenyl oxazoline was commercially available, so there was no need to synthesise any for use in subsequent reactions.

In the case of *o*-anisic acid, the method outlined by Meyers was used[39], which is well reported elsewhere in the literature.

a) $SOCl_2$; 2-amino-2-methyl-1-propanol; $SOCl_2$, NaOH
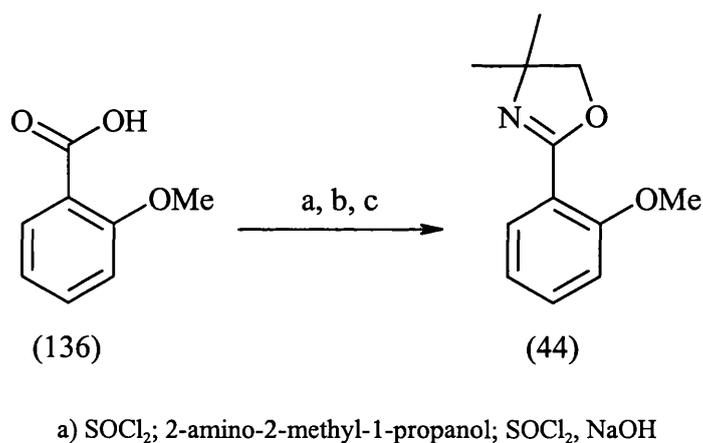
Scheme 61

It was found that this method worked reasonably well, and the oxazoline (44) was synthesised in 59 % yield. Although there are other methods for the same

transformation to be found elsewhere in the literature, only this procedure was used

with *o*-anisic acid.

COCl
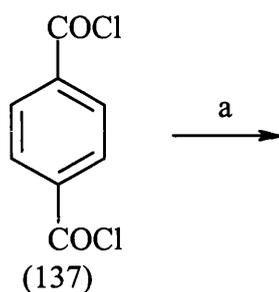
a) 2-amino-2-methyl-1-propanol; SOCl$_2$, NaOH

Scheme 62

It was desirable to synthesis a bis-oxazoline, and the same procedure was used as

before, scheme 62. However, it was found that the procedure was not suitable when

applied to terephthaloyl chloride (137). Very little product was obtained from the

reaction, so a different method was sought. A procedure was found in the literature in

which the authors had synthesised a bis-oxazoline similar to the desired compound

(139)[40,41]. In their synthesis, 2-amino ethanolamine is employed as the amino

alcohol and it is reacted with terephthalic acid. This procedure was repeated, using 2-

amino-2-methylpropan-1-ol as the amino alcohol, to give the desired bis-oxazoline in

a 27 % yield, scheme 63.

(138)   (139)
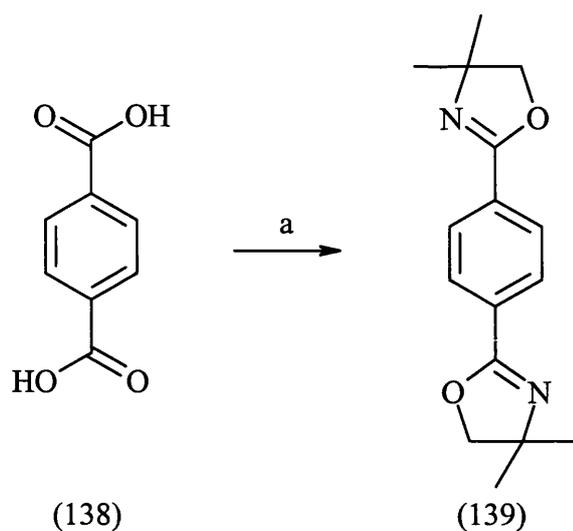
a) 2-Amino-2-methyl-1-propanol, acetonitrile, pyridine, triphenyl phosphine, carbon tetrachloride,

triethylamine

Scheme 63

The procedure proved simpler than that of Meyers to perform, as it was a one pot reaction and left at room temperature overnight. The yield was a little disappointing at 27 %, but the simplicity of the reaction, and the low cost of the reagents overshadowed this. The reaction itself relies upon the reaction between triphenyl phosphine and carbon tetrachloride. Hexachloroethane is more commonly used as more environmentally friendly solvent than carbon tetrachloride.

ORTHO-LITHIATION CHEMISTRY

The *ortho-* directing capabilities of the oxazoline group were assessed to determine the versatility of the procedure. It was already known that the oxazoline group is not as powerful as the benzamide group with respect to directed *ortho*-lithiation[16,17,42]. We reacted the oxazoline (46) with ^{n}butyllithium at -78 °C and quenched the reaction mixture with chlorotrimethyl silane.

(46)   (140)
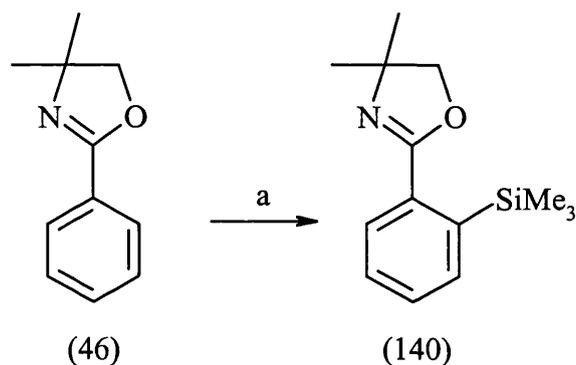
a) ^{n}BuLi, Me$_3$SiCl

Scheme 64

This gave the *ortho*-substituted product in a 44 % yield. When a similar reaction was attempted using ^{t}boc-aniline, the substituted product was obtained in an 85 % yield. Clearly the oxazoline group is only an average directing group.

We also wanted to see if the presence of an *ortho-* substituent would hinder the system if we were to attempt a second *ortho*-lithiation. To test this theory out, the trimethylsilyl compound (140) was reacted with a second equivalent of ^{n}butyllithium, and a different electrophile was used to trap the intermediate.
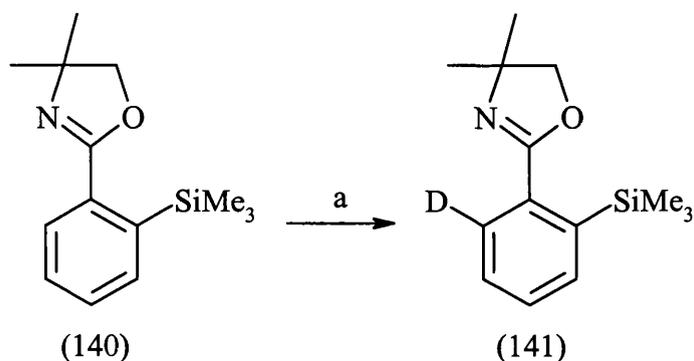
a) "BuLi, D₂O

Scheme 65

In the second *ortho*-lithiation reaction, deuterium oxide was used as the electrophile, and the product (141) was obtained in 30 % yield. Although it was not necessary to produce molecules with this substitution pattern, it did enable us to see whether or not the *ortho*- directing properties of the oxazoline would be diminished when one *ortho*-substituent was present. As it appeared that this was not the case, then the phenomena may affect us later when the possibility of over substitution could be a problem. No evidence of the di-substituted product was found in the first reaction, although one equivalent of butyllithium was used rather than an excess of the reagent. However, this question was addressed when the bis-oxazoline was employed.

Next, this methodology was extended to the bis-oxazoline. When one equivalent of butyllithium was added, there were four identical sites at which it could attack. Using an electrophile such as chloro'butyldimethyl silane gave us the expected product.

(139)   (142)
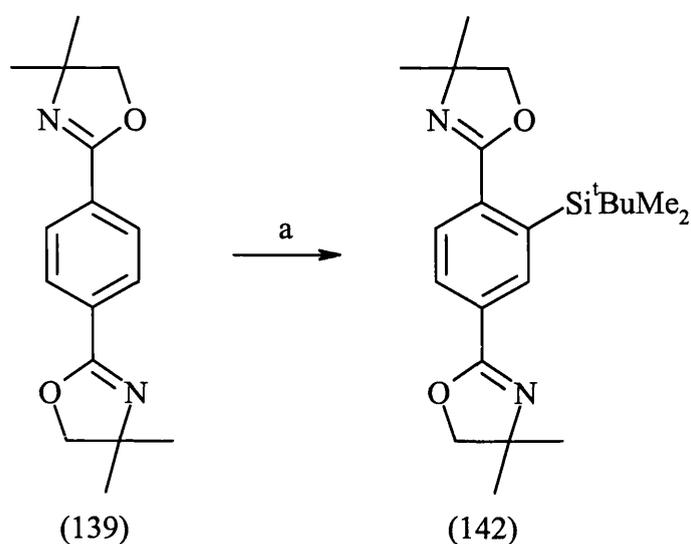
a) ^{t}BuLi, ClSi^{t}BuMe$_2$

Scheme 66

We then felt it was desirable to see if multiple substitutions could be performed concomitantly. It was believed that a di-substituted product would give the 2,5 product purely due to steric congestion. When, however the bis(oxazoline) was treated with an excess of ^{t}butyllithium the result was the incorporation of a ^{t}butyl group into the oxazoline, to give the di-^{t}butyl adduct (143) in 63 % yield.

(139)   (143)
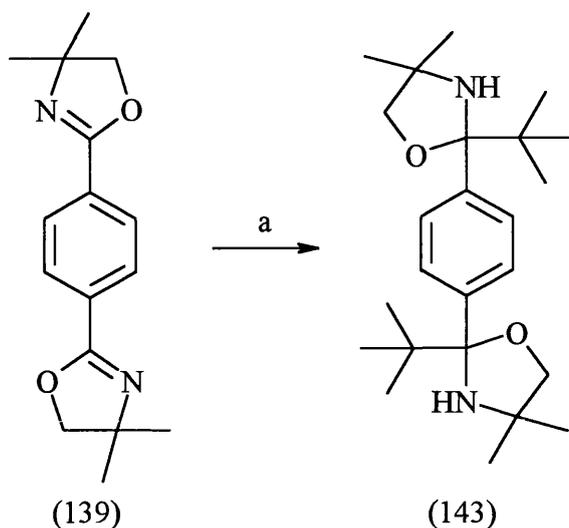
a) ^{t}BuLi, D$_2$O

Scheme 67

Oxazolines, as masking groups for carboxylic acids are relatively inert toward a variety of synthetic manipulations. Attack at the C=N link is a slow process, although not a completely unheard of occurrence[43]. The reaction is believed to follow a radical mechanism rather than a simple nucleophilic attack at the carbon centre. Due to the steric bulk of a ^{t}butyl group, it is not generally believed that it can perform a nucleophilic attack. In our case, the first step of the reaction must be the formation of a radical anion (148), scheme 68.

(139)   (144)
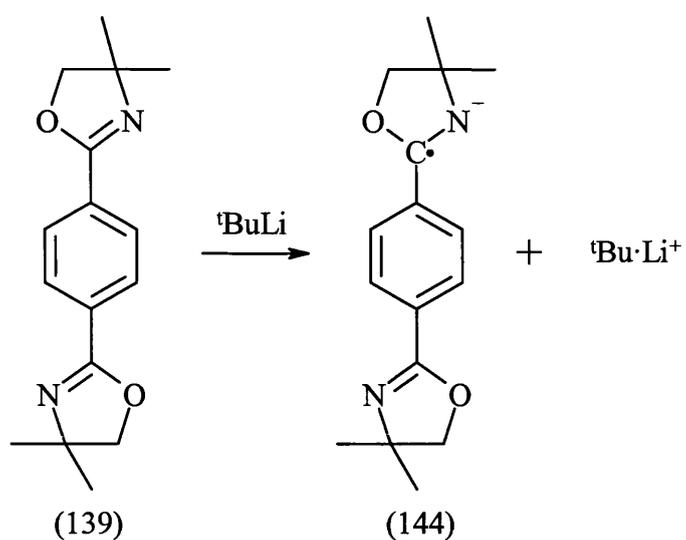
Scheme 68

The radical formed by treating the oxazoline with 'butyllithium can be stabilised by

resonance around the aromatic ring, scheme 69.
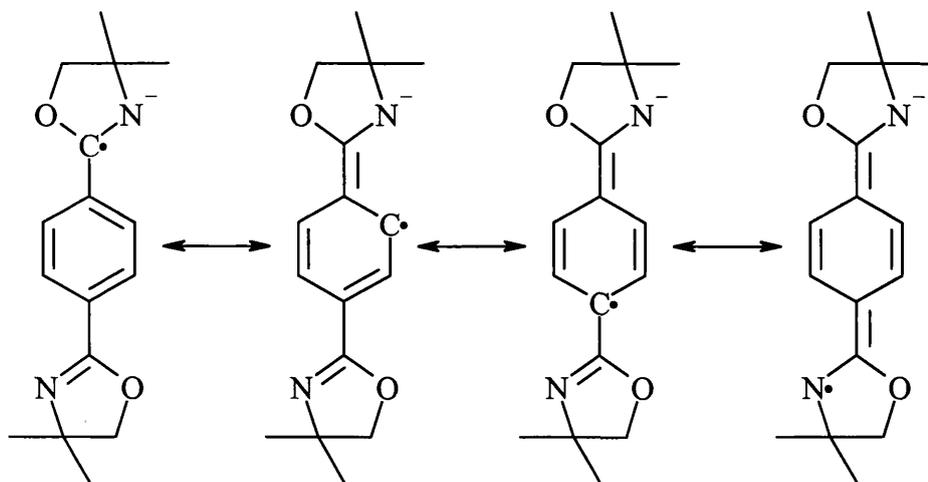
Scheme 69

The sequence is completed by attack by the ᵗbutyl radical, in this case at the initial

position of formation of the radical anion, to give the intermediate product (146),

scheme 70.

(144)   (145)   (146)
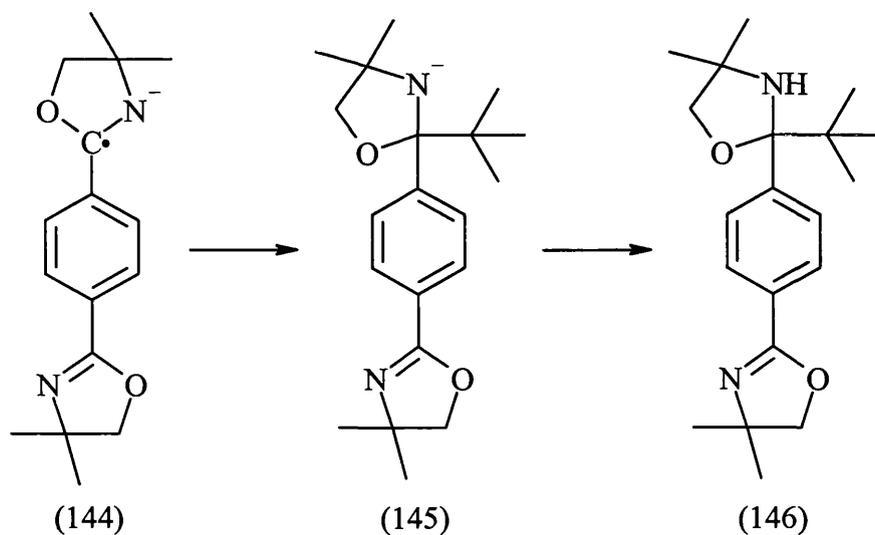
Scheme 70

After this transformation has taken place, the second oxazoline group can react in a

similar fashion, scheme 71.

(145)   (147)
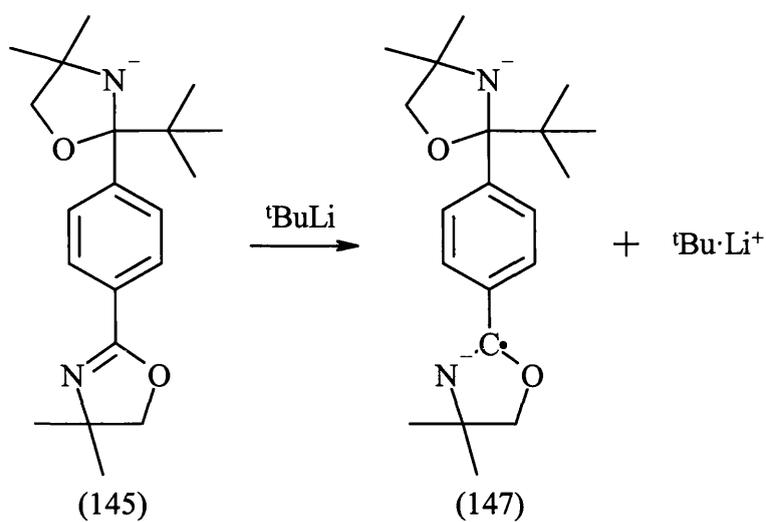
Scheme 71

Again, the radical can be stabilised by resonance around the aromatic ring, scheme 72.
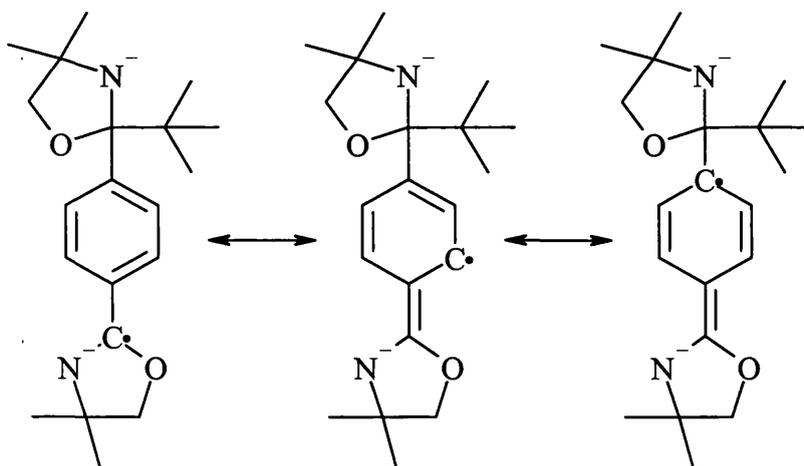
Scheme 72

Similarly, completing the reaction scheme sees the addition of the second ᵗbutyl group into the molecule, scheme 73.

