Studies Towards the Asymmetric Synthesis of Cyclochiral Rotaxanes and Au(III)-oxo Complexes as Catalysts

James Alan Thomas O'Neill

Submitted for the degree of Doctor of Philosophy

Heriot-Watt University

School of Engineering and Physical Sciences

April 2015

ABSTRACT

The work reported in this thesis consists of studies towards the asymmetric synthesis of mechanically planar chiral rotaxanes *via* desymmetrisation approach. It describes the synthesis of a novel macrocycle and the investigation of this macrocycle as a potential ligand in the Cadiot-Chodkiewicz and CuAAC 'click' reactions as part of the study towards the synthesis of asymmetric planar chiral rotaxanes. Furthermore, the use of Au(III)-oxo complexes as potential catalysts in a model hydroamination reaction are described. The thesis is divided into four chapters:

Chapter one is an introduction to rotaxanes and includes an overview of the synthesis of rotaxanes and chirality in rotaxanes.

Chapter two is an account of the synthesis of a novel macrocycle and details attempts to implement this macrocycle towards the synthesis of a rotaxane using the Cadiot-Chodkiewicz and CuAAC 'click' reactions.

Chapter three describes optimisation and multi-gram scale-up of the synthetic route towards a novel C1-symmetric bis(oxazoline) macrocycle first synthesised in our group by Pauline Glen.

Chapter four describes our investigation into the use of Au(III)-oxo complexes for use as catalysts in a model hydroamination reaction.

DEDICATION

I would like to dedicate this work to my wife, Andrea.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank Ai-Lan for the opportunity to work in the Lee group on what has been a challenging project and for all the support, advice and endless patience you have given me throughout my studies and the writing process.

Thanks to Pauline, Paul, Jamie, Sarah, Mari and Robert who have all provided support, guidance and continued friendship.

I would like to thank all the staff in the chemistry department at Heriot-Watt for the expertise they have passed on and for all the support throughout all the years I have been here. In particular, thank you to the members of the organic chemistry section who have provided invaluable help throughout this project and to Alan Boyd and Georgina Rosair for their guidance around NMR and Single Crystal X-Ray Diffraction. Special thanks also go to Christina Graham for all her help throughout my time at Heriot-Watt.

Thanks go to the EPSRC for providing the funding for this project.

Last, but not least, a big thank you to my family. Andrea, thank you for your love, support and encouragement throughout this work. Without it, I wouldn't have got there. To my Mum and Dad, thank you for always pushing me to achieve the best I can in life. I will always be grateful for your sacrifices over the years.

ACADEMIC REGISTRY

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ABBREVIATIONS

δ	NMR chemical shift
ν	wavenumber
Å	Angstrøm
Ac	acetyl
aq.	aqueous
Ar	aryl
BIPY/bipy	bypridine
Bn	benzyl
Box	bis(oxazoline)
bp	boiling point
br.	broad
Bu	butyl
c	concentration
C_1/C_2	symmetry point group
CAM	cerium ammonium molybdate
cm	centimetre(s)
cm^{-1}	wavenumbers
COD	cycloocta-1,5-diene
conc.	concentration
conv.	conversion
CuAAC	copper-catalyzed azide-alkyne cycloaddition
d	doublet
DCM	dichloromethane
de	diasteromeric excess
°C	degrees Celsius
deg	degrees
DIBAL	diisobutylaluminium hydride
DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N* dimethylformamide
DMSO	dimethsulfoxide
EDCI	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
en	ethylene diamine
EPSRC	Engineering and Physical Sciences Research Council
eq.	equivalents
ESI	electrospray ionisation

Et	ethyl
FTIR	Fourier transform infra-red
g	gram(s)
h	hour(s)
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole hydrate
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
i	*iso*
^{i}Pr	*iso*-propyl
IR	infra-red
J	NMR coupling constant
lit.	literature value
M	molar (mol/litre)
m	multiplet
Me	methyl
mg	milligrams
MHz	mega Hertz
min(s)	minute(s)
mL	millilitre(s)
mmol	millimole(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl (mesyl)
m/z	mass/charge ratio
NBS	*N*-bromosuccinimide
nm	nanometre(s)
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
p	*para*
Pd/C	palladium on activated charcoal
Ph	phenyl
PMA	phosphomolybdic acid
ppm	parts per million
Pr	propyl
q	quartet
quin.	quintet
R	undefined alkyl or aryl group
R_f	retention factor
RT	room temperature
s	singlet

sat.	saturated
t	triplet
t	*tertiary*
tert	*tertiary*
TBAF	tetrabutylammonium fluoride
TBTU	*O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate
^{t}Bu	*tert*-butyl
temp.	temperature
Tf	trifluoromethanesulfonate (triflate)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	tetramethylsilane
Ts	*para*-toluene sulfonate (tosyl)
UV	ultraviolet
wrt	with respect to
w/w	weight/weight

CHAPTER 1 – INTRODUCTION

1.1 Mechanically Interlocked Molecular Architectures

Mechanically interlocked molecular architectures are a ubiquitous class of "entangled" molecules which exist due to the stability inherent in their own characteristic topology. Significantly, mechanically interlocked architectures are neither supramolecular species nor can they be deemed complexes since separation of their component parts can only be achieved by strategic cleavage of covalent bonds.

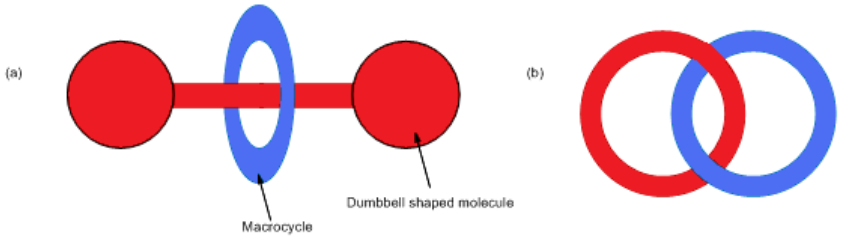


Figure 1.1 Morphology of (a) a basic rotaxane and (b) a catenane

Two of the most commonly studied interlocked molecular structures are *catenanes* and *rotaxanes*. The catenane species, derived from the Latin term *catena* meaning "chain", is comprised of a series of mechanically interlocked ring systems which can exhibit varied isomeric topology, although isolation of extended ring systems can be more synthetically challenging. Rotaxanes, from the Latin terms *rota* meaning "wheel" and *axle* meaning "axis", consist of a thread which has two sterically bulky stopper groups located at each end. The resulting dumbbell is encompassed within the cavity of a macrocycle; the stopper groups acting to prevent dethreading and decomposition of the rotaxane into it component parts. In the absence of these stopper groups the entanglement is known as a *pseudorotaxane* denoting its potential instability.

1.2 Nomenclature of Rotaxanes

So far, only basic rotaxane morphology has been considered, consisting of one ring and one dumbbell (Figure 1.1). This molecular system is defined as a [2]rotaxane, denoting the number of interlocked components in the molecule. As a general rule, an [*n*]rotaxane will contain *n*-1 ring systems threaded onto the dumbbell component, although for more complex systems the nomenclature proposed by Vögtle *et al.*[1] can be employed. Figure 1.2 shows two further common rotaxane topologies.

The concept of a single molecule comprising a cyclic moiety threaded by a linear chain was first proposed by Frisch and Wasserman in 1961 who claimed that such a structure could be kinetically stable.[2] Wasserman went on to synthesise the first catenane,[3] but it was Harrison and Harrison[4] and Schill and Zollenkopf[5] who almost simultaneously extended this concept to rotaxane synthesis. The term "hooplane", used by Harrison and Harrison was later succeeded by "rotaxane", coined by Schill and Zollenkopf.

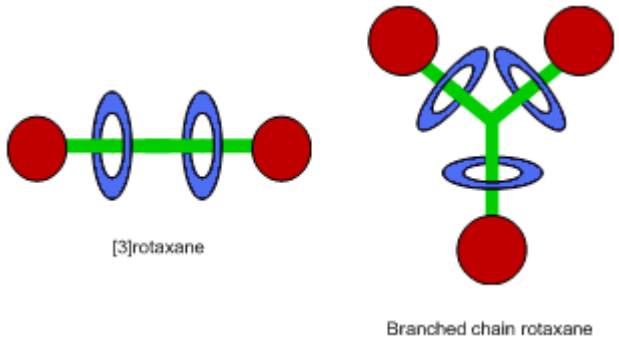


Figure 1.2 Illustration showing a [3]rotaxane and branched chain rotaxane

1.3 Applications of Molecular Interlocked Architectures

Since their conception, molecular interlocked architectures have progressed from subjects of academic curiosity to intense research interest not only due to their beauty but because of their interesting physical and chemical properties compared to their non-interlocked analogues. In addition, their inherent ability to allow controlled mechanical motion at the molecular scale has meant they have been exploited to yield potential applications in the field of nanotechnology.

Two such applications are the development of molecular switches[6] and molecular machines,[7] whereby an external stimulus controls the mechanical motion of the molecule with the aim of achieving some overall task. The very nature of mechanically interlocked structures makes them ideal candidates to form the basis of such molecular switches and machines. The ability of the components in catenanes and rotaxanes to move relative to one another, but still remain sufficiently restricted for motion to be controllable, has resulted in these structures having a central role in this field.

The use of rotaxanes has been particularly fruitful, having been utilised as both molecular shuttles and switches (Figure 1.3). The ability of the macrocycle to move along the thread from one "recognition" site to another is vital to the function of the machine. These recognition sites are locations situated along the axle with which the macrocycle can form some form of intramolecular interaction, e.g. hydrogen bonds. If movement of the macrocycle can be induced from one recognition site to another, a two-state system can result resembling a controllable switch.[8] A variety of external stimuli have been exploited to control such rotaxane based machines, including redox of a co-ordinated metal centre,[9] pH[6, 10] and light.[7]

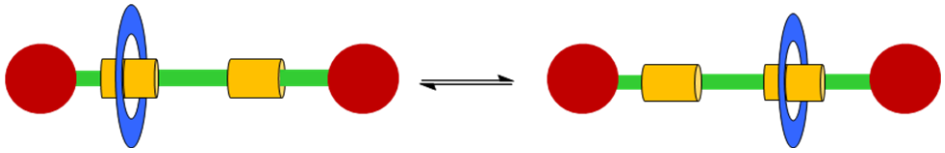
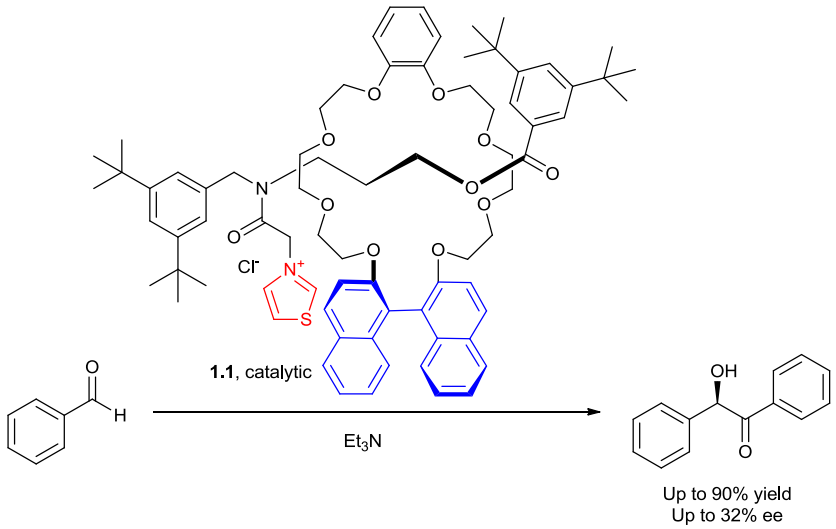


Figure 1.3 Schematic representation of a [2] rotaxane acting as a 2-state molecular switch

Rotaxanes have also seen application in the field of nanorecording,[11] whereby the rotaxane is deposited as a Langmuir-Blodgett film on indium-tin oxide (ITO) coated glass. Application of a voltage to the tip of a scanning tunneling microscope probe results in the macrocycle rings in the tip area switching to a different part of the dumbbell and the conformation afforded makes the molecules stick out from the surface by 0.3 nanometres. This height difference is sufficient for a memory dot.