(147)   (148)   (144)
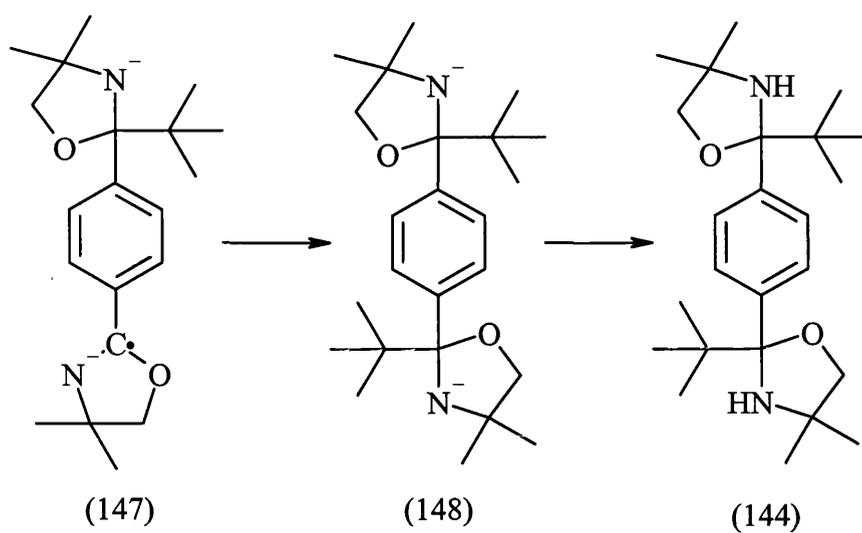
Scheme 73

We observed no substitution on the aromatic ring, as has been previously reported[43], although there is the opportunity for this to happen. We presume that the steric interactions between the oxazoline ring and the 'butyl group are sufficient to prevent this from happening.

EXPERIMENTAL

General Procedures

All NMR spectra were recorded on either a Jeol GX-270 or Jeol AX-400 spectrometer. Proton chemical shifts are reported in ppm downfield from TMS and ^{13}C resonances are recorded using the 77.0 ppm $CDCl_3$, or the 39.7 ppm DMSO-d_6, resonance of the solvent as an internal standard and are reported in ppm downfield from TMS. J values are given in Hz.

Solvents were distilled before use and reactions carried out under an inert atmosphere of nitrogen. Diethyl ether and tetrahydrofuran were distilled from sodium, using benzophenone ketyl as an indicator. Analytical TLC was carried out on precoated 0.2 mm thick Merck 60 F_{254} silica plates. Infra-red were recorded on a Perkin-Elmer 1600 series FT-IR. Petrol refers to 60-80°C boiling range petroleum ether. All solvents used in Suzuki coupling reactions were degassed before use.

2,5-Dibromo-4-methylbenzoic acid (52)
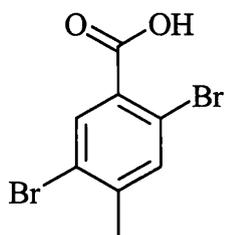
2,5-Dibromo-*p*-xylene (5.01 g, 19 mmol) was suspended in nitric acid (17 cm³) and water (21 cm³) and the mixture heated at reflux overnight. The mixture was extracted with diethyl ether (2 x 50 cm³). To the combined organic extracts was added water (100 cm³) followed by the addition of solid Na_2CO_3 until the aqueous layer was basic. The layers were then separated, and the aqueous layer made strongly acidic (pH1) by the addition of HCl (12M). To this mixture was added sodium chloride until the aqueous layer was saturated and the mixture was then extracted with diethyl ether (3 x 20 cm³). The combined organic fractions were dried over magnesium sulfate and the solvent was then removed *in vacuo* to leave a colourless solid. This was crystallised from 50 % diethyl ether/petrol to leave the title compound as colourless prisms (1.02 g, 18 %).

δ_H (270 MHz, $CDCl_3$) 2.43 (s, 3H, CH_3), 7.59 (s, 1H, H3), 8.18 (s, 1H, H6). mp 192-194 °C (Ref. 193-195 °C[19]).

2,5-Dibromoterephthalic acid (53) prepared by the oxidation of 2,5-dibromo-4-methylbenzoic acid (52)

$$O\underset{\quad}{\overset{\quad}{\diagdown}}OH$$
Br

Br

HO O
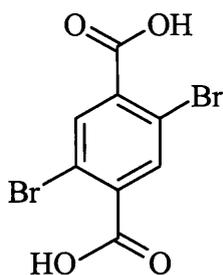
2,5-Dibromo-4-methylbenzoic acid (997 mg, 3.4 mmol) and potassium permanganate

(1.42 g, 9 mmol) were dissolved in a mixture of H_2O (7 cm^3) and saturated sodium

bicarbonate solution (7 cm^3) and the mixture heated at reflux for 2 hours. TLC

analysis (90 % ethyl acetate/petrol) showed no starting material remaining, and a new

more polar product. The reaction mixture was cooled and filtered through Celite®. The

residue was washed with saturated sodium bicarbonate solution and the filtrate made

strongly acidic (pH1) by the addition of HCl (12M). The aqueous phase was extracted

with diethyl ether (2 x 20 cm^3) and the combined organic extracts washed with brine

(20 cm^3). The organic phase was dried over magnesium sulfate and the solvent

removed *in vacuo* to leave the title compound (988 mg, 90 %).

δ_H (270 MHz, DMSO-d_6) 8.00 (s, 2H), 13.88 (brs, 2H). δ_C (68 MHz, DMSO-d_6) 119.0,

135.2, 137.2, 165.8. mp 316-319 °C (Ref. 318-320 °C[19]).

Methyl-2,5-dibromoterephthalate (54)

$$O\underset{\quad}{\overset{\quad}{\diagdown}}OMe$$
Br

Br

MeO O
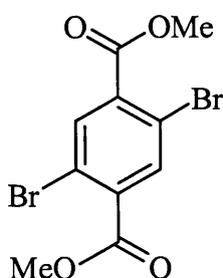
2,5-Dibromoterephthalic acid (43 mg, 0.13 mmol) in methanol (5 cm^3) was treated with thionyl chloride (0.5 cm^3) and the mixture was heated at reflux for 2 hours. The solvent was then removed and the residue re-dissolved in diethyl ether (10 cm^3). The organic phase was washed with saturated sodium bicarbonate solution (10 cm^3), followed by brine (10 cm^3) and then dried over magnesium sulfate. The solvent was removed *in vacuo* to leave a colourless solid (35 mg, 75 %).

Methyl 2,5-dibromoterephthalate (54) prepared by the oxidation of 2,5-dibromo-p-xylene (51) .

2,5-Dibromo-*p*-xylene (1.00 g, 3.8 mmol) and potassium permanganate (1.50 g, 9.5 mmol) were dissolved in H$_2$O (10 cm^3), 'BuOH (10 cm^3) and saturated NaHCO$_3$ solution (10 cm^3) and the mixture heated at reflux overnight. TLC analysis (40 % ethyl acetate/petrol) showed two spots due to a mixture of the mono and diacids. The mixture was filtered through Celite® and the filtrate extracted with diethyl ether (3 x 20 cm^3). The organic phase was discarded and the aqueous phase was made strongly acidic (pH1) by the addition of HCl (12M) and extracted with diethyl ether (3 x 20 cm^3). The combined organic extracts were dried over magnesium sulfate and the solvent was removed *in vacuo* to leave a colourless solid. This was dissolved in methanol (20 cm^3), H$_2$SO$_4$ (1 cm^3) and the mixture was heated at reflux for 6 hours. TLC analysis (40 % ethyl acetate/petrol) showed that none of the mono and diacids remained and two new products had formed. The mixture was cooled and the solvent removed *in vacuo* to leave a residue which was purified by flash chromatography (8 % ethyl acetate/petrol) to give the desired compound (89 mg, 15 %).

δ_H (270 MHz, CDCl$_3$) 3.96 (s, 6H), 8.06 (s, 2H). δ_C (68 MHz, CDCl$_3$) 52.9, 120.2, 135.4, 136.6, 164.5. MS FAB$^+$ [M+1]$^+$ 353.0. Found: C, 34.1; H, 2.3 %. Calc. for C$_{10}$H$_8$Br$_2$O$_4$: C, 34.1; H, 2.3 %. FTIR v_{max}/cm^{-1} (nujol) 1735.5 CO. mp 141-142 °C (Ref. 143.5-145 °C[19]).

Methyl 2,5-dibromo-4-methylbenzoate
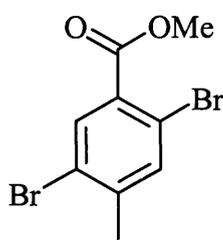
Methyl 2,5-dibromo-4-methylbenzoate was also collected (71 mg, 6 %).

δ_H (270 MHz, CDCl$_3$) 2.40 (s, 3H, CH$_3$), 3.93 (s, 3H, OCH$_3$), 7.53 (s, 1H), 8.00 (s, 1H).

2-Bromo-N-(tert-butoxycarbonyl)aniline (56)
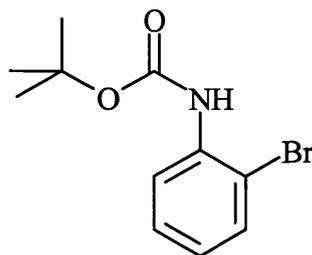
2-Bromoaniline (4.34 g, 25.2 mmol) was added to a suspension of sodium hydride (0.88 g, 27.5 mmol, 60 % dispersion in mineral oil) and THF (150 cm^3). This mixture

was heated at reflux for 1 hour and then allowed to cool to room temperature. Di-*tert*-

butyl dicarbonate (6.55 g, 30 mmol) was added and the mixture stirred for 0.5 hours.

A second portion of sodium hydride (0.88 g, 27.5 mmol, 60 % dispersion in mineral

oil) was added, and the mixture heated at reflux for 14 hours. The mixture was

allowed to cool to room temperature before quenching with water (30 cm^3). The

mixture was extracted with diethyl ether (3 x 20 cm^3), and the combined organic

extracts washed with saturated ammonium chloride solution (40 cm^3), saturated

sodium bicarbonate solution (40 cm^3) and then dried over sodium sulfate. The solvent

was removed *in vacuo* and the crude product was purified by flash chromatography

(10 % diethyl ether/petrol) to give the product as an oil (4.97 g, 73 %).

δ_H (270 MHz, CDCl$_3$) 1.47 and 1.5 (s, 9H, Rotamers), 6.89 (ddd, 1H, $^3J_{H-H}$ = 7.7, $^3J_{H-H}$

= 7.7, $^4J_{H-H}$ = 1.5, H4), 7.00 (brs, 1H, NH), 7.26 (dd, 1H, $^3J_{H-H}$ = 7.9, $^4J_{H-H}$ = 1.5, H5),

7.49 (dd 1H $^3J_{H-H}$ = 8.1, $^4J_{H-H}$ = 1.5, H3), 8.15 (dd, 1H, $^3J_{H-H}$ = 8.4, $^4J_{H-H}$ = 1.5, H6). δ_C

(68 MHz, CDCl$_3$) 28.3, 81.0, 112.4, 120.1, 123.8, 128.3, 132.2, 136.3, 152.3. Found:

C, 48.4; H, 5.2; N, 5.1 %. Calc. for C$_{11}$H$_{14}$BrNO$_2$: C, 48.6; H, 5.2; N, 5.2 %. FTIR

ν_{max}/cm^{-1} (neat) 1734.

α, α',2,5-Tetrabromo-p-xylene (58)
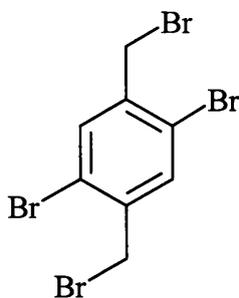
2,5-Dibromo-p-xylene (1.00 g, 3.78 mmol) and N-bromosuccinimide (6.74 g, 37.8 mmol) were dissolved in carbon tetrachloride (20 cm³). A catalytic amount of AIBN was added was added and the reaction mixture heated at reflux for three hours. TLC analysis (5 % diethyl ether/petrol) showed the absence of starting material and two new product spots. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. The residue was dissolved in chloroform (10 cm³) and was washed with water (10 cm³), HCl (2N, 10 cm³) and brine (10 cm³). The organic phase was dried over magnesium sulfate and the solvent removed *in vacuo* to leave a white solid (1.12 g, 70 %). The crude product was crystallised from toluene to leave the title compound as colourless crystals.

δ_H (270 MHz, CDCl₃) 4.52 (s, 4H), 7.60 (s, 2H).

N-(tert-Butoxycarbonyl)aniline (61)
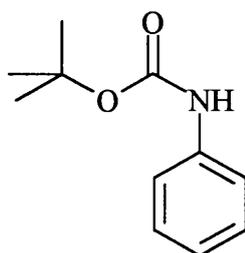
Aniline (5 cm³, 57.8 mmol) was dissolved in 1,4-dioxan (25 cm³) and water (25 cm³). Di-*tert*-butyl dicarbonate (13.88 g, 63.4 mmol) was added, and the mixture stirred at room temperature overnight. The mixture was then extracted with diethyl ether (3 x 20 cm³). The combined organic extracts were washed with saturated ammonium chloride (40 cm³) and brine (40 cm³) and then dried over magnesium sulfate. The solvent was removed *in vacuo* to give the crude product. The product was purified further by crystallisation from 60-80° petroleum ether (8.50 g, 76 %).

δ_H (270 MHz, CDCl$_3$) 1.62 (s, 9H), 6.58 (bs, 1H), 7.13 (ddd, 1H $^3J_{H\text{-}H}$ = 7.0, $^3J_{H\text{-}H}$ = 7.0, $^4J_{H\text{-}H}$ = 1.5, H4), 7.26 (dd, 2H, $^3J_{H\text{-}H}$ = 7.8, $^4J_{H\text{-}H}$ = 1.7, H2,6), 7.34 (ddd, 2H, $^3J_{H\text{-}H}$ = 8.1, $^3J_{H\text{-}H}$ = 8.1, $^4J_{H\text{-}H}$ = 1.7, H3,5). δ_C (68 MHz, CDCl$_3$) 28.3 C(CH_3)$_3$, 80.4 C(CH$_3$)$_3$, 118.5 C4, 122.9 C3, 128.9 C2, 138.3 C1, 152.7 CO. Found: C, 68.3; H, 8.0; N, 7.4 %. Calc. For C$_{11}$H$_{16}$NO$_2$: C, 68.4; H, 7.8; N, 7.3 %. MS EI [M]$^+$ 193.1. FTIR v_{max}/cm^{-1} (nujol) 1689 CO. mp 136-138 °C (Ref. 135-137 °C).

2-Trimethylsilyl-N-(tert-butoxycarbonyl)aniline (63)
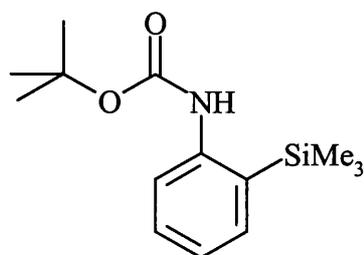
N-(tert-Butoxycarbonyl)aniline (200 mg, 1.03 mmol) was dissolved in anhydrous diethyl ether (3 cm^3) and cooled to -78 °C. ^{t}Butyllithium (1.53 cm^3 of a 1.7M solution in pentane, 2.6 mmol) was added dropwise to the solution. The reaction mixture was stirred at this temperature for fifteen minutes before allowing to warm to 0 °C, where the temperature was maintained for a further two hours. During this time the reaction mixture had changed colour from being colourless to pale orange. The reaction mixture was cooled to -78 °C and trimethylsilyl chloride (0.26 cm^3, 2.06 mmol) was added dropwise. The reaction mixture was then allowed to warm to 0 °C during which the colour of the mixture changed from pale yellow to a mustard yellow colour. TLC analysis (10 % ethyl acetate/petrol) showed no starting material remaining and the presence of a new compound. The reaction mixture was poured into saturated

ammonium chloride solution (20 cm³) and extracted with diethyl ether (2 x 10 cm³) the combined organic extracts were washed with brine (20 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* left the product as a colourless oil (232 mg, 85 %).

δ_H (270 MHz, CDCl₃) 0.35 (s, 9H, Si(CH_3)₃), 1.52 (s, 9H, C(CH_3)₃), 6.41 (brs, 1H, NH), 7.11 (ddd, 1H, $^3J_{H-H}$= 7.3, $^3J_{H-H}$ = 7.33, $^4J_{H-H}$ = 1.1), 7.36 (ddd, 1H, $^3J_{H-H}$= 7.8, $^3J_{H-H}$ = 7.8, $^4J_{H-H}$ = 1.5), 7.42 (dd, 1H, $^3J_{H-H}$ = 7.3, $^4J_{H-H}$ = 1.3), 7.67 (d, 1H, $^3J_{H-H}$ = 7.9).

N-(tert-Butoxycarbonyl)-2-amino-1-phenylboronic acid (57)

N-(*tert*-Butoxycarbonyl)aniline (200 mg, 1.04 mmol) was dissolved in diethyl ether (3 cm³) and the mixture cooled to -78 °C. ᵗButyllithium (0.2 cm³ of a 1.7M solution in pentane, 2.5 mmol) was added and the solution stirred for 15 minutes. The reaction mixture then allowed to warm to 0 °C and stirred for a further 2 hours. Trimethyl borate (0.59 cm³, 5.2 mmol) was added and the mixture stirred for a further two hours, before allowing to warm to room temperature. Hydrochloric acid (5 % v/v, 10 cm³) was added to the reaction mixture and stirred for 10 minutes. Sodium chloride was added until the solution was saturated and the solution extracted with diethyl ether (3 x 5cm³). The combined organic fractions were dried over sodium sulfate before removing the solvent *in vacuo* to leave the title compound as a colourless foam. The product was used without further purification in subsequent reactions.

Diethanolamine [N-(tert-Butoxycarbonyl)aniline] boronate (65)
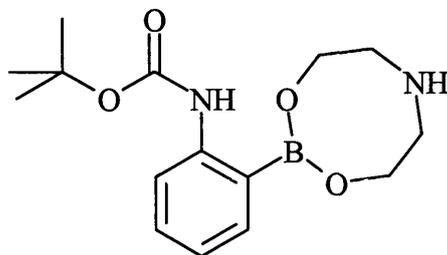
The crude boronic acid (50 mg) was dissolved in toluene (2 cm^3) and diethanolamine (100 mg) added. The solution was heated at reflux for 7 hours, monitoring the reaction by TLC (40 % diethyl ether/petrol). When the reaction was complete, the solvent was removed *in vacuo*. The residue was dissolved in $CHCl_3$ and washed with 2M Na_2CO_3 and brine. The organic was dried over magnesium sulfate, and the solvent removed *in vacuo* to leave a colourless solid (32 mg).

δ_H (270 MHz, $CDCl_3$) 1.47 (s, 9H), 2.70-2.80 (m, 2H), 3.19-3.30 (m, 2H), 3.95-4.00 (m, 4H), 5.00 (br s, 1H), 6.93 (ddd, 1H, $^3J_{H-H}$ = 7.3, $^3J_{H-H}$ = 7.3, $^4J_{H-H}$ = 1.5), 7.20 (ddd, 1H, $^3J_{H-H}$ = 6.7, $^3J_{H-H}$ = 6.7, $^4J_{H-H}$ = 2.0), 7.38 (dd, 1H, $^3J_{H-H}$ = 5.7, $^4J_{H-H}$ = 2.0), 7.91 (d, 1H, $^3J_{H-H}$ = 8.4), 9.20 (br s, 1H). δ_C (68 MHz, $CDCl_3$) 28.5, 51.3, 63.3, 79.1, 118.2, 121.9, 128.5, 133.9, 143.3, 153.6. HRMS FAB$^+$ Calc. for $C_{15}H_{23}{}^{11}BN_2O_4$: 306.1751. Found: 306.1755.

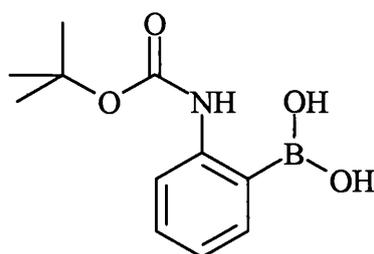*2-[2-(N-tert-Butoxycarbonylamino)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolidine*

(66)
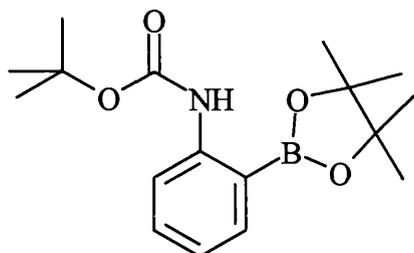
N-(*tert*-Butoxycarbonyl)aniline (200 mg, 1.04 mmol) was dissolved in diethyl ether (3 cm^3) and the mixture cooled to -78 °C. ^{t}Butyllithium (0.2 cm^3 of a 1.7M solution in pentane, 2.5 mmol) was added and the solution stirred for 15 minutes. The reaction mixture then allowed to warm to 0 °C and stirred for a further 2 hours. Trimethyl borate (0.59 cm^3, 5.2 mmol) was added and the mixture stirred for a further two hours. Pinacol (0.50 g, 4.2 mmol) in diethyl ether (5 cm^3) was added, and the mixture was allowed to warm to room temperature and left stirring for 48 hours. The mixture was filtered through Celite$^®$ to remove the excess pinacol, and the solvent removed *in vacuo*. The crude product was then purified by flash chromatography (5 % diethyl ether/petrol) to leave the product (131 mg, 39 %).

δ_H (270 MHz, CDCl$_3$) 1.36 (s, 12H, pinacol CH$_3$), 1.52 (s, 9H, C(CH$_3$)$_3$), 6.97 (ddd, 1H, $^3J_{H-H}$ = 7.4, $^3J_{H-H}$ = 7.4, $^4J_{H-H}$ = 1.0, H4), 7.42 (ddd, 1H, $^3J_{H-H}$ = 8.6, $^3J_{H-H}$ = 8.6, $^4J_{H-H}$ = 1.8, H5), 7.72 (dd, 1H, $^3J_{H-H}$ = 7.5, $^4J_{H-H}$ = 1.8, H3), 8.18 (d, 1H, $^3J_{H-H}$ = 8.4, H6), 8.69 (brs, 1H, NH). δ_C (68 MHz, CDCl$_3$) 24.8 pinacol CH$_3$, 28.3 C(CH$_3$)$_3$, 79.7 *C*(CH$_3$)$_3$, 84.1 BO*C*(CH$_3$)$_2$, 117.6 C4, 121.5 C3, 132.7 C5, 136.1 C1, 145.2 C2, 153.1 CO. HRMS FAB$^+$ Calc. for C$_{17}$H$_{26}$^{11}BNO$_4$: 319.1955. Found: 319.1959.

1,4-Bis-(2-formylphenyl)benzene (79)
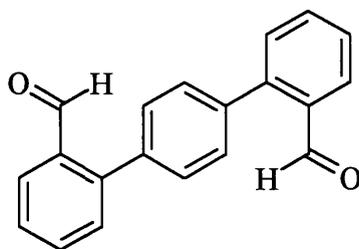
1,4-Diiodobenzene (147 mg, 0.44 mmol) was dissolved in toluene (4 cm^3) and *tetrakis-*

(triphenylphosphine) palladium(0) (30 mg, 3 mol %) added, and the mixture stirred at

room temperature for 30 minutes. A solution of 2-formylbenzeneboronic acid (200 mg,

1.3 mmol) in methanol (2 cm^3) and Na$_2$CO$_3$ (2M, 2 cm^3) were added and the mixture

heated at reflux for 24 hours. TLC analysis (20 % diethyl ether/petrol) showed a

mixture of two new products. The solvent was removed *in vacuo* and the residue

dissolved in diethyl ether (10 cm^3) and washed with brine (10 cm^3). The organic phase

was dried over magnesium sulfate and the solvent removed. Purification by column

chromatography (20 % diethyl ether/petrol) gave two compounds, which were

identified by NMR spectroscopy as the mono- and di-substituted products.

Yield=26 mg, 22 %. δ_H (270 MHz, CDCl$_3$) 7.50-7.60 (m, 8H), 7.72 (ddd, 2H, $^3J_{H\text{-}H}$ =

7.5, $^3J_{H\text{-}H}$ = 7.5, $^4J_{H\text{-}H}$ = 1.5), 8.08 (dd, 2H, $^3J_{H\text{-}H}$ = 7.5, $^4J_{H\text{-}H}$ = 1.5), 10.03 (s, 2H,

CHO). δ_C (68 MHz, CDCl$_3$) 127.7, 128.0, 128.3, 128.5, 130.1, 130.7, 131.7, 133.6,

137.6, 145.0, 191.7. MS EI$^+$ [M]$^+$ 286.2.

2-Formyl-4'-iodobiphenyl (78)
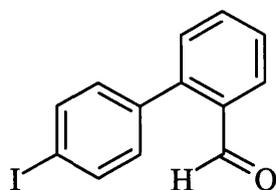
Yield=48 mg, 35 %. δ_H (270 MHz, CDCl$_3$) 7.12 (dd, 2H, $^3J_{H-H}$ = 8.5, $^4J_{H-H}$ = 1.5), 7.41

(dd, 1H, $^3J_{H-H}$ = 6.2, $^4J_{H-H}$ = 1.3), 7.51 (ddd, 1H, $^3J_{H-H}$ = 6.2, $^3J_{H-H}$ = 6.2, $^4J_{H-H}$ = 1.3),

7.65 (ddd, 1H, $^3J_{H-H}$ = 6.2, $^3J_{H-H}$ = 6.2, $^4J_{H-H}$ = 1.3), 7.81 (dd, 2H, $^3J_{H-H}$ = 8.5, $^4J_{H-H}$ =

1.5), 8.02 (dd, 1H, $^3J_{H-H}$ = 6.2, $^4J_{H-H}$ = 1.3), 9.97 (s, 1H, CHO). δ_C (68 MHz, CDCl$_3$)

94.2, 128.0, 128.2, 130.6, 131.8, 133.7, 137.3, 137.6, 144.6, 191.9. MS EI [M]$^+$ 308.0.

HRMS EI$^+$ Calc. for C$_{13}$H$_9$IO 307.9700. Found 307.9684.

The same procedure was repeated, adding 2-formylbenzene boronic acid (200 mg, 1.3

mmol) as a solution in toluene (2 cm^3) in place of methanol. The monosubstituted

product was collected in 17 % yield, and no disubstituted product was collected.

The same procedure was repeated, using DME (4 cm^3) as the solvent for 1,4-

diiodobenzene (147 mg, 0.44 mmol) and 2-formylbenzene boronic acid (200 mg, 1.3

mmol) was added as a solution in DME (2 cm^3). The monosubstituted product was

collected in 14 % yield and the disubstituted product collected in 25 % yield.

2',5'-Dimethyl-p-terphenyl (85)
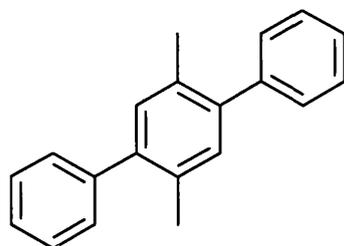
2,5-Dibromo-*p*-xylene (200 mg, 0.76 mmol) and PdCl$_2$(dppf) (trace) were dissolved

in anhydrous THF (2 cm^3). Phenylmagnesium bromide (0.79 cm^3 of a 3.0M solution

in THF, 2.28 mmol) was added dropwise at room temperature. The reaction mixture

was then heated at reflux overnight. After this time TLC analysis (petrol) showed no

starting material remaining. The reaction was quenched by adding silica followed by

removal of the solvent *in vacuo*. The silica added directly to the top of a column

which was eluted with petrol to give the title compound (157 mg, 80 %).

δ_H (270 MHz, CDCl$_3$) 2.28 (s, 6H, CH$_3$), 7.16 (s, 2H, H3',6'), 7.45-7.33 (m, 10H, Ar

H). δ_C (100 MHz, CDCl$_3$) 19.9, 126.7, 128.1, 129.2, 131.8, 132.6, 140.8, 141.7. MS

FAB$^+$ [M]$^+$ 258.2. HRMS FAB$^+$ Calc. for C$_{20}$H$_{18}$: 258.1409. Found: 258.1405. mp

181-183 °C (Ref. 182-184 °C[30]).

Also collected from the column was the monosubstituted product (84), (18 mg, 9 %).

4-Bromo-2,5-dimethylbiphenyl (84)
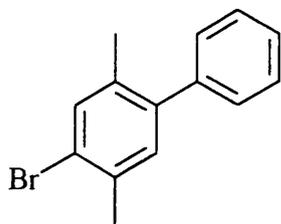
δ_H (270 MHz, CDCl$_3$) 2.20 (s, 3H, CH$_3$), 2.37 (s, 3H, CH$_3$), 7.08 (s, 1H), 7.44-7.24 (m, 6H).

2',5'-Dimethyl-p-terphenyl (85) prepared via a Suzuki coupling

2,5-Dibromo-*p*-xylene (100 mg, 0.38 mmol), phenylboronic acid (93 mg, 0.76 mmol), sodium carbonate (159 mg, 1.5 mmol) and *tetrakis*-(triphenylphosphine) palladium(0) (13 mg, 0.01 mmol) were dissolved in water (2 cm^3) and DME (3 cm^3), and heated at reflux. The reaction was monitored by TLC analysis (petrol), which showed the formation of 2',5'-dimethyl-*p*-xylene. The reaction was allowed to cool to room temperature and extracted with diethyl ether (3 x 2 cm^3). The combined organic extracts were dried over magnesium sulfate and the solvent removed *in vacuo*. The crude material was purified by column chromatography, eluting with petrol. The product was obtained as a colourless solid (25 mg, 25 %). Also collected was the monosubstituted product as a colourless oil (7 mg, 7 %)

2,5-Dibromo-*p*-xylene (1 g, 3.8 mmol) was dissolved in toluene (20 cm^3). *Tetrakis*-(triphenylphosphine) palladium(0) (263 mg, 3 mol %) was added and stirred at room temperature for 30 minutes, during which the solution changed colour from yellow to

red. Benzeneboronic acid (920 mg, 7.6 mmol) and caesium carbonate (4.94 g, 15.2 mmol) were added, and the mixture heated at reflux for 24 hours. TLC analysis (petrol) showed no starting material remaining and a mixture of the mono- and di-substituted products. The solvent was removed *in vacuo* and the residue partitioned between water (20 cm^3) and diethyl ether (20 cm^3). The organic phase was washed with brine (20 cm^3) and dried over magnesium sulfate. Purification by column chromatography (petrol) gave the monosubstituted product as a colourless oil (241 mg, 24 %), and the disubstituted product as a colourless solid (411 mg, 42 %).

The same procedure was repeated using potassium phosphate (3.2 g, 15.2 mmol) in place of caesium carbonate. The monosubstituted product was collected as an colourless oil (423 mg, 43 %) and the disubstituted product was collected as a colourless solid (230 mg, 23 %).

The same procedure was also used using Ba(OH)$_2$.8H$_2$O (7.2 g, 15.2 mmol) as the base. The monosubstituted product was collected as an colourless oil (333 mg, 34 %) and the disubstituted product was collected as a colourless solid (9 mg, 9 %).

g, 15.2 mmol) were added, and the mixture heated at reflux for 24 hours. TLC

analysis (petrol) showed no starting material remaining and a mixture of the mono-

and di- substituted products. The solvent was removed *in vacuo* and the residue

partitioned between water (20 cm^3) and diethyl ether (20 cm^3). The organic phase was

washed with brine (20 cm^3) and dried over magnesium sulfate. Purification by column

chromatography (petrol) gave the monosubstituted product as a colourless oil (241

mg, 24 %), and the disubstituted product as a colourless solid (411 mg, 42 %).

The same procedure was repeated using potassium phosphate (3.2 g, 15.2 mmol) in

place of caesium carbonate. The monosubstituted product was collected as an

colourless oil (423 mg, 43 %) and the disubstituted product was collected as a

colourless solid (230 mg, 23 %).

The same procedure was also used using Ba(OH)$_2$.8H$_2$O (7.2 g, 15.2 mmol) as the

base. The monosubstituted product was collected as an colourless oil (333 mg, 43 %)

and the disubstituted product was collected as a colourless solid (9 mg, 23 %).

2,5-Diphenylterephthalic acid (86)
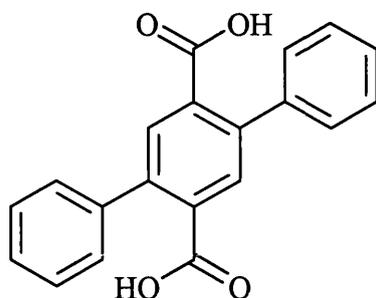
2',5'-Dimethyl-*p*-terphenyl (1.48 g, 5.7 mmol) was dissolved in a pyridine/water mixture (9:1, 20 cm^3) and potassium permanganate (3.60 g, 22.9 mmol) was added and the mixture heated to reflux. When the purple colour of the permanganate had disappeared, a second portion of potassium permanganate was added (3.60 g, 22.9 mmol) followed by water (5 cm^3). This procedure was repeated several times, slowly reducing the amount of potassium permanganate, until a persistent purple colour remained. The mixture was then filtered through Celite® to remove the manganese dioxide. The filter contents were washed twice with hot water (20 cm^3) to leave a clear filtrate. The filtrate was then treated with decolourising charcoal and heated. After cooling, the charcoal was filtered off to leave a yellow filtrate. The solution was made strongly acidic (pH1) by the addition of HCl (12M), which gave a white precipitate. The precipitate was collected by suction filtration and washed with cold water. The precipitate was then dissolved in saturated sodium carbonate solution (20 cm^3) and washed with diethyl ether (2 x cm^3). The aqueous phase was made strongly acidic with the addition of HCl (12M), which gave a white precipitate. The precipitate was collected by suction filtration, washed with cold water and dried *in vacuo* at 60 °C (435 mg, 24 %).

δ_H (270 MHz, DMSO-d_6) 7.58-7.70 (m, 10H), 7.90 (s, 2H, H3,6), 12.23 (s, 2H). δ_C (68

MHz, DMSO-d_6) 127.8, 128.5, 131.1, 134.4, 139.7, 139.8, 168.9. MS FAB$^+$ [M+1]$^+$

319.1. FAB$^-$ [M-1]$^+$ 317.2. HRMS FAB$^+$ [M+1]$^+$ 319.0962. Calc. for $C_{20}H_{15}O_4$

319.0970. mp 301-303 °C (Ref. 303-305 °C[29]).

Methyl 2,5-diphenylterephthalate (89)
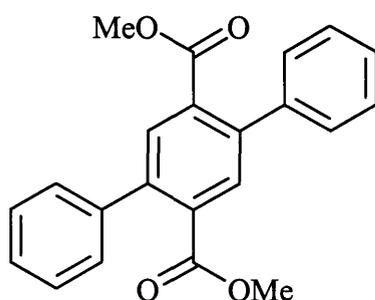
2,5-Diphenylterephthalic acid (176 mg, 0.5 mmol) was dissolved in methanol (2 cm^3)

and sulfuric acid (0.1 cm^3) and heated at reflux. TLC analysis (60 % diethyl

ether/petrol) showed the formation of a new less polar compound. The reaction

mixture was cooled to room temperature and made basic by the addition of sodium

hydroxide solution (1 M). The aqueous phase was extracted with diethyl ether (3 x 10

cm^3) and the combined organic extracts were dried over magnesium sulfate. Removal

of the solvent *in vacuo* gave the title compound as a colourless gum (10 mg , 5 %).

δ_H (270 MHz, CDCl$_3$) 3.66 (s, 6H, OCH$_3$), 7.26-7.44 (m, 10H, Ar H), 7.83 (s, 2H,

H3,6). δ_C (68 MHz, CDCl$_3$) 52.2 OCH$_3$, 127.7, 128.2, 128.3, 132.0, 133.1, 139.89,

139.94, 168.3 CO.