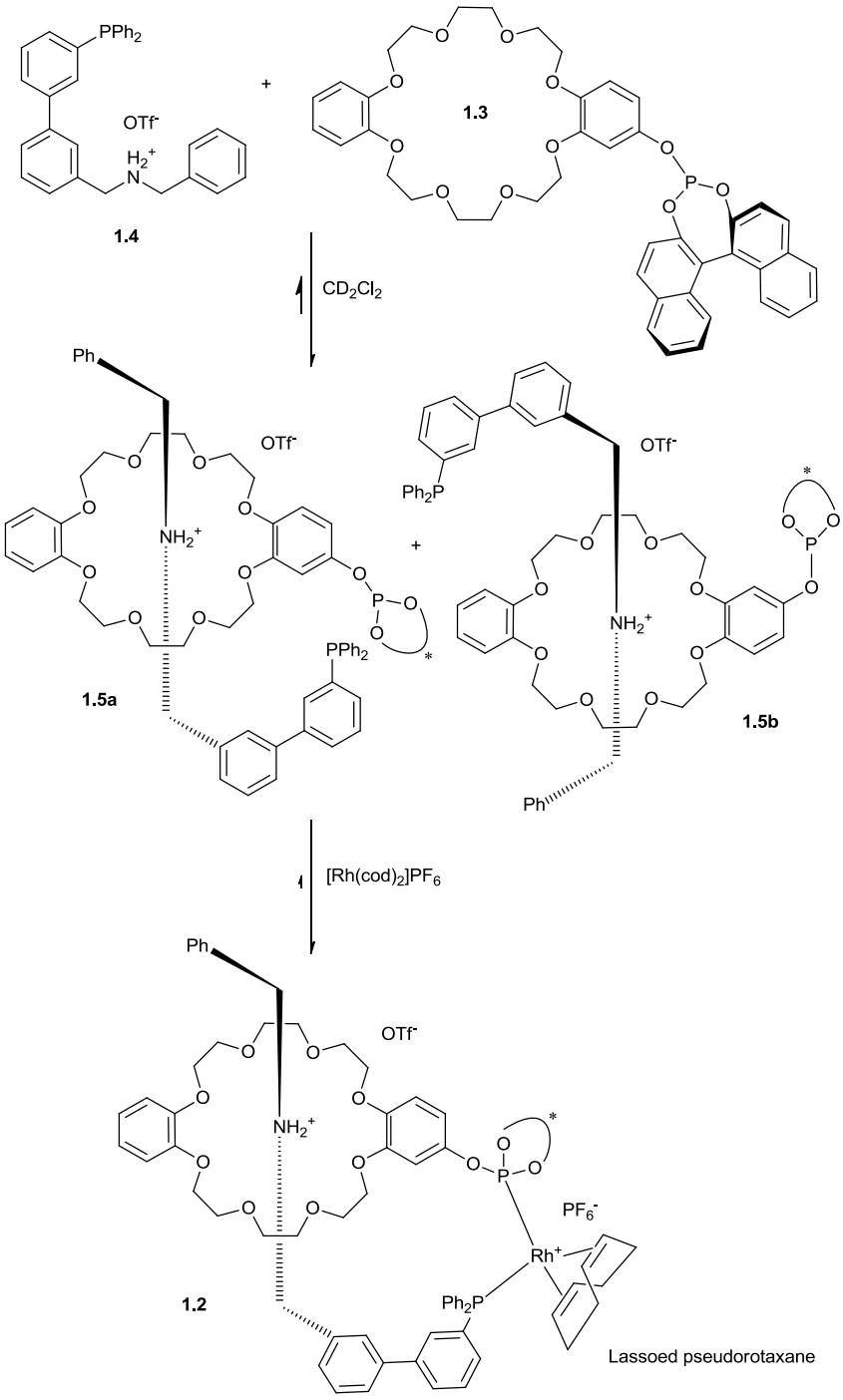
A more recent application of rotaxanes is in the rapidly developing field of asymmetric catalysis. The first example of an enantioselective reaction catalysed by a chiral rotaxane, was shown by Takata and co-workers.[12] They demonstrated that the chemical field formed by rotaxane components provided a chiral transfer field, based on non-covalent bonding, and that axial chirality from the (BINOL-derived) wheel could be transferred to the achiral catalytic site (thiazolium moiety) on the axle (Scheme 1.1). Rotaxane **1.1** was found to catalyse the benzoin condensation of benzaldehyde in up to 32% ee. Takata and co-workers proposed that in such a rotaxane where the chiral wheel component surrounds an achiral thiazolium salt moiety on the axle, the rotaxane field may be regarded as an enzyme-like asymmetric reaction field.[13] Although the enantioselectivities achieved in this proof-of-concept study are quite modest, the unique chirality transfer illustrates the potential of exploiting rotaxanes for chemical functions.



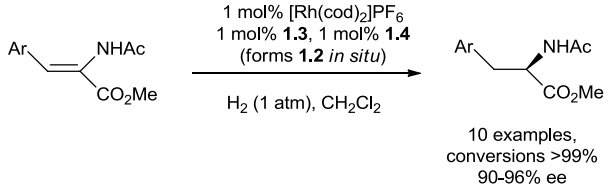
Scheme 1.1 Asymmetric benzoin condensation catalysed by chiral rotaxane 1.1 "through space" chirality transfer

Nishibayashi and co-workers went on to develop a novel chelating bidentate chiral ligand, based on a pseudorotaxane structure, which was effectively utilised in rhodium-catalysed enantioselective hydrogenation of enamides.[14] Nishibayashi's "lassoed" pseudorotaxane **1.2** was formed through addition of chiral crown ether **1.3** with the ammonium thread **1.4** to form a diastereomeric mixture of **1.5a** and **1.5b**. Subsequent addition of $[Rh(cod)_2]PF_6$ formed only one diastereomer of **1.2** (Scheme 1.2). Rhodium-catalysed enantioselective hydrogenation of enamides with pseudorotaxane **1.2** (formed *in situ*) proceeded with high conversions and high enantioselectivities, and this worked represented the first example of a pseudorotaxane being exploited as a chiral ligand in transition-metal catalysed enantioselective catalysis (Scheme 1.3).

Fan and co-workers have also reported similar pseudorotaxanes for rhodium-catalysed enantioselective hydrogenation of enamides, however the reduced products were afforded in lower enantioselectivities (68-88% ee) when compared with Nishibayashi's lassoed pseudorotaxane.[15]