2',5'-Bis(bromomethyl)-p-terphenyl (96)
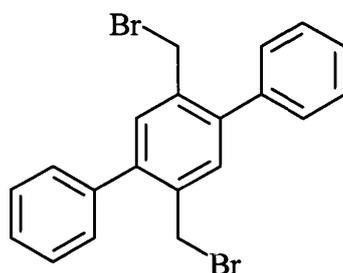
2',5'-Dimethyl-*p*-terphenyl (1.00 g, 3.9 mmol), *N*-bromosuccinimide (1.38 g, 7.7 mmol) and benzoyl peroxide (10 mg) were dissolved in carbon tetrachloride (15 cm^3) and heated at reflux for 3 hours. The mixture was then allowed to cool to room temperature, and the precipitate formed (succinimide) was removed by filtration. The filtrate was stirred at 0 °C overnight, after which a white precipitate had formed. The precipitate was isolated by suction filtration to give the crude product (1.63 g). The crude product was used directly in the next step, where it was easier to purify. The product could be purified, with considerable loss, by several crystallisations from carbon tetrachloride.

δ_H (270 MHz, CDCl$_3$) 4.40 (s, 4H), 7.2-7.5 (m, 12H). Found: C, 57.5; H, 3.8 %. Calc. for C$_{20}$H$_{16}$Br$_2$: C, 57.7; H, 3.9 %. mp 164-165 °C (Ref. 165 °C[31]).

2',5'-Bis(acetoxymethyl)-p-terphenyl (98)
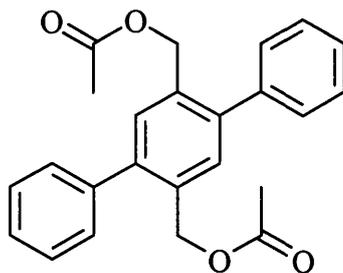
A mixture of crude 2',5'-bis(bromomethyl)-p-terphenyl (1.00 g) and anhydrous sodium acetate (820 mg, 10 mmol) in glacial acetic acid (7.5 cm^3) were heated at reflux overnight. After cooling to room temperature, the reaction mixture was poured into water (40 cm^3). The precipitate formed was collected by suction filtration and purified by column chromatography, eluting with dichloromethane. The title compound was collected as a colourless solid (390 mg).

δ_H (270 MHz, CDCl$_3$) 2.03 (s, 6H, COCH$_3$), 5.07 (s, 4H, -CH$_2$-), 7.37-7.44 (m, 12H, Ar H). Found: C, 77.1; H, 6.0 %. Calc. for C$_{24}$H$_{22}$O$_4$: C, 77.0; H, 5.9 %. mp 124-126 °C. (Ref. 125-126 °C[31]).

2',5'-Bis(hydroxymethyl)-p-terphenyl (99)
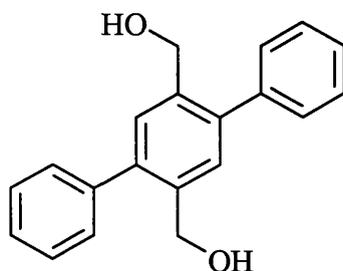
A suspension of 2',5'-bis(acetoxymethyl)-p-terphenyl (200 mg, 0.5 mmol) in methanol (4 cm^3) and 15 % (w/v) sodium hydroxide (0.5 cm^3) was stirred at 50 °C for 4 hours. On cooling to room temperature, the mixture solidified. Water was added to the mixture which was then filtered. The filter contents were washed with cold water and allowed to dry on the filter. The product was crystallised from dichloromethane to give the product as colourless crystals (126 mg, 81 %).

δ_H (270 MHz, CDCl$_3$) 1.57 (brs, 2H, OH), 4.66 (s, 4H, -CH$_2$-), 7.42-7.49 (m, 12H, Ar

H). Found: C, 82.7; H, 6.2 %. Calc. for C$_{20}$H$_{18}$O$_2$: C, 82.7; H, 6.3 %. mp 177-178 °C

(Ref. 180 °C[31]).

2',5'-Dicarbaldehyde-p-terphenyl (95)
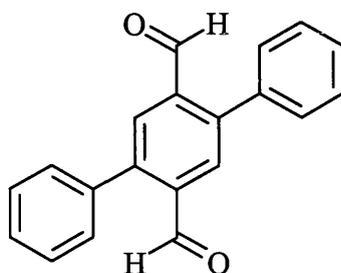
A suspension of PCC (163 mg, 0.76 mmol) in dichloromethane (1 cm^3) was added

dropwise to a solution of 2',5'-bis(hydroxymethyl)-*p*-terphenyl (100 mg, 0.34 mmol)

in dichloromethane (1 cm^3) and stirred at room temperature. After 2 hours, TLC

analysis (5 % diethyl ether/petrol) showed a new product forming. When the reaction

was complete, the reaction mixture was washed with water (2 x 5 cm^3), and dried over

magnesium sulfate. Purification by column chromatography, eluting with

dichloromethane, gave the title compound as a yellow solid (48 mg, 49 %).

δ_H (270 MHz, CDCl$_3$) 7.42-7.53 (m, 10H, Ar H), 8.11 (s, 2H, H3,6), 10.08 (s, 2H,

CHO). Found: C, 83.7; H, 5.0 %. Calc. for C$_{12}$H$_8$N$_2$O$_4$: C, 83.9; H, 4.9 %. mp 189-191

°C (Ref. 191 °C[31]).

O,O,O,O-Tetraacetoxy-2,5-dibromo-1,4-bis(dihydroxymethyl)benzene (102)
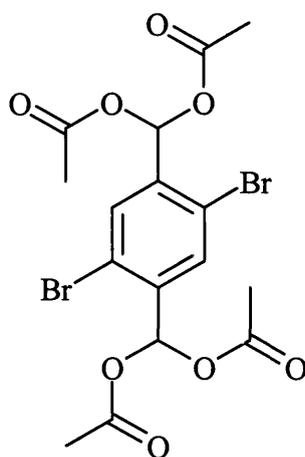
2,5-Dibromo-*p*-xylene (5.0 g, 18.9 mmol) was dissolved in acetic acid (30.0 g), acetic

anhydride (60.0 g) and sulfuric acid (9.0 g) and the solution cooled to 0 °C in an ice

bath. Chromium trioxide (6.0 g, mmol) was added portionwise, and the mixture left

stirring overnight. The reaction mixture was poured into water (200 cm^3) and cooled

using an ice bath. The precipitate that formed was collected by suction filtration,

before being crystallised from 95 % ethanol to give the desired compound as

colourless prisms (2.14 g, 23 %).

δ_H (270 MHz, CDCl$_3$) 2.16 (s, 12H), 7.75 (s, 2H) 7.84 (s, 2H). δ_C (68 MHz, CDCl$_3$)

20.6, 87.9, 121.4, 132.5, 137.8, 168.1. Found: C, 38.5; H, 3.2 %. Calc. for

C$_{16}$H$_{16}$Br$_2$O$_8$: C, 38.7; H, 3.3. MS CI [C$_8$H$_4$Br$_2$O$_2$]$^+$ 292.9. FTIR v_{max}/cm^{-1} (nujol) 1753

CO. mp 218-220 °C.

2,5-Dibromoterephthalaldehyde ethyl acetal (103)
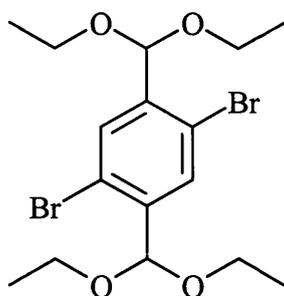
O,O,O,O-Tetraacetoxy-2,5-dibromo-1,4-bis(dihydroxymethyl)benzene (1 g, 2.0 mmol) was dissolved in water (10 cm^3), ethanol (10 cm^3) and sulfuric acid (1 cm^3). The reaction mixture was heated at reflux for four hours and allowed to cool to room temperature. The solvent was removed *in vacuo* to leave the crude product as an off white solid. The crude product was crystallised from 95 % ethanol to leave the title compound as a colourless solid, (558 mg, 63 %).

δ_H (400 MHz, CDCl$_3$) 1.25 (t, 12H, $^3J_{H-H}$ = 7.1, CH_3), 3.57 (q, 2H, $^3J_{H-H}$ = 7.2, CH_2), 3.59 (q, 2H, $^3J_{H-H}$ = 7.2, CH_2), 3.65 (q, 2H, $^3J_{H-H}$ = 7.2, CH_2), 3.67 (q, 2H, $^3J_{H-H}$ = 7.1, CH_2), 5.59 (s, 2H, Ar-CH), 7.81 (s, 2H, Ar-H). δ_C (100 MHz, CDCl$_3$) 15.1 CH$_3$, 62.5 CH$_2$, 100.5 Ar-CH, 121.7 C2,5, 132.4 C3,6, 139.6 C1,4. MS FAB$^+$ [M-C$_2$H$_5$O]$^+$ 395.0. Found: C, 43.7; H, 5.5 %. Calc. for C$_{16}$H$_{24}$Br$_2$O$_4$: C, 43.7; H, 5.5 %. mp 80 °C.

N-Acetyl-2-bromoaniline (105)
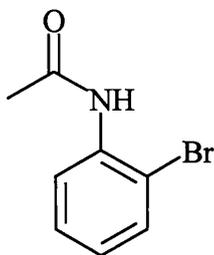
2-Bromoaniline (1.00 g, 5.8 mmol) was dissolved in acetic anhydride (20 cm^3) and stirred at room temperature. Sulfuric acid (18M, 0.5 cm^3) was then added, causing the reaction mixture to darken. TLC analysis (40 % ethyl acetate/petrol) showed the disappearance of starting material and the presence of a new more polar product. The mixture was poured into water (100 cm^3) and extracted with ethyl acetate (4 x 20 cm^3). The combined organic extracts were dried over magnesium sulfate and the solvent removed *in vacuo*. The residue was crystallised from 20 % ethyl acetate/petrol to leave the product as colourless prisms (352 mg, 28 %).

δ_H (270 MHz, CDCl$_3$) 2.24 (s, 3H, COCH_3), 6.98 (dd, 1H, $^3J_{H-H}$ = 7.7, $^3J_{H-H}$ = 7.7, H4), 7.31 (dd, 1H, $^3J_{H-H}$ = 7.8, $^3J_{H-H}$ = 7.8, H5), 7.53 (d, 1H, $^3J_{H-H}$ = 8.0, H3), 7.61 (brs, 1H, NH), 8.33 (d, 1H, $^3J_{H-H}$ = 8.0, H6). δ_C (68 MHz, CDCl$_3$) 24.9, 121.9, 125.2, 128.4, 132.2, 135.7, 168.6. Found: C, 44.9; H, 3.7; N, 6.5 %. Calc. For C$_8$H$_8$BrNO: C, 44.9; H, 3.8; N, 6.5. MS FAB$^+$ [M+1]$^+$ 216.1. mp 97-99 °C (Ref. 98-99 °C).

N-Benzyl-2-bromoaniline (113)
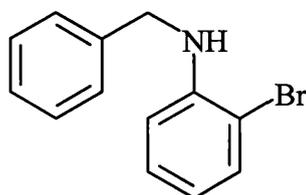
2-Bromoaniline (200 mg, 1.2 mmol) was dissolved in THF (5 cm^3) and cooled to

-78 °C. "Butyllithium (0.65 cm^3 of a 1.8M solution in hexane, 1.2 mmol) was added

dropwise and the mixture left stirring for 30 minutes. Benzyl bromide (0.14 cm^3, 1.2

mmol) was added and the mixture allowed to warm to room temperature overnight.

The reaction mixture was poured into brine (10 cm^3) and extracted with diethyl ether

(2 x 10 cm^3). The combined organic extracts were dried over magnesium sulfate and

the solvent removed *in vacuo* to leave a colourless solid (247 mg, 81 %).

δ_H (270 MHz, CDCl$_3$) 4.50 (s, 2H, NCH_2), 4.58 (br s, 1H, NH), 6.54-6.65 (m, 2H),

7.09 (dd, 1H, $^3J_{H-H}$ = 8.8, $^4J_{H-H}$ = 1.5), 7.24-7.44 (m, 6H). mp 34-36 °C (Ref. 34-35

°C[44]).

N,N-Dibenzyl-2-bromoaniline (115)
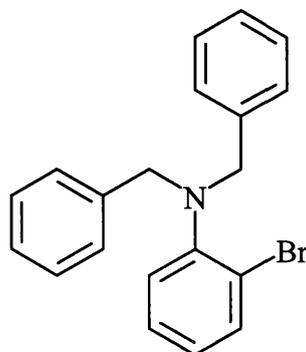
2-Bromoaniline (512 mg, 2.98 mmol) was dissolved in saturated sodium bicarbonate solution (10 cm^3) and benzyl bromide (0.89 cm^3, 7.44 mmol) added. The mixture was heated at reflux for 2 hours and then allowed to cool to room temperature. The reaction mixture was extracted with diethyl ether (2 x 10 cm^3) and the combined organic extracts dried over magnesium sulfate. Removal of the solvent *in vacuo* left the title compound as a colourless gum (805 mg, 77 %).

δ_H (270 MHz, CDCl$_3$) 4.16 (s, 4H), 6.80-6.90 (m, 1H), 7.04-7.14 (m, 1H), 7.17-7.39 (m, 12H).

Diisopropylbenzamide boronic acid (118)
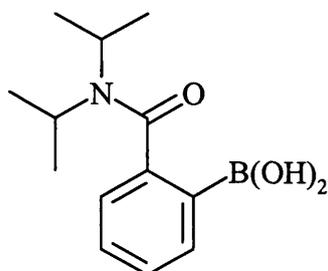
N,*N*-Diisopropylbenzamide (1.00 g, 4.9 mmol) was dissolved in dry diethyl ether (10 cm^3) and cooled to -78 °C. 'Butyllithium (4.9 mmol) was added dropwise, and the mixture stirred for 1 hour. Triisopropyl borate (3.4 cm^3, 14.7 mmol) was added, and the mixture warmed to room temperature overnight. The solvent was removed *in vacuo* to leave a colourless solid. The product was used without further purification in subsequent reactions.

Diethanolamine boronate ester of Diisopropylbenzamide boronic acid (119)
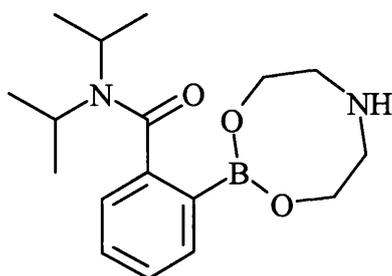
The crude boronic acid (50 mg) was dissolved in toluene (2 cm^3) and diethanolamine

(100 mg) added. The solution was heated at reflux for 7 hours, monitoring the reaction

by TLC (40 % diethyl ether/petrol). When the reaction was complete, the solvent was

removed *in vacuo*. The residue was dissolved in CHCl$_3$ and washed with 2M Na$_2$CO$_3$

and brine. The organic was dried over magnesium sulfate, and the solvent removed *in*

vacuo to leave a colourless solid (37 mg).

δ_H (270 MHz, CDCl$_3$) 1.11 (dd, 6H, $^3J_{H-H}$ = 7.5, $^3J_{H-H}$ = 7.5), 1.53 (dd, 6H, $^2J_{H-H}$ = 15.2,

$^3J_{H-H}$ = 6.8), 2.75 (m, 2H), 3.20 (m, 1H), 3.46-4.15 (m, 5H), 7.01 (dd, 1H, $^3J_{H-H}$ = 6.8,

$^4J_{H-H}$ = 1.5), 7.19-7.35 (m, 2H), 7.82 (dd, 1H, $^3J_{H-H}$ = 5.9, $^4J_{H-H}$ = 1.7). δ_C (68 MHz,

CDCl$_3$) 15.4, 19.5, 33.1, 44.1, 48.9, 49.6, 61.0, 61.4, 123.2, 125.74, 126.5, 131.6,

133.8, 141.5, 174.3. MS FAB$^+$ [M+1]$^+$ 319.3. FAB$^-$ [M-1]$^+$ 317.3. FTIR v_{max}/cm^{-1}

(nujol) 1609 CO. mp 201-203 °C.

N,N-Dibenzylbenzamide (120)
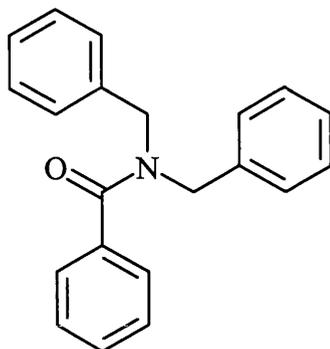
Dibenzylamine (5.8 cm^3, 0.03 mmol) was dissolved in THF (40 cm^3) and cooled to -78 °C. ^{n}Butyllithium (12 cm^3 of a 2.5M solution in hexane, 0.03 mmol) was added dropwise to the solution and stirred for 15 minutes. Ethyl benzoate (4.3 cm^3, 0.03 mmol) was added dropwise and the reaction mixture allowed to warm to room temperature overnight. The reaction mixture was poured into hydrochloric acid (10 % v/v, 100 cm^3) and extracted with diethyl ether (3 x 20 cm^3). The organic phase was washed with brine (20 cm^3) and dried over magnesium sulfate. The solvent was removed *in vacuo* to leave the product as a solid. The crude product was crystallised from 95 % ethanol to leave the product as a colourless solid (7.1 g, 78 %).

N,N-Dibenzyl-2-bromobenzamide (121)
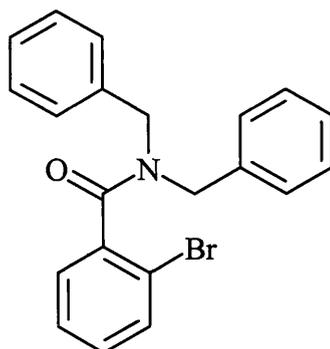
Dibenzylamine (5.77 cm^3, 30 mmol) was dissolved in anhydrous THF (40 cm^3) and cooled to -78 °C. ^{n}BuLi (12 cm^3 of a 2.5M solution in hexane, 30 mmol) was added dropwise and stirred for thirty minutes. Methyl 2-bromobenzoate (4.20 cm^3, 30 mmol) was added dropwise to the reaction mixture and allowed to warm to room temperature. The reaction mixture was poured into brine (30 cm^3) and extracted with diethyl ether (3 x 20 cm^3). The combined organic extracts were dried over magnesium sulfate and the solvent removed *in vacuo*. The residue was purified by column chromatography (20 % diethyl ether/petrol) to leave a colourless solid (4.83 g, 42 %).

δ_H (400 MHz, CDCl$_3$) 4.14 (m, 2H), 4.31 (d, 1H, $^2J_{H-H}$ = 15.9), 5.31 (d, 1H, $^2J_{H-H}$ = 14.7), 7.11 (d, 1H, $^3J_{H-H}$ = 6.7), 7.21 (ddd, 1H, $^3J_{H-H}$ = 7.6, $^3J_{H-H}$ = 7.6, $^4J_{H-H}$ = 1.8), 7.26-7.39 (m, 11H), 7.57 (d, 1H, $^3J_{H-H}$ = 7.6). δ_C (100 MHz, CDCl$_3$) 46.4, 50.7, 119.4, 127.4, 127.6, 127.6, 127.8, 128.0, 128.3, 128.5, 128.7, 128.7, 129.0, 130.3, 132.9, 135.7, 136.2, 137.9, 169.6. Found: C, 66.3; H, 4.7; N, 3.6 %. Calc. For C$_{21}$H$_{18}$BrNO: C, 66.3; H, 4.8; N, 3.7 %. MS FAB$^+$ [M]$^+$ 380.2. mp 135-137 °C.

N,N-Diisopropyl-4'-bromo-2-biphenylbenzamide (122)
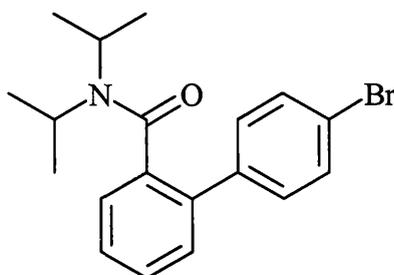
1,4-Dibromobenzene (250 mg, 1.1 mmol) and *tetrakis*-triphenylphosphine palladium(0) were suspended in DME (3 cm^3) and stirred at room temperature for 30 minutes. *N,N*-Diisopropylbenzamidephenyl boronic acid (530 mg, 2.2 mmol) was added as a solution in DME (2 cm^3) to the reaction mixture followed by sodium carbonate solution (2M, 2.5 cm^3). The reaction mixture was heated at reflux for 24 hours. TLC analysis (10 % diethyl ether/petrol) showed the presence of a new product and the disappearance of the starting material. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (10 % diethyl ether/petrol) to leave the title compound as a colourless solid, (71 mg, 18 %).

δ_H (270 MHz, CDCl$_3$) 0.43 (d, 3H, $^3J_{H-H}$ = 6.6, CH$_3$), 0.91 (d, 3H, $^3J_{H-H}$ = 6.8, CH$_3$), 1.30 (d, 3H, $^3J_{H-H}$ = 6.8, CH$_3$), 1.52 (d, 3H, $^3J_{H-H}$ = 6.8, CH$_3$), 3.26 (heptet, 1H, $^3J_{H-H}$ = 6.8, ^{i}PrCH), 3.41 (heptet, 1H, $^3J_{H-H}$ = 6.8, ^{i}PrCH), 7.28-7.53 (m, 8H, Ar-H). δ_C (68 MHz, CDCl$_3$) 19.5 *C*H$_3$, 20.6 *C*H$_3$, 45.6 ^{i}Pr*C*H, 50.6 ^{i}Pr*C*H, 121.8 C4', 126.5, 127.9, 128.6, 129.1, 130.9 C2', 131.3 C3', 136.3, 137.7 C1', 138.7 C2, 169.9 CO. MS FAB$^+$ [M+1]$^+$ 360.1. HRMS FAB$^+$ Requires for C$_{19}$H$_{23}$^{79}BrNO 360.0963, found 360.0960.

Copper thiophene-2-carboxylate (125)
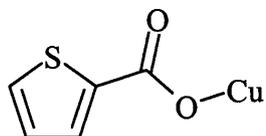
2-Thiophenecarboxylic acid (10.00 g, 78 mmol) and copper (I) oxide (2.79 g) were

suspended in toluene (30 cm³) and placed in a flask equipped with a Dean-Stark trap.

The reaction mixture was heated at reflux for 6 hours and then cooled to 60 °C. The

resultant suspension was filtered through a medium pore glass filter funnel, and the

collected product was kept under a stream of nitrogen. The product was washed with

methanol, followed by diethyl ether before drying *in vacuo*. The collected product was

a mixture of a tan solid and also a light blue solid. As this was also reported to be the

case in the literature, the product was used in further studies without further

purification.

2-Tributylstannyl-N-(tert-butoxycarbonyl)aniline (126)
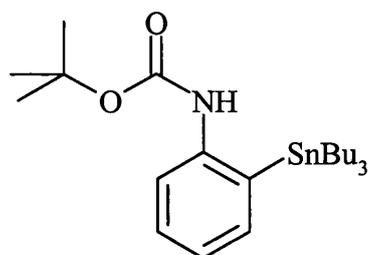
To a solution of *N*-(*tert*-butoxycarbonyl)aniline (0.50 g, 2.6 mmol) in dry diethyl ether

(5 cm³) was cooled to -20 °C and 'butyllithium (3.35 cm³ of a 1.7M solution in

pentane, 5.7 mmol) added dropwise. When the addition was complete, the mixture

was stirred at -10 °C for 3 hours. The mixture was then cooled to -78 °C and

tributyltin chloride (0.77 cm^3, 2.85 mmol) added. The mixture was allowed to warm to

room temperature overnight, and then washed with brine (10 cm^3). The organic phase

was dried over Na$_2$SO$_4$ and the solvent removed *in vacuo*. Purification by column

chromatography gave the product as a colourless oil (490 mg, 39 %).

δ_H (270 MHz, CDCl$_3$) 0.82-0.91 (m, 9H, CH$_2$C*H$_3$*), 1.07-1.13 (m, 6H), 1.32-1.38 (m,

12H), 1.5 (s, 9H, C(CH$_3$)$_3$), 6.3 (brs, 1H, NH), 7.09 (ddd, 1H, $^3J_{H-H}$ = 8, $^3J_{H-H}$ = 8, $^4J_{H-H}$ =

2), 7.25-7.34 (m, 2H), 7.70 (d, 1H, $^3J_{H-H}$ = 8). δ_C (68 MHz, CDCl$_3$) 10.0, 13.6, 27., 28.,

29.0, 80.1, 121.9, 124.0, 129.1, 132.7, 136.8, 143.4, 153.3. δ_{Sn} (149 MHz, CDCl$_3$) -

43.63. MS FAB$^-$ [M-1]$^+$ 482.2. Ref. [45].

1,4-Bis[(trifluoromethanosulfonyl)oxy]benzene (127)
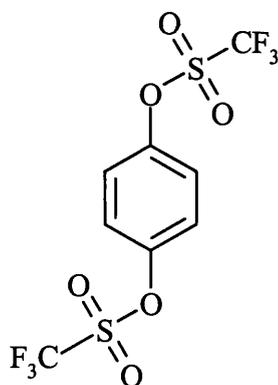
1,4-Dihydroxybenzene (1 g, 9.0 mmol) was dissolved in pyridine (12.5 cm^3) and

cooled to 0 °C. Trifluoromethanesulfonic anhydride (3.27 cm^3, 19.9 mmol) was added

dropwise and the mixture stirred for a further 5 minutes, before allowing the reaction

mixture to warm to room temperature overnight. The mixture was poured into water

(20 cm^3) and extracted with diethyl ether (3 x 20 cm^3). The combined organic extracts

were washed with hydrochloric acid (10% v/v, 2 x 20 cm^3) and brine (20 cm^3). The

organic phase was dried over magnesium sulfate and the solvent removed *in vacuo*.

The residue was purified by flash chromatography (petrol) to leave the title compound

(2.87 g, 84 %).

δ_H (270 MHz, CDCl$_3$) 7.40 (s, 4H). δ_C 118.68 (q $^1J_{C-F}$ = 321 Hz), 123.5 C-H, 148.4

C-O. MS EI [M]$^+$ 373.9. Found: C, 25.65; H, 1.07 %. Calc. for C$_8$H$_4$F$_6$O$_6$S$_2$: C, 25.68;

H, 1.08 %. FTIR ν_{max}/cm^{-1} (nujol) 1490, 1418, 1211, 1131, 1014, 903, 849. mp 54-56

°C (Ref. 52-53 °C[34]).

N,N'-Bis('butoxycarbonyl)-2,2'-diaminobiphenyl (128)

1,4-Bis[(trifluoromethanosulfonyl)oxy]benzene   (200   mg,   0.5   mmol),   2-

tributylstannyl-*N*-(tert-butoxycarbonyl)aniline (530 mg, 1.0 mmol) and CuTC (5

mmol) were dissolved in NMP (5 cm^3) and stirred at room temperature overnight.

TLC analysis (20 % diethyl ether/petrol) showed the absence of starting material and

the presence of a new product. The reaction mixture was poured into water (20 cm^3)

and extracted with diethyl ether (3 x 10 cm^3). The combined organic extracts were

washed with 10 % v/v HCl (20 cm^3) and brine (20 cm^3) and dried over MgSO$_4$. The

solvent was removed *in vacuo* to leave the title compound as a colourless solid (40

mg, 42 %).

δ_H (270 MHz, CDCl$_3$) 1.44 and 1.52 (s, 9H, Rotamers), 6.25 (brs, 1H, NH), 7.10-7.15

(m, 2H), 7.23-7.42 (m, 4H), 8.22 (d, 2H, $^3J_{H-H}$ = 9.0). δ_C (68 MHz, CDCl$_3$) 28.2

C(CH$_3$)$_3$, 80.7 C(CH$_3$)$_3$, 119.8 C3, 123.3 C5, 126.3 C1, 129.4 C4, 130.4 C6, 136.4

C2, 152.7 CO. Found: C, 68.7; H, 7.4; N, 7.1 %. Calc. for C$_{22}$H$_{28}$N$_2$O$_4$: C, 68.7; H,

7.3; N, 7.3 %. MS FAB$^+$ [M+1]$^+$ 385.1, FAB$^-$ [M-1]$^+$ 383.2, EI [M+1]$^+$ 385.0. HRMS

FAB$^+$ Requires for C$_{22}$H$_{29}$N$_2$O$_4$ 385.2127, found 385.2126. FTIR v_{max}/cm^{-1} (nujol)

1727 CO. mp 99-100 °C.

2,2'-Dinitrobiphenyl (130)
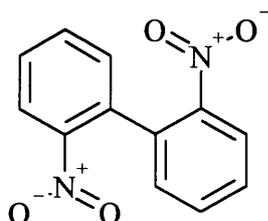
Iodo-2-nitrobenzene (4.22 g, 16.95 mmol), 1,4-dibromobenzene (1.00 g, 4.24 mmol),

copper bronze (1.00 g), copper sulfate (trace) and DMAP (trace) were suspended in

acetonitrile (25 cm^3) and heated at reflux. The reaction was followed by TLC analysis

(20 % diethyl ether/petrol), and a new more polar compound was observed to be

forming. When the reaction had gone to completion, the mixture was cooled to room

temperature and filtered through Celite$^®$ and the solvent removed *in vacuo*. The

residue was purified by flash chromatography using 20 % diethyl ether/petrol as the

eluent. The product was further purified by crystallisation from 95 % ethanol to leave

the title compound as yellow needles (0.86 g, 41 %).

δ_H (270 MHz, CDCl$_3$) 7.29 (d, 1H, $^3J_{H-H}$ = 7.5), 7.56 (dd, 1H, $^3J_{H-H}$ = 7.5, $^3J_{H-H}$ = 7.5),

7.67 (dd, 1H, $^3J_{H-H}$ = 7.5, $^3J_{H-H}$ = 7.5), 8.18 (d, 1H, $^3J_{H-H}$ = 8.0). δ_C (68 MHz, CDCl$_3$)

124.5, 129.0, 130.8, 133.4, 134.0, 147.0. Found: C, 58.7; H, 3.3; N, 11.5 %. Calc. for

C$_{12}$H$_8$N$_2$O$_4$: C, 59.0; H, 3.3; N, 11.5 %. MS CI [M+1]$^+$ 245.2. FTIR ν_{max}/cm^{-1} (nujol)

1520, 1354, 853. mp 123-124 °C (Ref. 124 °C).

*N,N'-Bis-(biphenyl-2-yl)urea (133)*
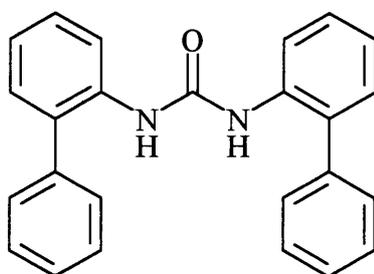
2-Aminobiphenyl (200 mg, 1.2 mmol) and carbonyl diimidazole (196 mg, 1.2 mmol)

were dissolved in dichloromethane (5 cm^3) and the mixture heated at reflux for two

hours. TLC analysis (40 % ethyl acetate/petrol) showed the presence of a new

product. The reaction mixture was allowed to cool to room temperature. Silica was

added to the reaction mixture and the solvent was removed *in vacuo*. The preabsorbed

silica was added to the top of a column and eluted with 40 % ethyl acetate/petrol. The

title compound was collected as a crystalline solid (25 mg, 6 %).

δ_H (270 MHz, CDCl$_3$) 6.40 (brs, 2H), 7.10-7.37 (m, 14H), 7.73 (d, 2H, $^3J_{H-H}$ = 7.5). δ_C

(67 MHz, CDCl$_3$) 122.8, 124.5, 127.6, 128.5, 128.6, 129.0, 130.1, 134.0, 134.7,

138.2, 153.3. MS CI [M]$^+$ 364.1.

6-Methyphenanthridine (135)
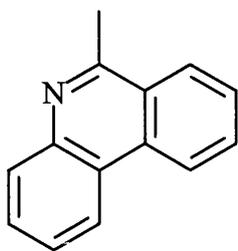
2'-Bromoacetophenone (100 mg, 0.5 mmol) and *tetrakis*-triphenylphosphine palladium(0) (17 mg, 3 mol %) were dissolved in DME (1.5 cm³) and stirred at room temperature for 30 minutes. During this time a colour change from yellow to red was observed. 2-[2-(N-tert-Butoxycarbonylamino)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolidine (175 mg, 0.55 mmol) and 2M sodium carbonate solution (0.6 cm³) were added and the mixture heated at reflux overnight. TLC analysis (20 % diethyl ether/petrol) indicated the absence if the 2'-bromoacetophenone and a new product component. The reaction mixture was made acidic by the addition of sulfuric acid (18M) and stirred for an hour. Sodium hydroxide solution (1M) was added until the reaction mixture was alkaline and it was then extracted with diethyl ether (3 x 10cm³). The combined organic extracts were dried over sodium sulfate and the solvent removed *in vacuo*. Purification by column chromatography (20 % diethyl ether/petrol) afforded the title compound (79 mg, 82 %).

δ_H (270 MHz, CDCl₃) 3.04 (s, 3H, CH₃), 7.64 (t, 2H, $^3J_{H-H}$ = 8.3), 7.70 (t, 1H, $^3J_{H-H}$ = 7.5), 7.82 (t, 1H, $^3J_{H-H}$ = 7.5), 8.1 (d, 1H, $^3J_{H-H}$ = 8.3), 8.21 (d, 1H, $^3J_{H-H}$ = 8.1), 8.52 (d, 1H, $^3J_{H-H}$ = 8.1), 8.61 (d, 1H, $^3J_{H-H}$ = 8.3). δ_C (68 MHz, CDCl₃) 23.4, 121.9, 122.3, 123.8, 125.9, 126.3, 126.5, 127.3, 128.6, 129.3, 130.5, 132.7, 143.8, 158.9. mp 79-80 °C (Ref. 79-81 °C[19]).

4,5-Dihydro-2-(2-methoxyphenyl)-4,4-dimethyloxazole (44)
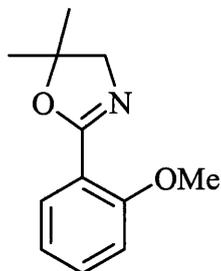
Thionyl chloride (5 cm^3) was added to 2-methoxybenzoic acid (200 mg, 1.3 mmol) and heated at reflux for 1 hour. The thionyl chloride was removed *in vacuo* and the residue dissolved in dry dichloromethane (5 cm^3) and stirred under nitrogen. 2-Amino-2-methyl-1-propanol (0.25 cm^3, 2.6 mmol) was added and the reaction mixture stirred overnight. The hydrochloride salt of the amine was removed by suction filtration and the solvent removed *in vacuo*. The residue was dissolved in dry dichloromethane (5 cm^3) and thionyl chloride (0.1 cm^3, 1.4 mmol) was added. The mixture was stirred for 1 hour before the solvent was removed *in vacuo* and the residue was purified by Kügelrohr distillation, leaving colourless crystals (149 mg, 59 %).

δ_H (270 MHz, CDCl$_3$) 1.38 (s, 6H, C(CH$_3$)$_2$), 3.86 (s, 3H, OCH$_3$), 4.08 (s, 2H, -CH$_2$-), 6.95 (m, 2H), 7.39 (ddd, 1H, $^3J_{H-H}$ = 7.9, $^3J_{H-H}$ = 7.9, $^4J_{H-H}$ = 1.5), 7.72 (dd, 1H, $^3J_{H-H}$ = 7.3, $^4J_{H-H}$ = 1.8, H6). δ_C (68 MHz, CDCl$_3$) 28.2 C(CH$_3$)$_2$, 55.9 OCH$_3$, 67.3 -CH$_2$-, 78.2 C(CH$_3$)$_2$, 111.8 , 117.7 , 120.2 , 131.3 , 132.0 , 158.2 , 161.1. MS FAB$^+$ [M+1]$^+$ 206.2. Found: C, 70.4; H, 7.5; N, 6.8 %. Calc. for C$_{12}$H$_{15}$NO$_2$: C, 70.2; H, 7.4; N, 6.8 %. FTIR v_{max}/cm^{-1} (nujol) 1642.5 C=N. mp 70-72 °C (Ref. 68-69.5 °C[46]).