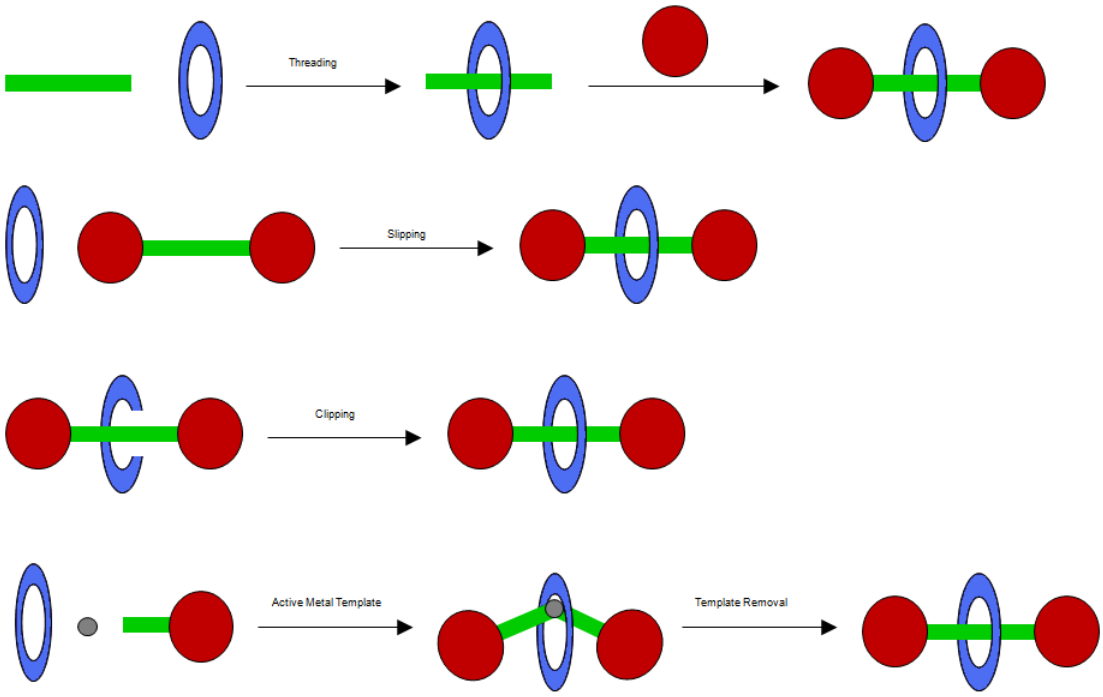


Scheme 1.2 Formation of a "lassoed" pseudorotaxane[13-14]



Scheme 1.3 Enantioselective hydrogenation of enamides employing a "lassoed" pseudorotaxane[13-14]

1.4 Overview of Classical Synthetic Methodologies of Rotaxanes



Scheme 1.4 Illustration showing four methodologies leading to mechanically interlocked architectures

The basic principles towards the synthesis of mechanically interlocked architectures are outlined in Scheme 1.4.[16]

Using a *threading* methodology, a thread is passed through the cavity of a macrocycle, often aided by exploiting molecular recognition between the thread and macrocycle. The resulting pseudorotaxane is then stoppered using sterically bulky groups to prevent dethreading, yielding the desired interlocked species (e.g. [2]rotaxane).

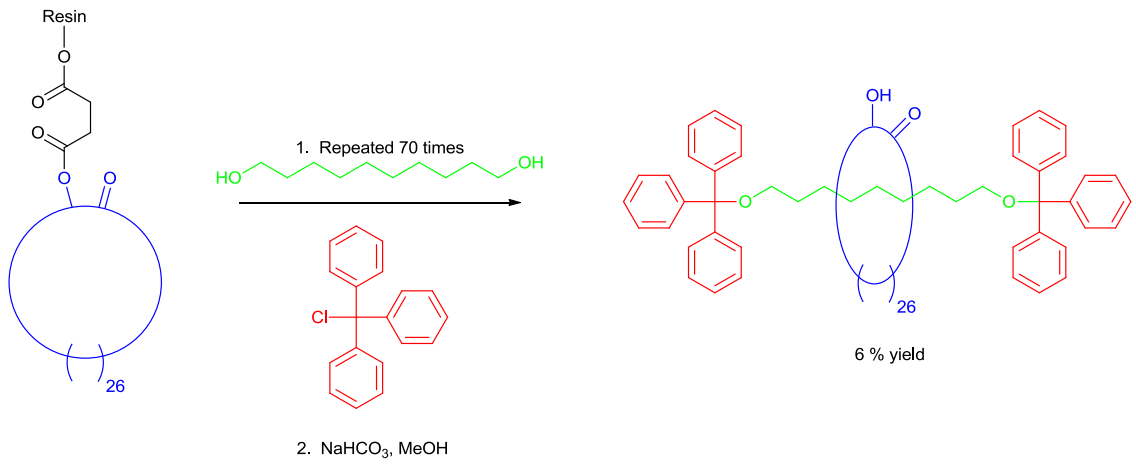
Similarly, the *slipping* methodology threads a macrocycle over a pre-stoppered thread. This is often achieved by applying thermal motion, whereby a temporary increase in ring diameter is achieved which, upon cooling, returns to its normal size and thus prevents dissociation of the ring.

An alternative approach, termed *clipping*, involves exploiting molecular recognition to attach a turn onto a pre-stoppered thread. Subsequent macrocyclisation of this turn around the thread leads to the isolation of the desired interlocked species.

Finally, the *active metal template* methodology utilises an active template (a metal ion) to bring together *and* catalyse the formation of covalent bonds between two pre-stoppered half threads- directly through the cavity of a macrocycle. Removal of the template by demetallation results in the interlocked species being formed.

1.4.1 Early Statistical Approaches

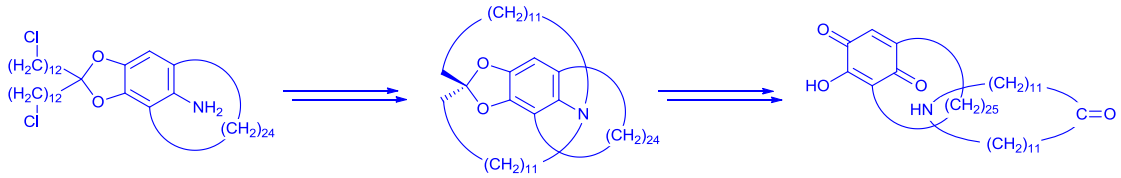
Despite the fact that Frisch and Wasserman were the first to introduce the idea of interlocked molecular architectures and that their subsequent synthesis of the first [2]catenane relied on the probability of threading through a macrocycle, it was Harrison and Harrison who extended this concept to rotaxane synthesis.[4] They adopted the approach of repeatedly treating a Merrifield resin bound macrocycle with decane-1,10-diol and triphenylmethyl chloride on a column. This resulted in a 6 % yield of the [2]rotaxane shown in Scheme 1.5. Their strategy centred on entropic effects for the formation of the rotaxane as often there are few attractive forces (e.g. only Van der Waals forces) presenting little or no interaction between the component parts.



Scheme 1.5 The first preparation of a [2]rotaxane by Harrison and Harrison using a Merrifield resin

1.4.2 Directed Synthesis by Covalent Bond Formation

The term "directed synthesis" was first used by Schill and co-workers in 1964 when they employed templating covalent bonds during key stages of a [2]catenane synthesis, to ensure the desired topology of the product (Scheme 1.6).[17]



Scheme 1.6 Key intermediates during the directed synthesis of a [2] catenane by Schill *et al.*[17]

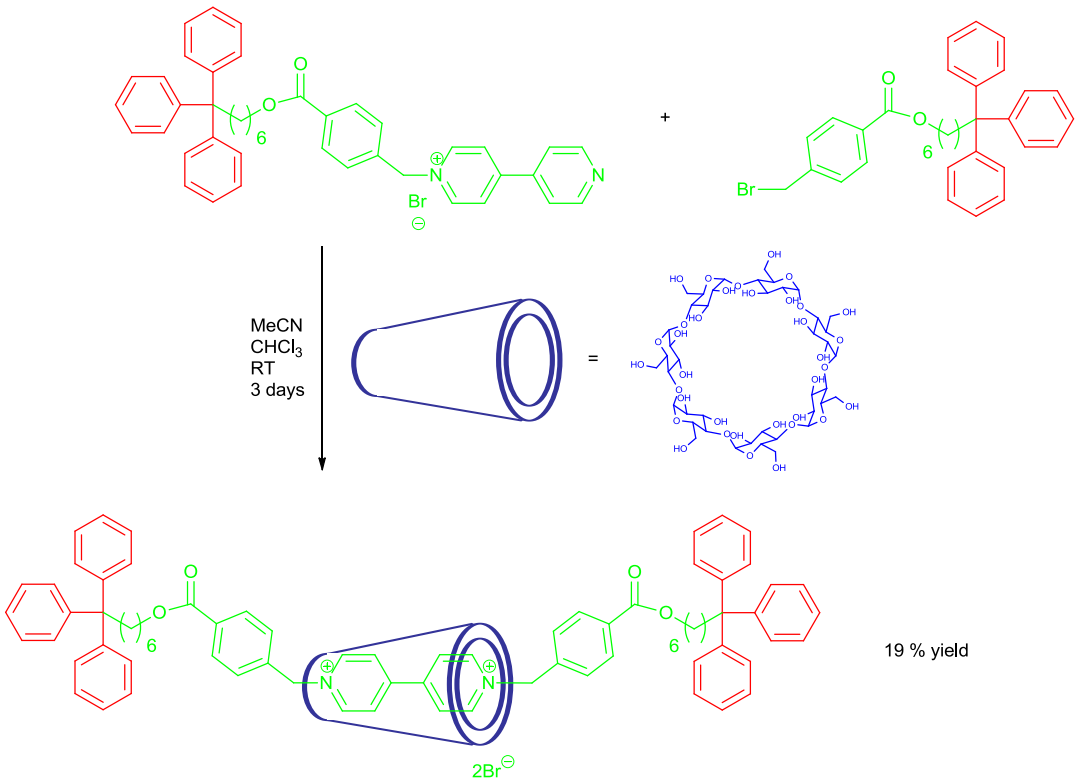
The tetrahedral geometry at the acetal group directed formation of one ring around the other, resulting in a 30 % yield of covalently bound *catenate*. Subsequent hydrolysis finally gave rise to the desired [2]catenane. This technique overcame the drawback of relying solely on chance (statistical approach) and a host of elegant template strategies have since ensued.

1.4.3 Cyclodextrin Mediated Template Synthesis

Cyclodextrins (or cyclic amylases) are a series of cyclic oligosaccharides which are known to afford a range of complexes, some with high association constants.[18-20] Their inherent amphiphilic properties allow them to encapsulate an organic molecular guest within their hydrophobic cavity whilst they retain water solubility due to their hydrophilic exterior. Coupled with their fixed geometry, there is selectivity for guests with respect to size and shape. Ogino and co-workers were the first to develop the complexing abilities of cyclodextrins in the field of rotaxane synthesis, utilising Co(III) complexes as the stopper groups.[21-23]

A typical example by Wenz *et al.* is shown in Scheme 1.7. A β-cyclodextrin threads a mono-stoppered 4,4'-bipyridine and is subsequently stoppered *in situ* to yield a [2]rotaxane in 19 % yield.[24]

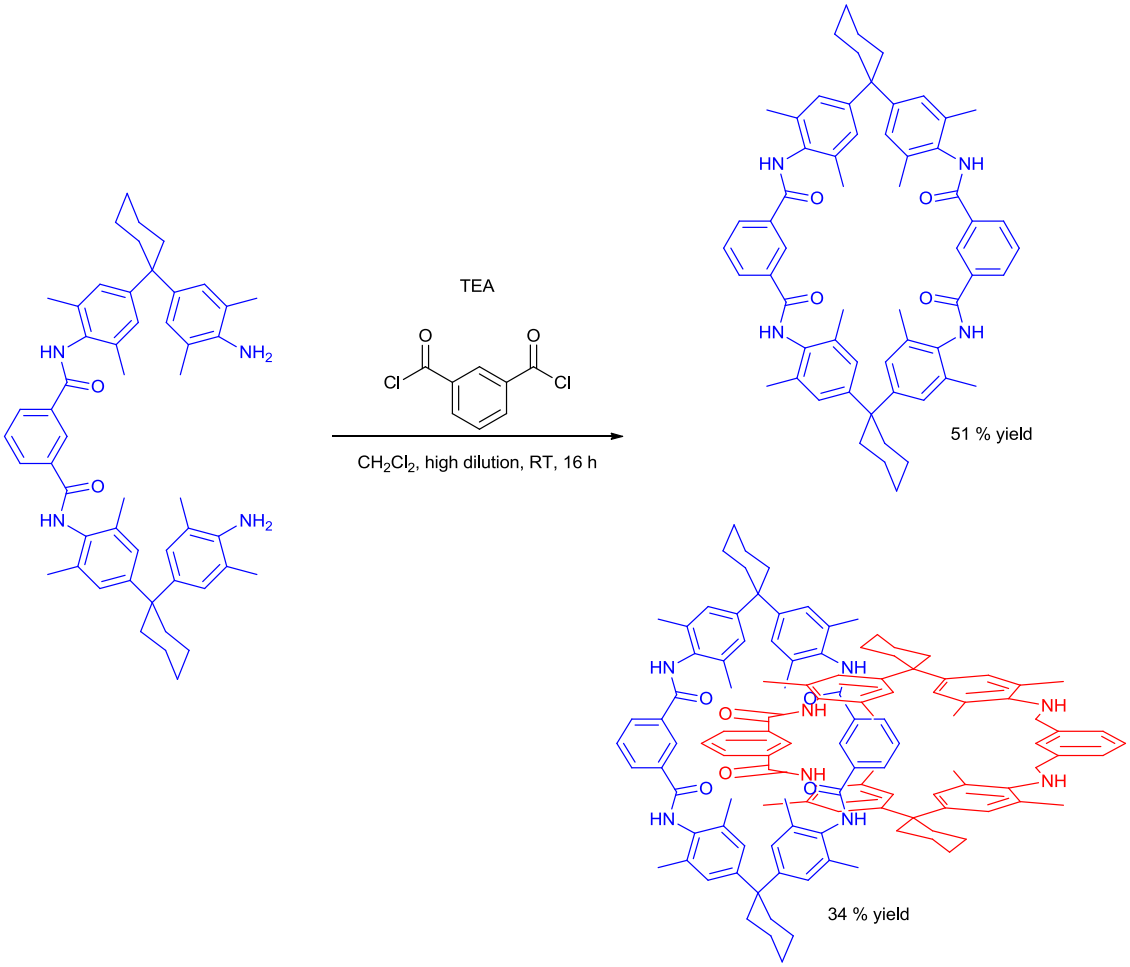
The range of applications for cyclodextrin based rotaxanes is varied, including foundations in photochemically switchable molecular shuttles[25-26] and in the encapsulation of dyes[27-28] for protection or modification of properties. Furthermore, cyclodextrins can form supramolecular assemblies with a variety of polymers, yielding polyrotaxanes or "molecular necklaces".[29] More recently, the synthesis of a persistent paramagnetic rotaxane with a cyclodextrin ring has also been reported.[30]