1,4-Bis(5,5-dimethyloxazolin-2-yl)benzene (139)
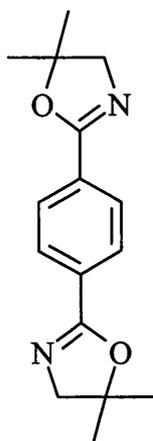
Terephthalic acid (100 mg, 0.6 mmol) was dissolved in acetonitrile (5 cm³) and

pyridine (5 cm³). To this solution was added 2-amino-2-methyl-1-propanol (143 mg,

1.5 mmol), triphenylphosphine (944 mg, 3.6 mmol), carbon tetrachloride (1 cm³) and

triethylamine (0.5 ml, 3.6 mmol). After stirring at room temperature overnight, the

mixture was filtered to remove any triphenylphosphine oxide that had precipitated and

the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane (10

cm³) and the solution washed with saturated CuSO₄ solution (10 cm³), saturated

sodium bicarbonate solution (10 cm³) and brine (10 cm³). The organic phase was dried

over magnesium sulfate and the solvent removed to leave a yellow solid. This was

purified by flash chromatography (diethyl ether) to leave the required dioxazoline (44

mg, 27 %).

δ_H (270 MHz, CDCl₃) 1.39 (s, 12H), 4.12 (s, 4H), 7.96 (s, 4H). δ_C (68 MHz, CDCl₃)

28.4 CH₃, 67.7 -CH₂-, 79.2 N-C, 128.1 Ar-H, 130.4 Ar-C, 161.5 N=C. MS FAB⁺

[M+1]⁺ 273.2. HRMS FAB⁺ Requires for C₁₆H₂₁N₂O₂ 273.1603, found 273.1588. mp

119-121 °C.

4,5-Dihydro-2-(2-(trimethylsilyl)phenyl)-4,4-dimethyloxazole (140)
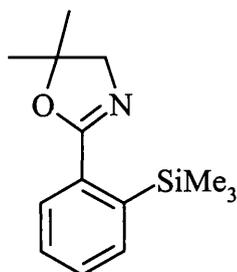
4,5-Dihydro-2-phenyl-4,4-dimethyloxazole (0.1 cm^3, 0.57 mmol) was dissolved in anhydrous diethyl ether (5 cm^3) and cooled to -78 °C. ^{n}Butyllithium (0.4 cm^3 of a 1.7M solution in hexane, 0.69 mmol) was added dropwise to the solution and stirring continued for 15 minutes. The solution was warmed to 0 °C and stirred for a further hour. Trimethylsilyl chloride (0.09 cm^3, 0.69 mmol) was added to the mixture whereupon TLC analysis (40 % diethyl ether/petrol) showed a new product had formed leaving only a small amount of starting material. Silica was added to the solution, and the solvent removed *in vacuo*. The product was obtained after purification by flash chromatography (20 % diethyl ether/petrol) as a colourless oil (58 mg, 44 %).

δ_H (270 MHz, CDCl$_3$) 0.24 (s, 9H, Si(CH$_3$)$_3$), 1.31 (s, 6H, C(CH$_3$)$_2$), 4.02 (s, 2H, -CH$_2$-), 7.33 (m, 2H), 7.55 (dd, 1H, $^3J_{H-H}$ = 7.0, $^4J_{H-H}$ = 2.0), 7.79 (dd, 1H, $^3J_{H-H}$ = 7.0, $^4J_{H-H}$ = 2.0).

4,5-Dihydro-2-(6-deutero-2-(trimethylsilyl)phenyl)-4,4-dimethyloxazole (141)
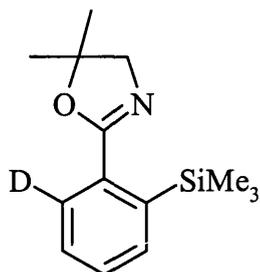
4,5-Dihydro-2-(2-(trimethylsilyl)-phenyl)-4,4-dimethyloxazole (51 mg, 0.22 mmol) was dissolved in anhydrous diethyl ether (2 cm^3) and the solution cooled to -78 °C. ^{n}Butyllithium (0.26 mmol) was added dropwise and the stirring continued for 15 minutes. The solution was then warmed to 0 °C and stirring continued for a further hour. A drop of deuterium oxide was added and the solution allowed to warm to room temperature. Silica was added and the solvent removed *in vacuo*. The product was purified by flash chromatography (20 % diethyl ether/petrol) as an oil (30 %).

δ_H (270 MHz, CDCl$_3$) 0.32 (s, 9H, Si(CH$_3$)$_3$), 1.39 (s, 6H, C(CH$_3$)$_2$), 4.10 (s, 2H, -CH$_2$-), 7.41 (m, 2H), 7.62 (dd, 1H, $^3J_{H\text{-}H}$ = 6.8, $^4J_{H\text{-}H}$ = 2.2).

1,4-Bis(5,5-dimethyloxazolin-2-yl)-2-dimethyl'butylsilylbenzene (142)
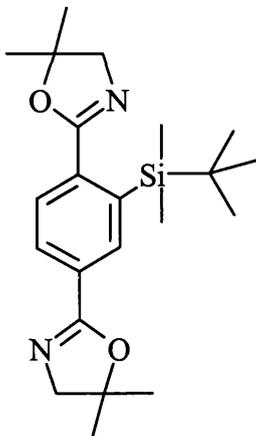
1,4-Bis(5,5-dimethyloxazolin-2-yl)benzene (500 mg, 1.8 mmol) was dissolved in anhydrous THF (5 cm^3) and cooled to -78 °C. 'Butyllithium (2.2 cm^3 of a 1.7M solution in pentane, 3.7 mmol) was added dropwise, and the mixture stirred for 2 hours. Chloro'butyldimethyl silane (0.4 cm^3, 2.2 mmol) was added and the mixture stirred at -78 °C for a further 30 minutes. The mixture was then warmed to room temperature overnight.

The reaction mixture was poured into saturated ammonium chloride solution (20 cm^3) and extracted with diethyl ether (3 x 10cm^3). The combined organic extracts were washed with brine (20 cm^3) and dried over magnesium sulfate. The solvent was removed *in vacuo* to leave the title compound as a colourless oil.

δ_H (270 MHz, CDCl$_3$) 0.09 (s, 6H), 0.86 (s, 9H), 1.26 (s, 6H), 4.10 (s, 4H), 7.42 (s, 1H, H3), 7.60 (d, 1H, $^3J_{H\text{-}H}$ = 8.4, H5), 7.84 (d, 1H, $^3J_{H\text{-}H}$ = 8.6, H5)

*1,4-Bis-2-(2-'butyl-4,4-dimethyl-1,3-oxazolidine)benzene (143)*
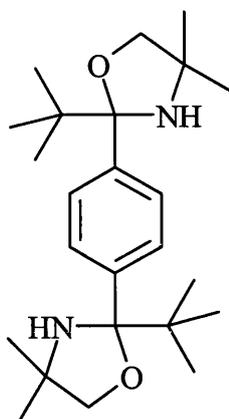
1,4-Bis(5,5-dimethyloxazolin-2-yl)benzene (200 mg, 0.7 mmol) was dissolved in anhydrous diethyl ether (5 cm³) and cooled to -78 °C. 'Butyllithium (2.6 cm³ of a 1.7M solution in pentane, 4.4 mmol) was added dropwise, and the mixture stirred for 2 hours. Deuterium oxide (0.4 cm³, 2.9 mmol) was added and the mixture stirred at -78 °C for a further 30 minutes. The mixture was then warmed to room temperature overnight.

The reaction mixture was poured into saturated ammonium chloride solution (20 cm³) and extracted with diethyl ether (3 x 10cm³). The combined organic extracts were washed with brine (20 cm³) and dried over magnesium sulfate. The solvent was removed *in vacuo* to leave the title compound as a colourless gum (182 mg, 65 %).

δ_H (270 MHz, CDCl₃) 0.71 (s, 6H, 2 x CH₃), 0.95 (s, 18H, C(CH₃)₃), 1.26 (s, 6H, 2 x CH₃), 2.31 (brs, 2H, NH), 3.46 (d, 2H, $^2J_{H-H}$ = 20.9 *geminal*, -CH₂-), 3.49 (d, 2H, $^2J_{H-H}$ = 20.9 *geminal*, -CH₂-), 7.44 (s, 4H). δ_C (68 MHz, CDCl₃) 25.87, 27.53, 28.44, 37.64, 59.2, 77.47, 103.65 , 127.19, 132.72, 140.77. MS FAB⁺ [M+2]⁺ 390.3.

APPENDIX A

Spectra for 2,5-dibromoterephthalaldehyde ethyl acetal (103)

¹H-NMR Spectrum
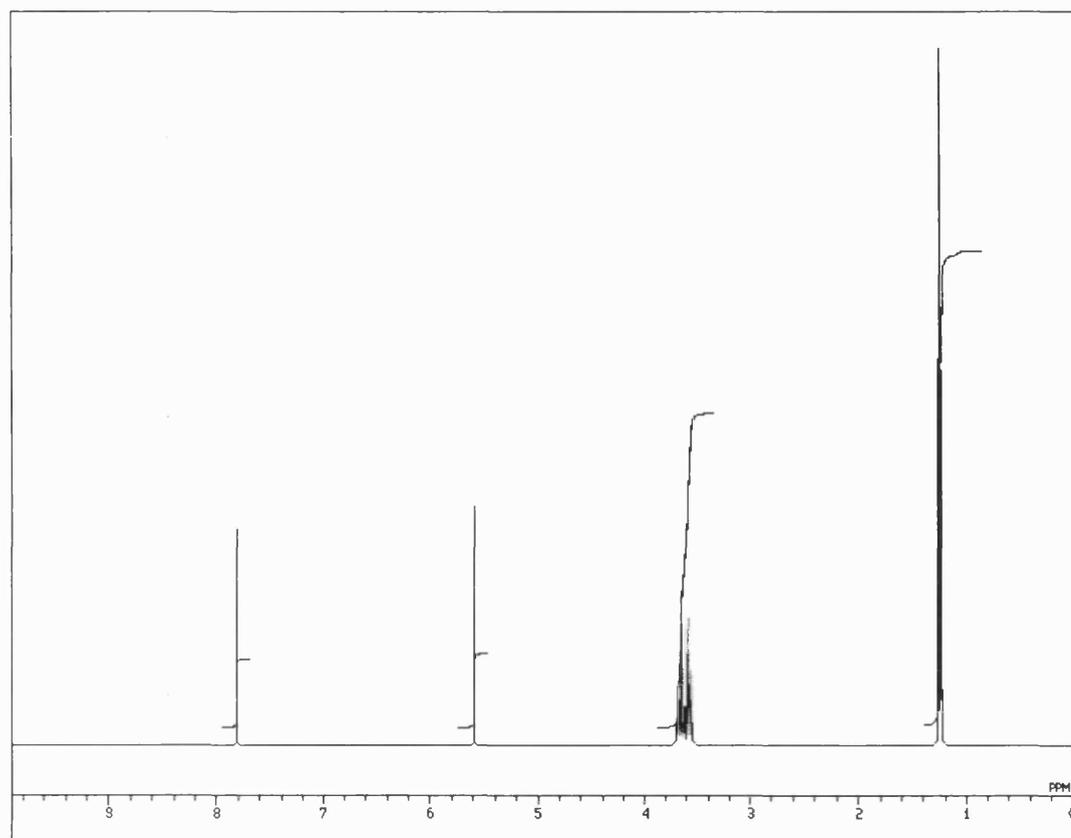
¹³C-NMR Spectrum
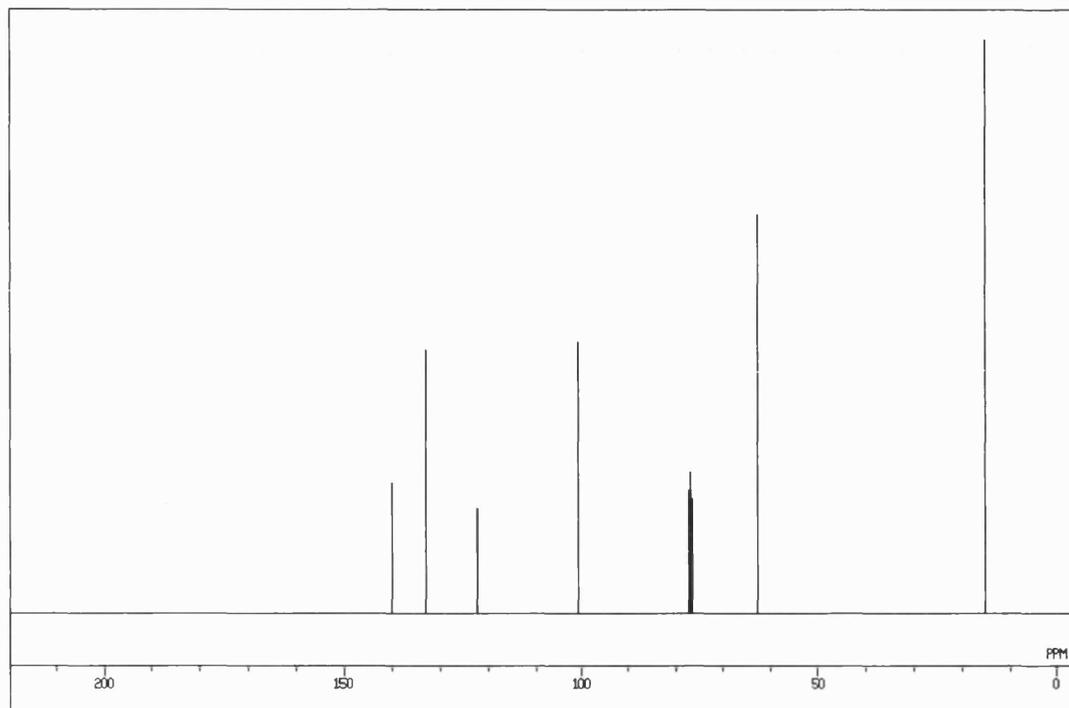
^{1}H-^{1}H Correlation Spectrum
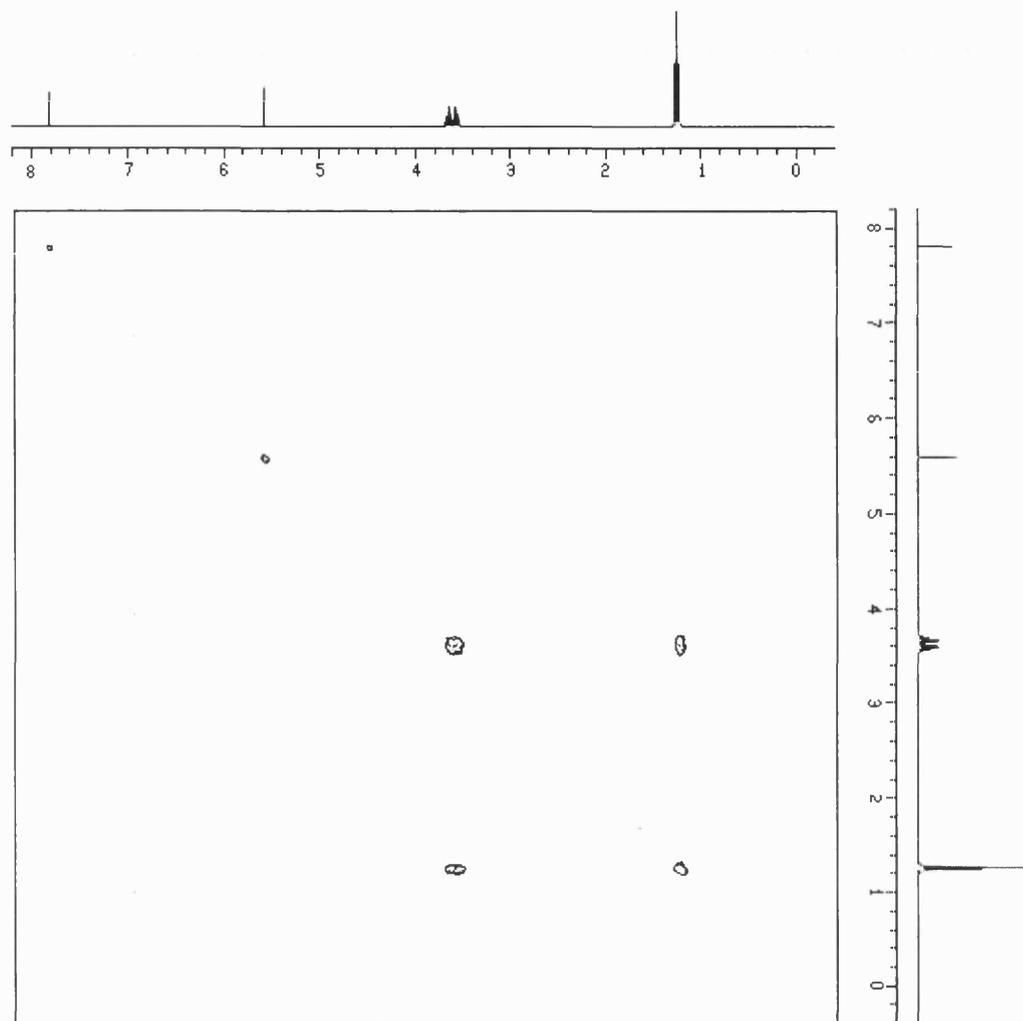
¹H-¹³C Correlation Spectrum
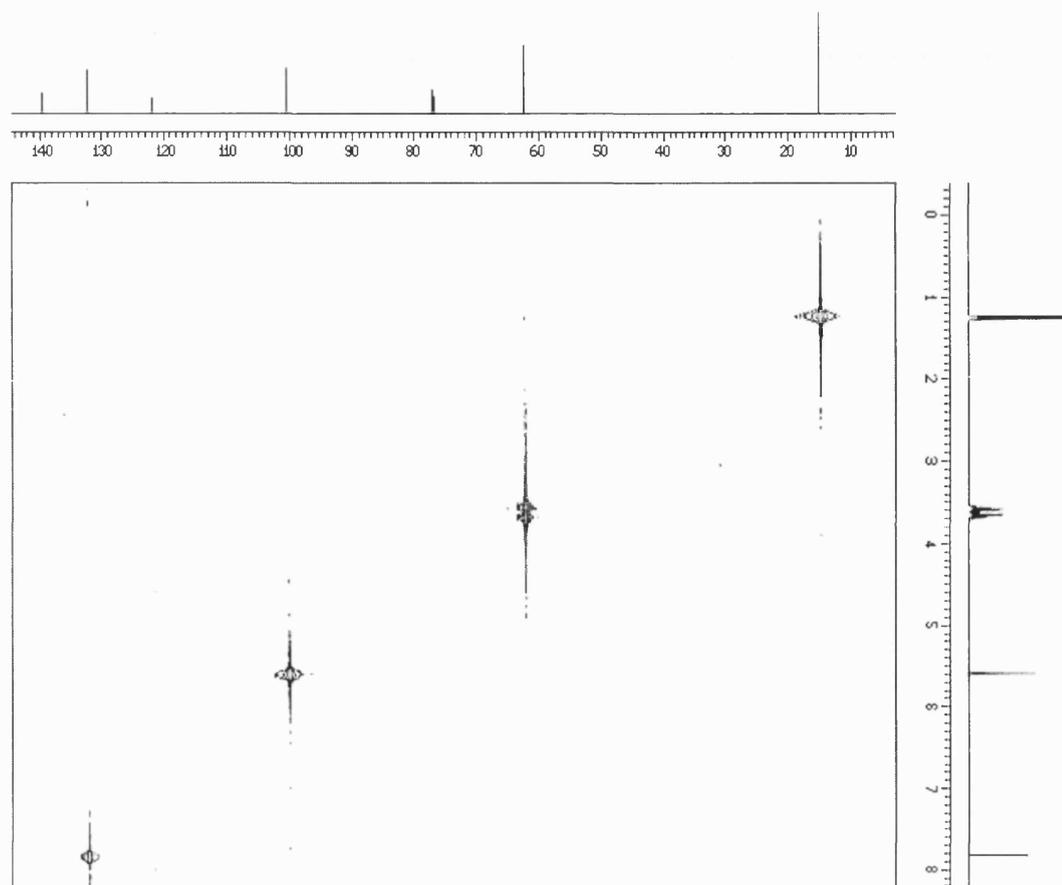
Spectra for *N*,*N*-dibenzyl-2-bromobenzamide

^{1}H NMR CDCl$_3$ 22°C
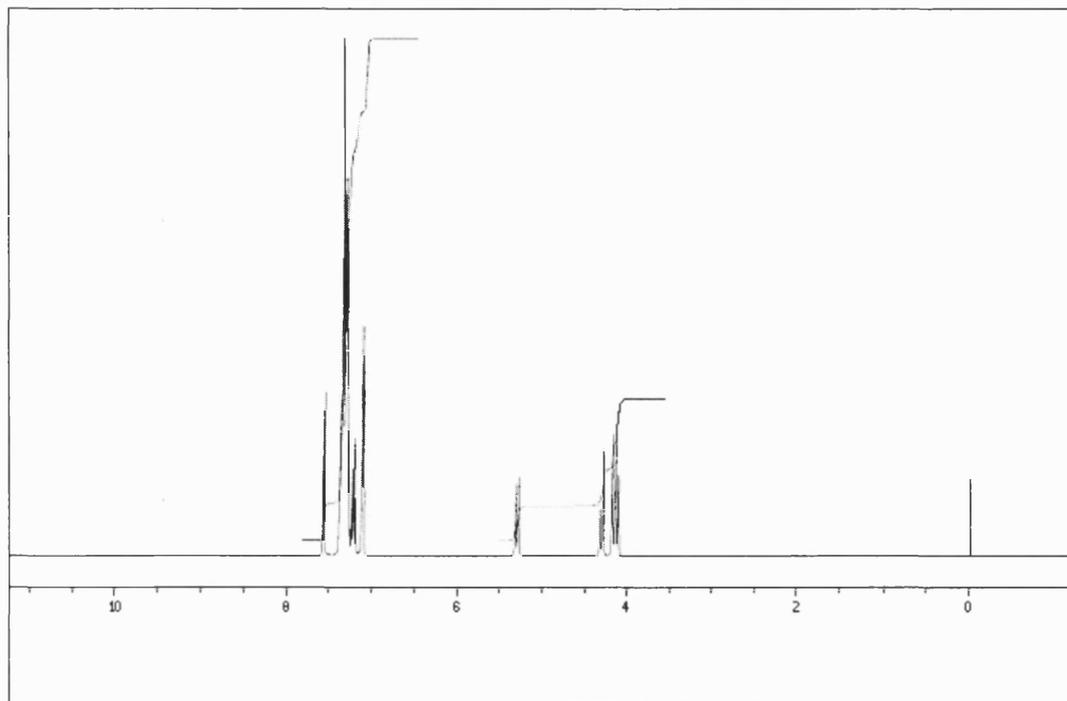
^{1}H NMR CDCl$_3$ 50°C
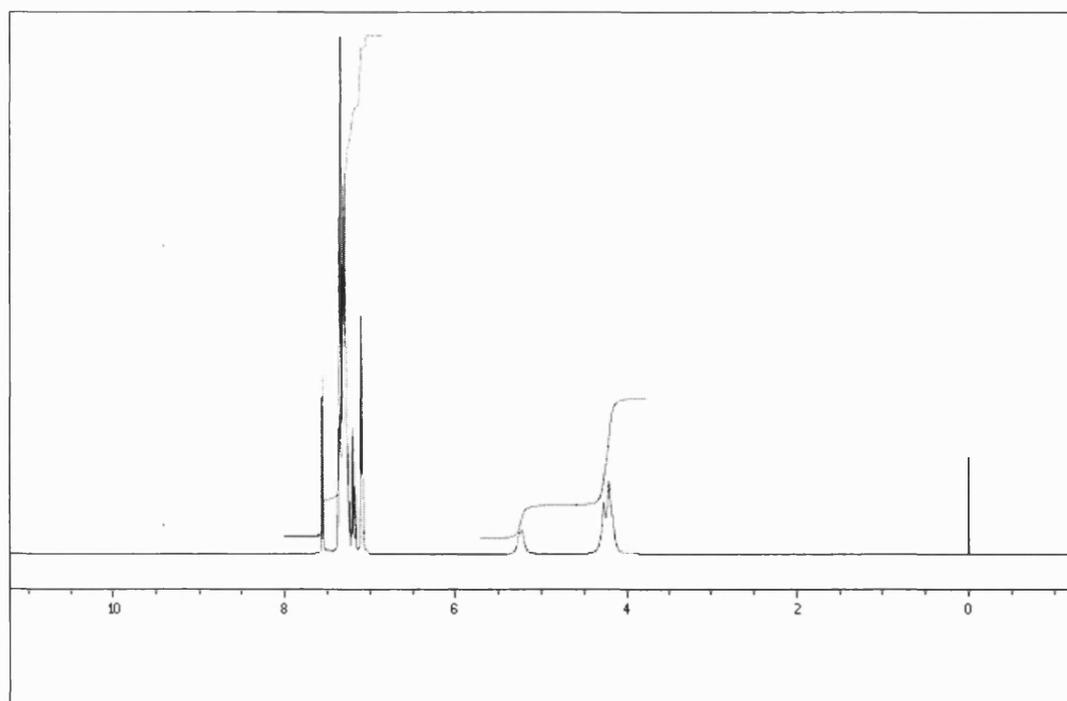
¹H NMR DMSO-*d6* 22°C
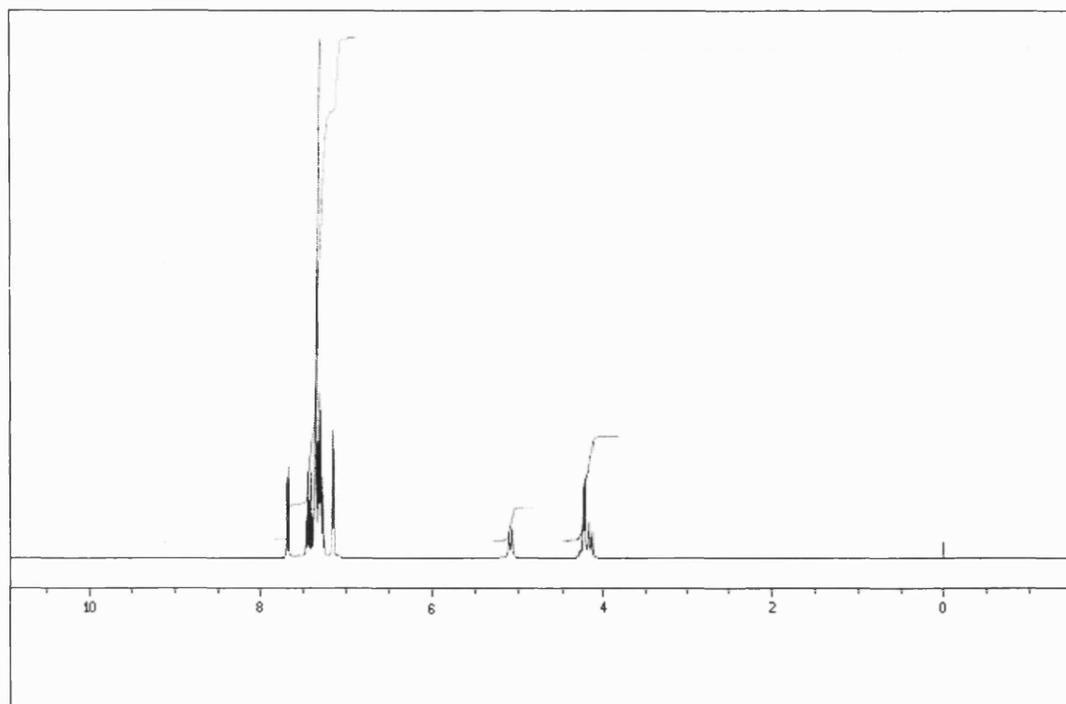
¹H NMR DMSO-*d6* 150°C
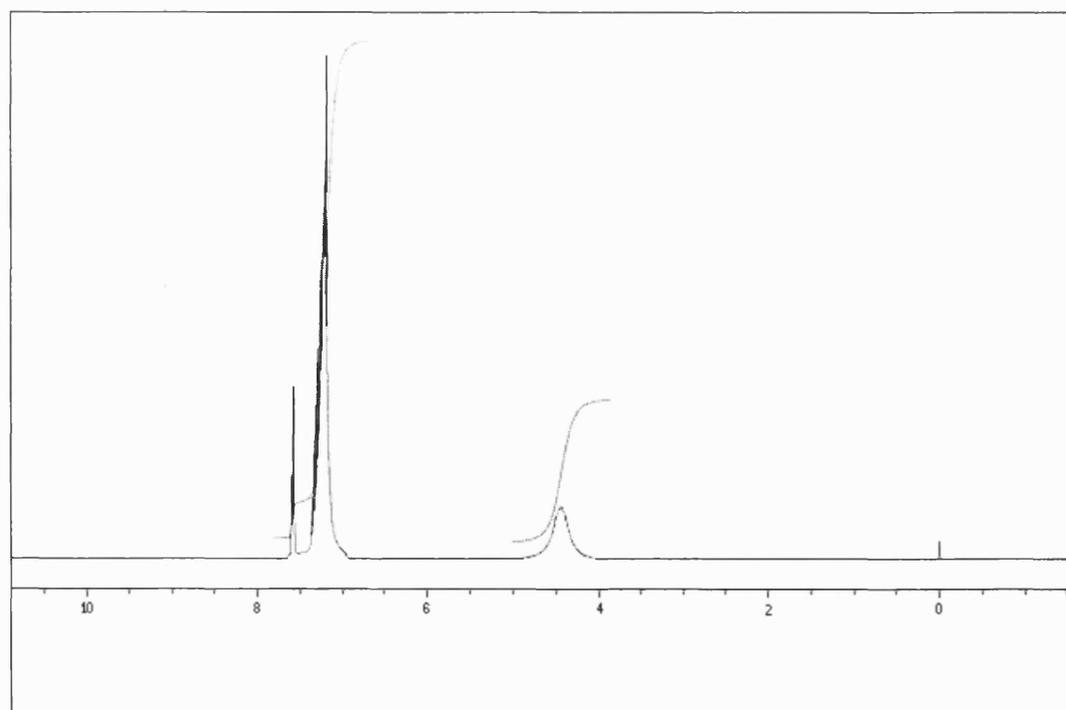
^{13}C NMR CDCl$_3$ 22°C
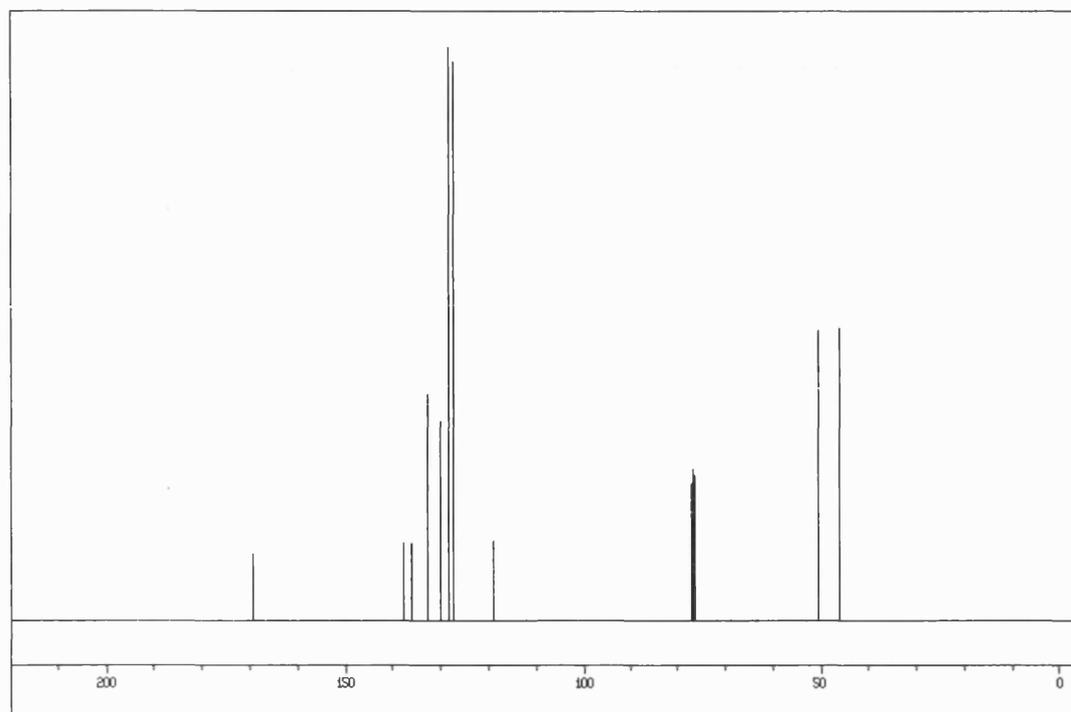
^{13}C NMR DEPT Experiment CDCl$_3$ 22°C
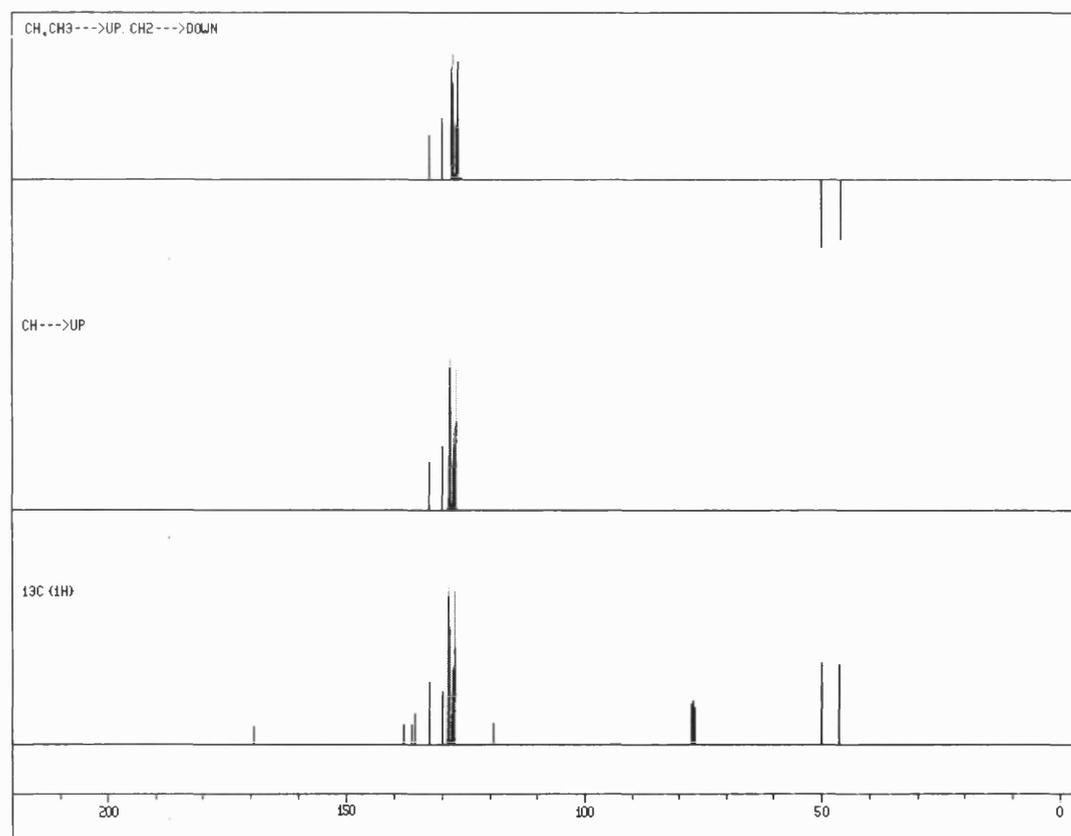
¹³C NMR DEPT Experiment CDCl₃ 22°C, Expansions
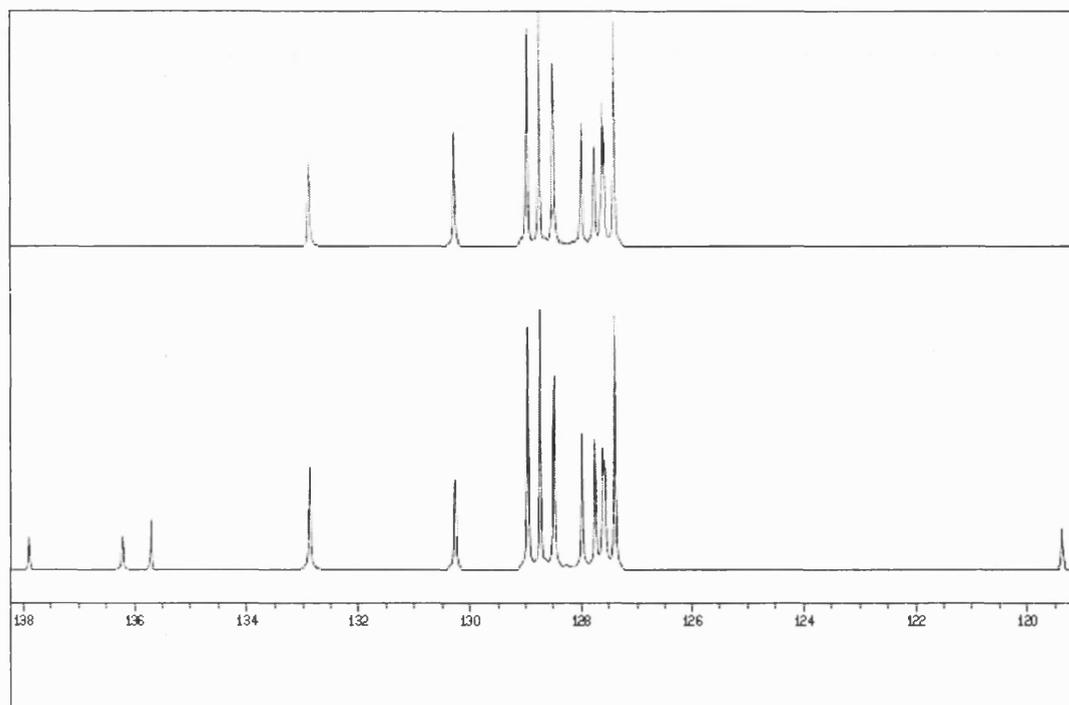
APPENDIX B