Scheme 1.7 A representative example of the synthesis of a [2]rotaxane using β-cyclodextrin as a macrocycle[24]

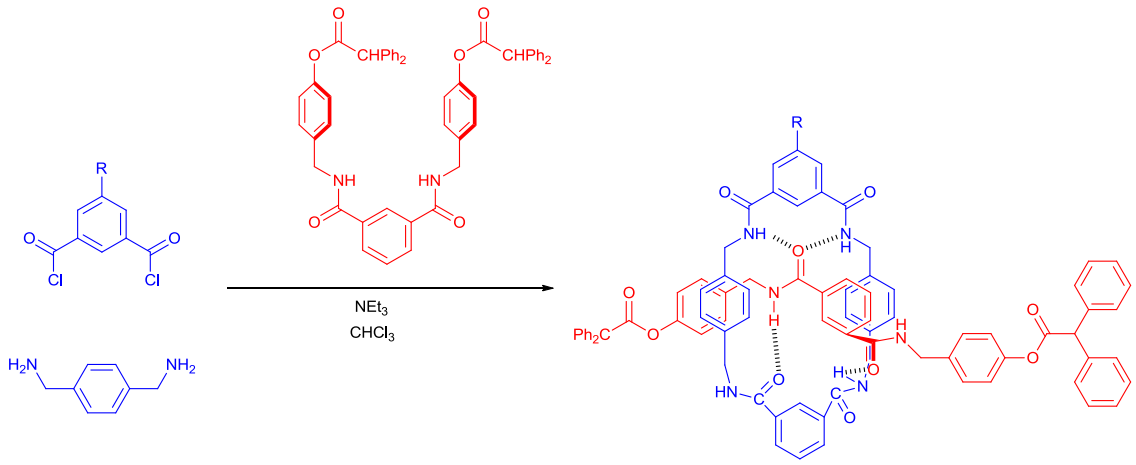
1.4.4 Hydrogen Bond Mediated Templating

The phenomenon of hydrogen bonding in connection with templating of interlocked architectures was first discovered by chance in 1992 by Hunter and co-workers (Scheme 1.8).[31] Whilst optimising the reaction conditions for the synthesis of a target macrocycle, Hunter reported formation of a [2]catenane as a by-product in 34% yield. The [2]catenane resulted from the macrocyclic precursors clipping around an existing molecule of the target macrocycle. Hydrogen bonding interactions between the precursor amine and carbonyl moieties acted as a template, holding each part in place whilst macrocyclisation occurred.



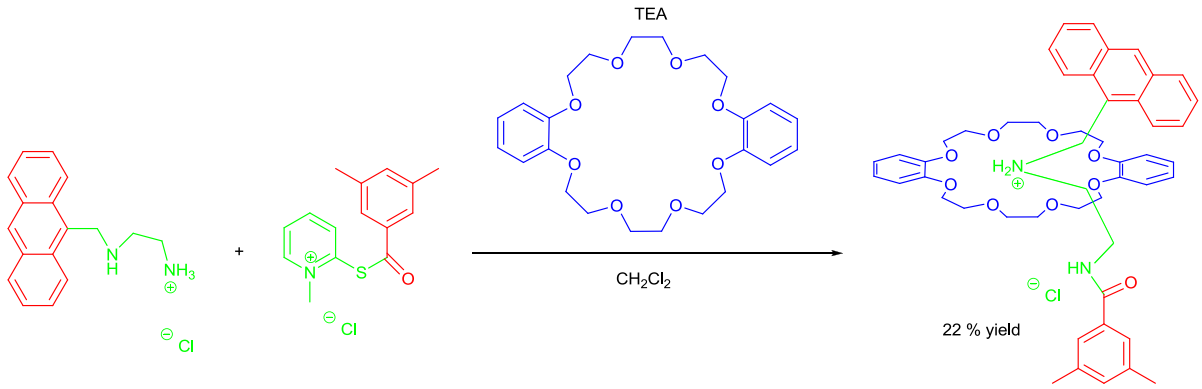
Scheme 1.8 The synthesis of a [2]catenane by Hunter[31]

This phenomenon has been exploited by Leigh and co-workers where they were able to synthesise an amide macrocycle around an amide thread using a clipping strategy aided by complementary hydrogen bonding sites (Scheme 1.9). The resulting [2]rotaxane satisfies the hydrogen bonding requirements of both the thread and the macrocycle, the consequence of which was a rotaxane, 10^5 times more soluble in chloroform than the free macrocycle.[32]



Scheme 1.9 Hydrogen bond assisted clipping of a macrocycle around a thread to give the corresponding [2]rotaxane

A related synthetic methodology to interlocked systems exploiting hydrogen bonding involves using complexing interactions. This technique has been employed for the formation of rotaxanes by Busch *et al.*[33] and by Stoddart and co-workers.[34-36] Typically, the hydrogen bonding site is an electron deficient ammonium ion which is centrally located within the molecular thread (Scheme 1.10). The ammonium ion shows an affinity for the electron rich oxygen atoms positioned in the crown ether macrocycle, thus promoting of rotaxane formation in a modest 22% yield.[33]