Notes on 2,5-dibromoterephthalaldehyde ethyl acetal

A crystal of approximate dimensions 0.2 x 0.3 x 0.2 mm was used for data collection.

Crystal data: $C_{16}H_{24}Br_2O_4$, M = 440.17, Triclinic , a = 7.435(2), b = 7.986(2), c = 8.880(2) Å , α = 83.51(2), β = 76.84(2), γ = 65.57(2)°, U = 467.3(2) Å^3, space group $P\bar{1}$, Z = 1, D_c = 1.564 gcm^{-3}, μ(Mo-K_α) = 4.350 mm^{-1}, F(000) = 222. Crystallographic measurements were made at 293(2)° K on a CAD4 automatic four-circle diffractometer in the range 2.35<θ<23.92°. Data (1472 reflections) were corrected for Lorentz and polarisation and also for absorption [47]. (Max. and Min absorption corrections; 1.000, 0.091 respectively).

The asymmetric unit in this crystal structure was seen to consist of one half of a molecule, the remainder being generated *via* a crystallographic inversion centre.

In the final least squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions where relevant.

The solution of the structure (SHELX86)[48] and refinement (SHELX93)[49] converged to a conventional [i.e. based on 1316 F^2 data with Fo>4σ(Fo)] $R1$ = 0.0589 and $wR2$ = 0.1501. Goodness of fit = 1.020. The max. and min. residual densities were 0.672 and -0.865 eÅ^{-3} respectively. The asymmetric unit (shown in Fig. 1), along with the labelling scheme used was produced using ORTEX.[50] Final fractional atomic co-ordinates and isotropic thermal parameters, bond distances and angles are given in Tables 1, 2 and 3 respectively. Tables of anisotropic temperature factors are available as supplementary data.
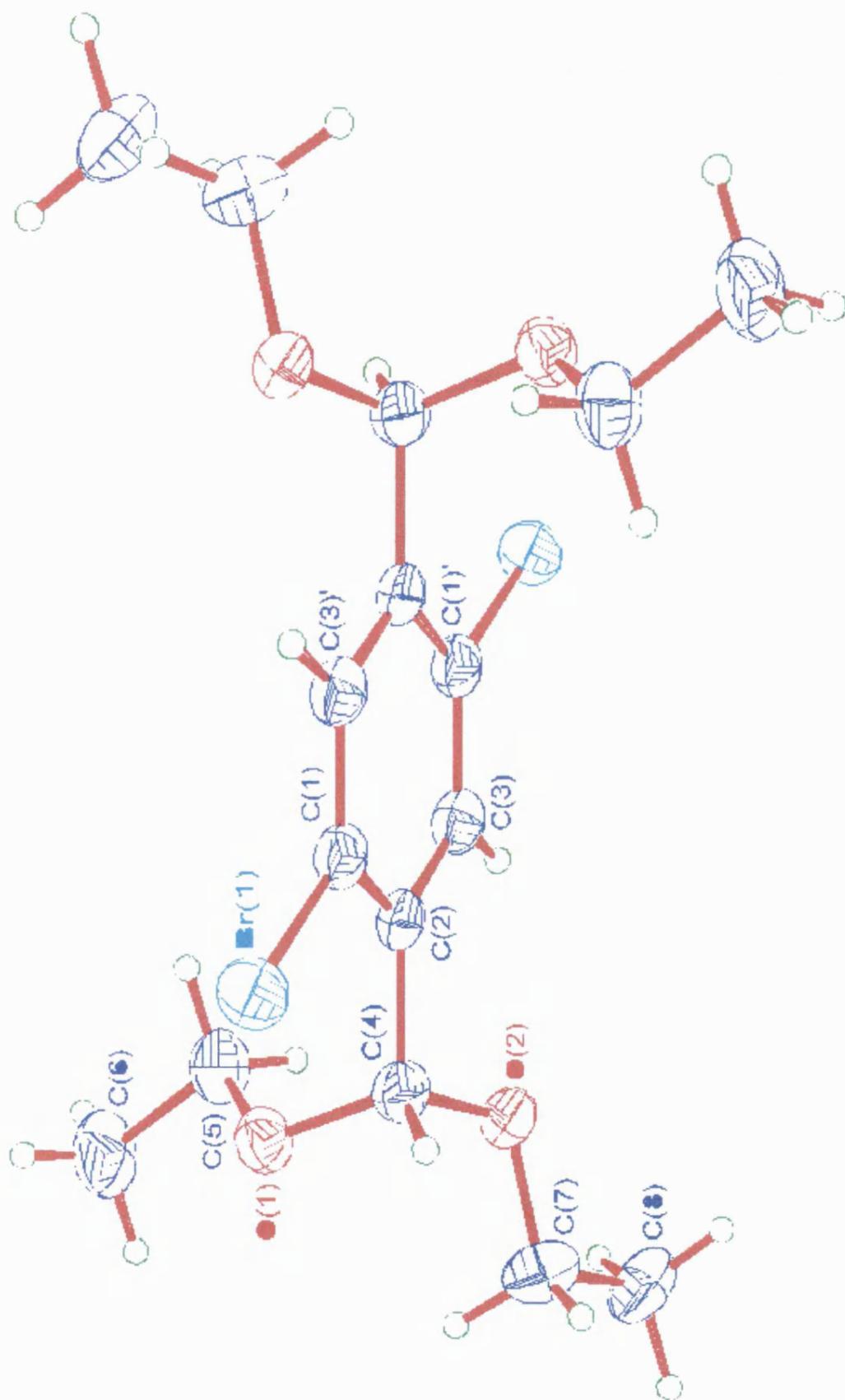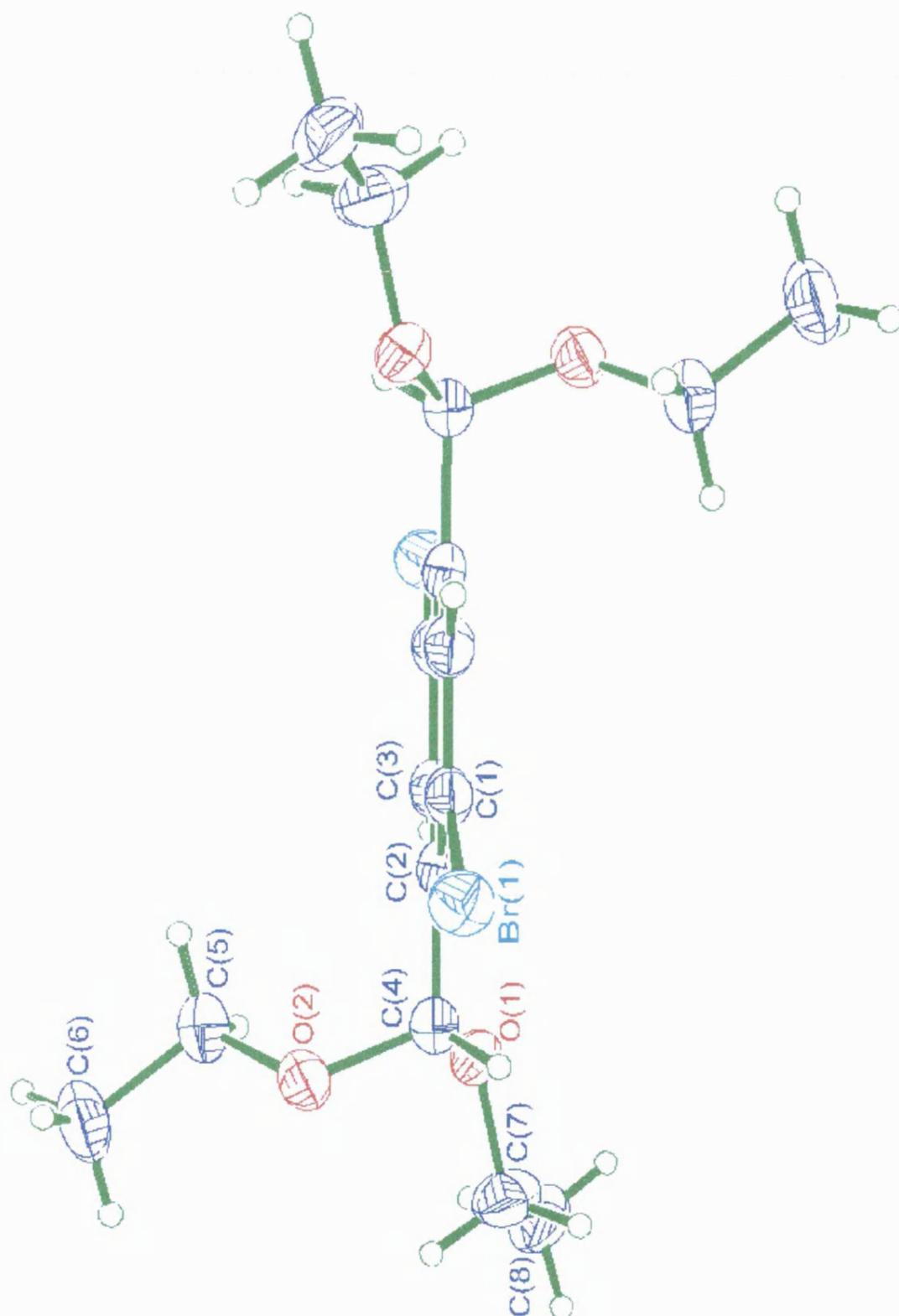
Table 1. Crystal data and structure refinement for 1.

Identification code	97ms3/n.smith
Empirical formula	$C_{16}H_{24}Br_2O_4$
Formula weight	440.17
Temperature	293(2) K
Wavelength	0.70930 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.435(2)Å α = 83.51(2)°
	b = 7.986(2)Å β = 76.84(2)°
	c = 8.880(2)Å γ = 65.57(2)°
Volume	467.3(2) Å^3
Z	1
Density (calculated)	1.564 Mg/m^3
Absorption coefficient	4.350 mm^{-1}
F(000)	222
Crystal size	0.2 x 0.3 x 0.2 mm
Theta range for data collection	2.35 to 23.92 °.
Index ranges	-8<=h<=8; -8<=k<=9; 0<=l<=10
Reflections collected	1472
Independent reflections	1472 [R(int) = 0.0000]
Absorption correction	DIFABS
Max. and min. transmission	1.000 and 0.091
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1469 / 0 / 103
Goodness-of-fit on F2	1.020
Final R indices [I>2s(I)]	R1 = 0.0589 wR2 = 0.1501
R indices (all data)	R1 = 0.0676 wR2 = 0.1634
Largest diff. peak and hole	0.672 and -0.865 eÅ^{-3}
Weighting scheme	calc w=1/[σ^2(Fo^2)+(0.1312P)^2+0.3293P] where P=(Fo^2+2Fc^2)/3
Extinction coefficient	0.0097(80)
Extinction expression	Fc*=kFc[1+0.001xFc$^2\lambda^3$/sin(2θ)]$^{-1/4}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters

($Å^2$ x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij

tensor.

Atom	x	y	z	U(eq)
Br(1)	1786(1)	3746(1)	1393(1)	60(1)
O(1)	-2864(6)	7571(6)	1983(5)	55(1)
O(2)	-1948(6)	9485(5)	3154(5)	54(1)
C(1)	718(8)	4515(8)	3470(7)	49(1)
C(2)	-625(8)	6315(8)	3813(6)	47(1)
C(3)	-1302(8)	6782(8)	5358(6)	49(1)
C(4)	-1328(9)	7754(8)	2558(7)	51(1)
C(5)	-4649(9)	7765(10)	3102(8)	65(2)
C(6)	-6297(12)	8052(13)	2259(11)	88(2)
C(7)	-2190(12)	10914(10)	1987(9)	75(2)
C(8)	-2955(13)	12710(10)	2715(10)	80(2)

Table 3. Bond lengths [Å] and angles [°] for 1.

Br(1)-C(1)	1.897(6)
O(1)-C(4)	1.417(7)
O(1)-C(5)	1.427(8)
O(2)-C(4)	1.389(7)
O(2)-C(7)	1.434(7)
C(1)-C(3)#1	1.391(8)
C(1)-C(2)	1.389(8)
C(2)-C(3)	1.386(8)
C(2)-C(4)	1.522(8)
C(3)-C(1)#1	1.391(8)
C(5)-C(6)	1.504(9)
C(7)-C(8)	1.471(11)
C(4)-O(1)-C(5)	115.3(5)
C(4)-O(2)-C(7)	113.2(5)
C(3)#1-C(1)-C(2)	120.9(5)
C(3)#1-C(1)-Br(1)	118.0(4)
C(2)-C(1)-Br(1)	121.0(4)
C(3)-C(2)-C(1)	117.6(5)
C(3)-C(2)-C(4)	120.2(5)
C(1)-C(2)-C(4)	122.1(5)
C(2)-C(3)-C(1)#1	121.4(5)
O(2)-C(4)-O(1)	112.2(5)
O(2)-C(4)-C(2)	108.5(5)
O(1)-C(4)-C(2)	111.5(5)
O(1)-C(5)-C(6)	108.3(6)
O(2)-C(7)-C(8)	109.9(6)

Symmetry transformations used to generate equivalent atoms:

#1   -x,-y+1,-z+1

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for 1. The anisotropic

displacement factor exponent takes the form:

$-2\,pi^2\,[h^2\,a^*\,2\,U11\,+\,...\,+\,2\,h\,k\,a^*\,b^*\,U12\,]$

Atom	U11	U22	U33	U23	U13	U12
Br(1)	59(1)	62(1)	55(1)	-3(1)	-10(1)	-22(1)
O(1)	52(2)	57(2)	61(2)	-1(2)	-18(2)	-22(2)
O(2)	59(2)	49(2)	61(2)	6(2)	-16(2)	-28(2)
C(1)	44(3)	49(3)	62(3)	2(2)	-16(2)	-25(2)
C(2)	48(3)	51(3)	55(3)	5(2)	-14(2)	-31(2)
C(3)	43(3)	45(3)	62(3)	-4(2)	-10(2)	-19(2)
C(4)	46(3)	55(3)	58(3)	5(2)	-14(2)	-25(2)
C(5)	49(3)	74(4)	77(4)	-6(3)	-11(3)	-28(3)
C(6)	61(4)	99(6)	120(7)	-4(5)	-35(4)	-39(4)
C(7)	81(5)	62(4)	75(4)	18(3)	-15(4)	-26(4)
C(8)	82(5)	57(4)	104(6)	12(4)	-15(4)	-38(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x

10^3) for 1.

Atom, x, y, z, U(eq)

Atom	x	y	z	U(eq)
H(3)	-2165(8)	7989(8)	5617(6)	59
H(4)	-175(9)	7573(8)	1700(7)	62
H(5A)	-5039(9)	8808(10)	3749(8)	78
H(5B)	-4408(9)	6668(10)	3758(8)	78
H(6A)	-7535(26)	8273(96)	2992(13)	132
H(6B)	-5943(50)	6974(38)	1684(65)	132
H(6C)	-6464(73)	9092(59)	1561(60)	132
H(7A)	-3128(12)	10916(10)	1385(9)	90
H(7B)	-904(12)	10692(10)	1294(9)	90
H(8A)	-3039(89)	13651(15)	1926(10)	120
H(8B)	-2057(49)	12684(29)	3349(57)	120
H(8C)	-4270(40)	12965(39)	3344(56)	120

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