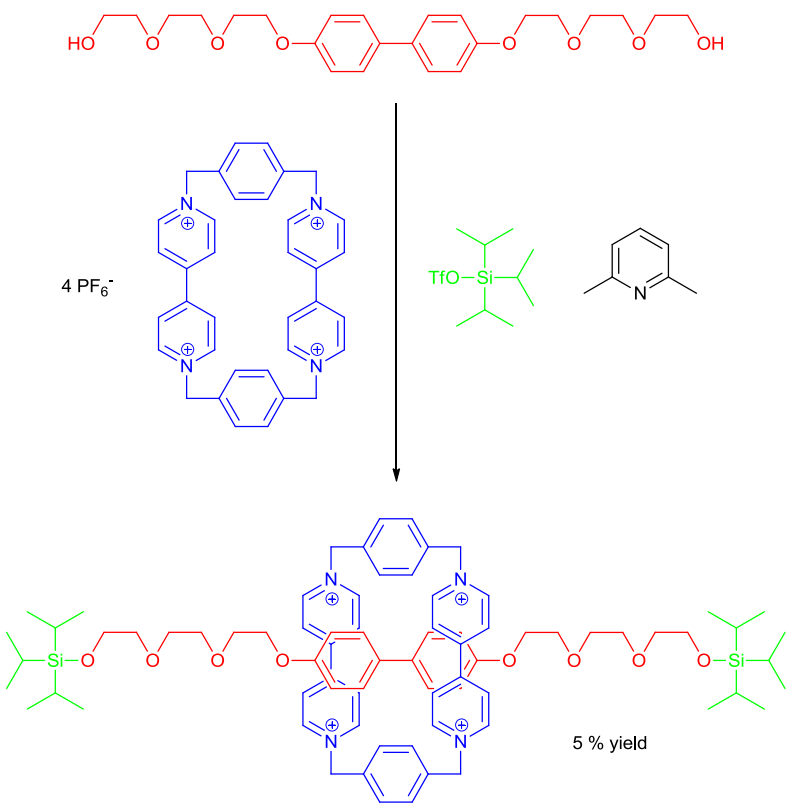
Scheme 1.10 A [2]rotaxane synthesised by Busch *et al.* exploiting complexing interactions between ammonium ions and crown ether.[33]

More recently, Leigh and co-workers achieved an unprecedented yield for a rotaxane forming reaction using an adapted hydrogen bonding template (97%). This was achieved by exploiting the structural rigidity and the pre-organisation of thread-binding sites, coupled with effective hydrogen bond acceptors (amides). Moreover, this efficient template allowed even poor hydrogen bond acceptors (e.g. esters) to be used to prepare hydrogen bond-assembled rotaxanes.[37] These amide rotaxanes have been

further developed to form the basis of sophisticated molecular shuttles which operate in response to a variety of stimuli.

1.4.5 π-electron donor/π-electron acceptor interactions

During the late 1980s, Stoddart and co-workers discovered that selected bipyridinium salts complexed efficiently with benzo crown ethers during the design of a receptor unit for paraquat (a molecule containing π-electron deficient bipyridinium rings).[38-39] Paraquat-based salts are co-ordinated within the parallel aromatic rings of π-electron rich benzo crown ethers, resulting in pseudorotaxane type structures, which can be subsequently stoppered to give the corresponding rotaxane. A selected example is shown in Scheme 1.11, where a cyclobis(paraquat-*p*-phenylene) macrocycle is threaded by an extended 4,4'-biphenol species.[39]



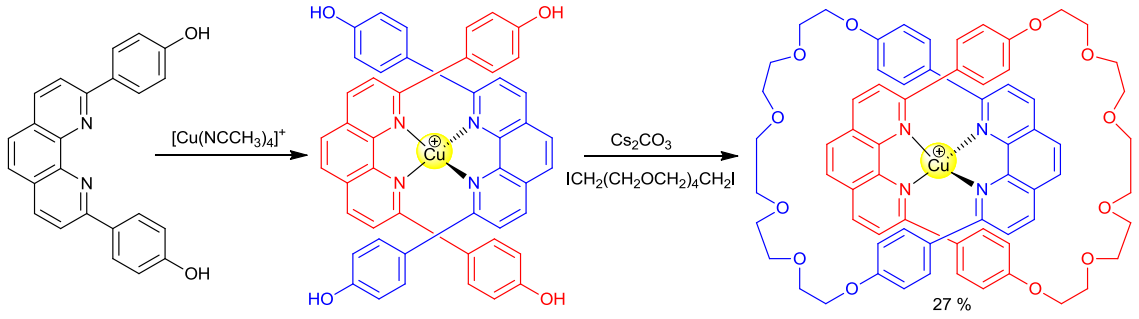
Scheme 1.11 Synthesis of a [2]rotaxane exploiting π-π interactions by Stoddart and co-workers. The reaction proceeds in 5 % yield.[39]

The development of π-π interactions as a viable route to interlocked architectures has led to a wide variety of catenane and rotaxane systems being synthesised with two[40-46], three[47-51] and more[49, 52] aromatic donor sites.

1.4.6 Transition Metal Templating

The application of transition metals to hold ligands in a precise orientation, directing bond formation to favour an interlocked product, is very attractive to the synthetic chemist. In addition to the interactions being strong, the shapes of the resulting supramolecular complexes are often highly ordered, typically dictated by the preferred geometry at the metal centre. There are many examples found in the literature where structures are held together at certain points by transition metals. However, the transition metal template methodology differs somewhat in that although the presence of the metal aids in the formation of the molecule, it is not essential once formed.

This pioneering concept was first developed by Sauvage and co-workers where the tetrahedral geometry of Cu(I) was used to hold two 1,10-phenanthroline fragments orthogonally, allowing formation of a [2]catenane (Scheme 1.12).[53] During the earliest work, the ring systems were closed using a Williamson ether synthesis[53] but later work reported greater success could be achieved using ring closing metathesis[54] and a full paper resulted in 1999.[55]

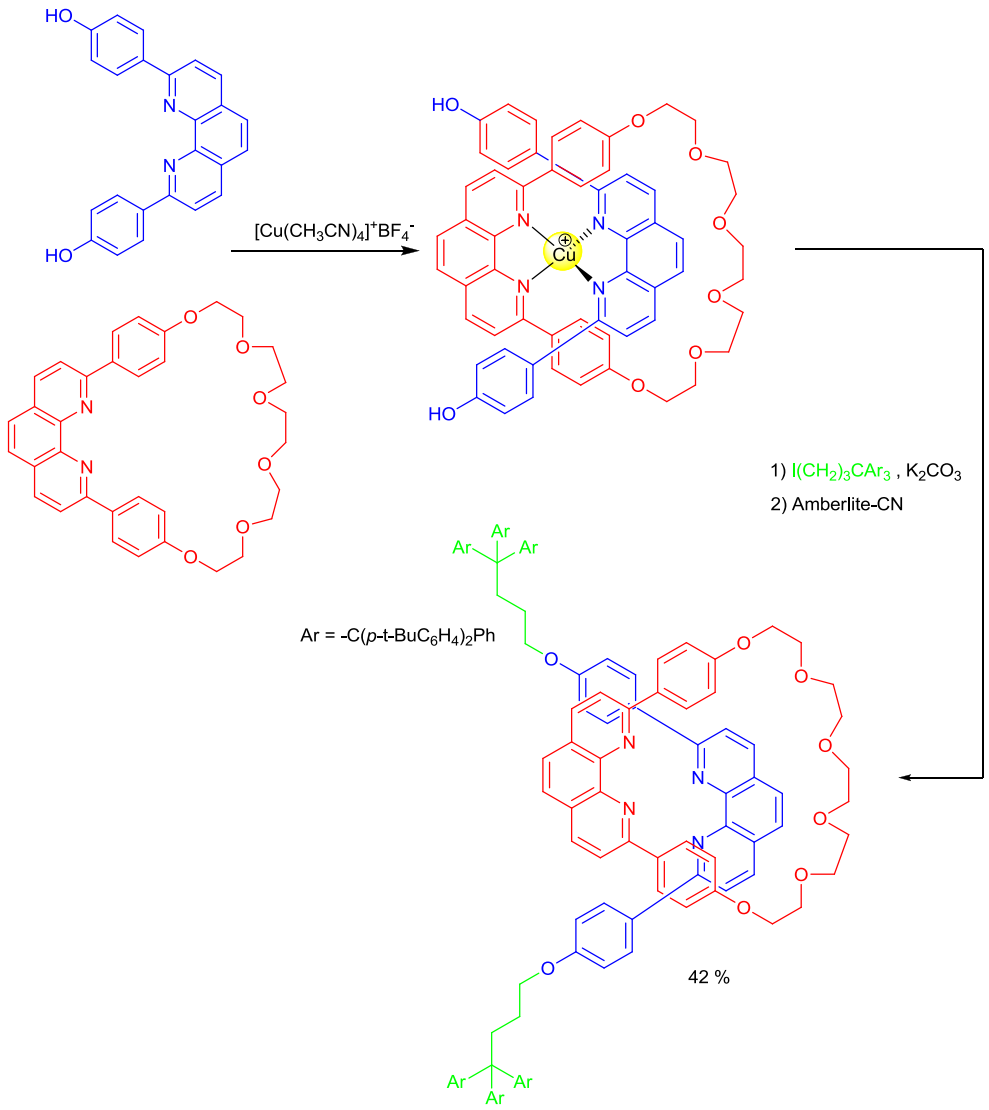


Scheme 1.12 Transition metal template assembly of a [2[catenane by Sauvage and co-workers. The reaction proceeds in a surprising 27 % yield, given that statistical and directed routes at the time were laborious and low yielding (<1 %).[53]

Gibson and co-workers extended this work using a similar Cu(I)-phenanthroline type ligand complex (Scheme 1.13), leading to the first synthesis of a transition metal template directed rotaxane in 42 % yield.[56]

Since the ground-breaking conception of transition metal template mediated rotaxane synthesis, the scope of the technique has grown to encompass other metals besides Cu; namely, Fe, Co, Ni, Zn, Cd and Hg.[57-60] This, in turn, has led to a greater understanding

of the mechanistic detail including the co-ordination requirements of the respective metal template ion.

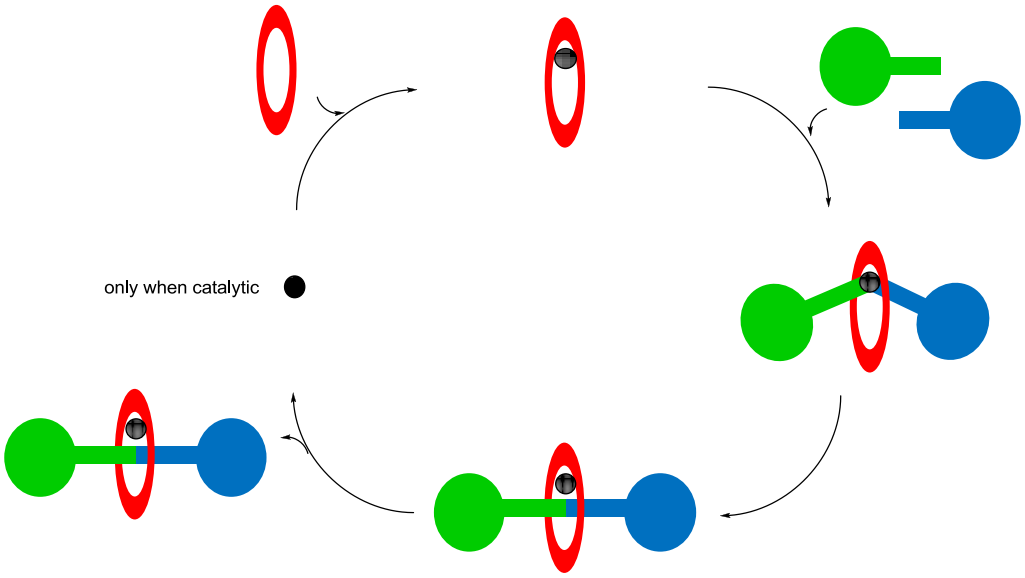


Scheme 1.13 The first synthesis of a 2[rotaxane] by Gibson and co-workers in 1991 exploiting the templating effect of a transition metal ion.[56]

1.5 Active Metal Template Synthesis of Rotaxanes

Whilst classical metal template approaches have revolutionised the synthesis of catenanes, rotaxanes and other related interlocked molecular architectures, providing the impetus for the development of other template methodologies, they do not fully exploit the chemistry intrinsic to metal ions. As discussed, the metal is merely used to hold the reactive components in place so as to allow direct bond formation. Further extension of this concept has led to a novel strategy in which the metal template ion has a dual role: in the reaction, acting as a template for bringing the reaction precursors together, *and* to catalyse the final covalent bond-forming reactions which interlock the final structure.

This new strategy is called the "active" metal template approach. It relies upon the ability of a given macrocycle to bind a metal ion endotopically within its cavity. When this method is applied to rotaxane synthesis, the metal is chosen such that it promotes covalent bond formation between two appropriately functionalised "half-thread" units, through the centre of the macrocycle (Scheme 1.14).



Scheme 1.14 Schematic illustration of the underlying principles of active metal template synthesis. The metal catalyst (shown in grey) promotes formation of a covalent bond between the two "half-threads" (shown in green and blue) to form a rotaxane axle. This is directed though the cavity of the macrocycle (shown in red) by the coordination requirements of the metal ion.

The advantages that such an approach towards rotaxane synthesis offer are numerous: (i) having the macrocycle-metal complex perform multiple functions during the reaction pathway is both efficient and flexible; (ii) permanent recognition sites on each reaction precursor are not essential, thus increasing rotaxane structural diversity and enabling "traceless" formation of the interlocked species; (iii) some applications permit sub-stoichiometric quantities of metal template to be used; (iv) this strategy could potentially be applicable to other well-known transition metal-catalysed and organocatalytic reactions; (v) reactions which proceed through a threaded intermediate may provide a route to mechanically interlocked architectures which are currently inaccessible; and, ultimately, (vi) an insight into the mechanism of the metal catalysed reactions may become apparent through the co-ordination requirements of the metal during key steps of the catalytic cycle.[61]

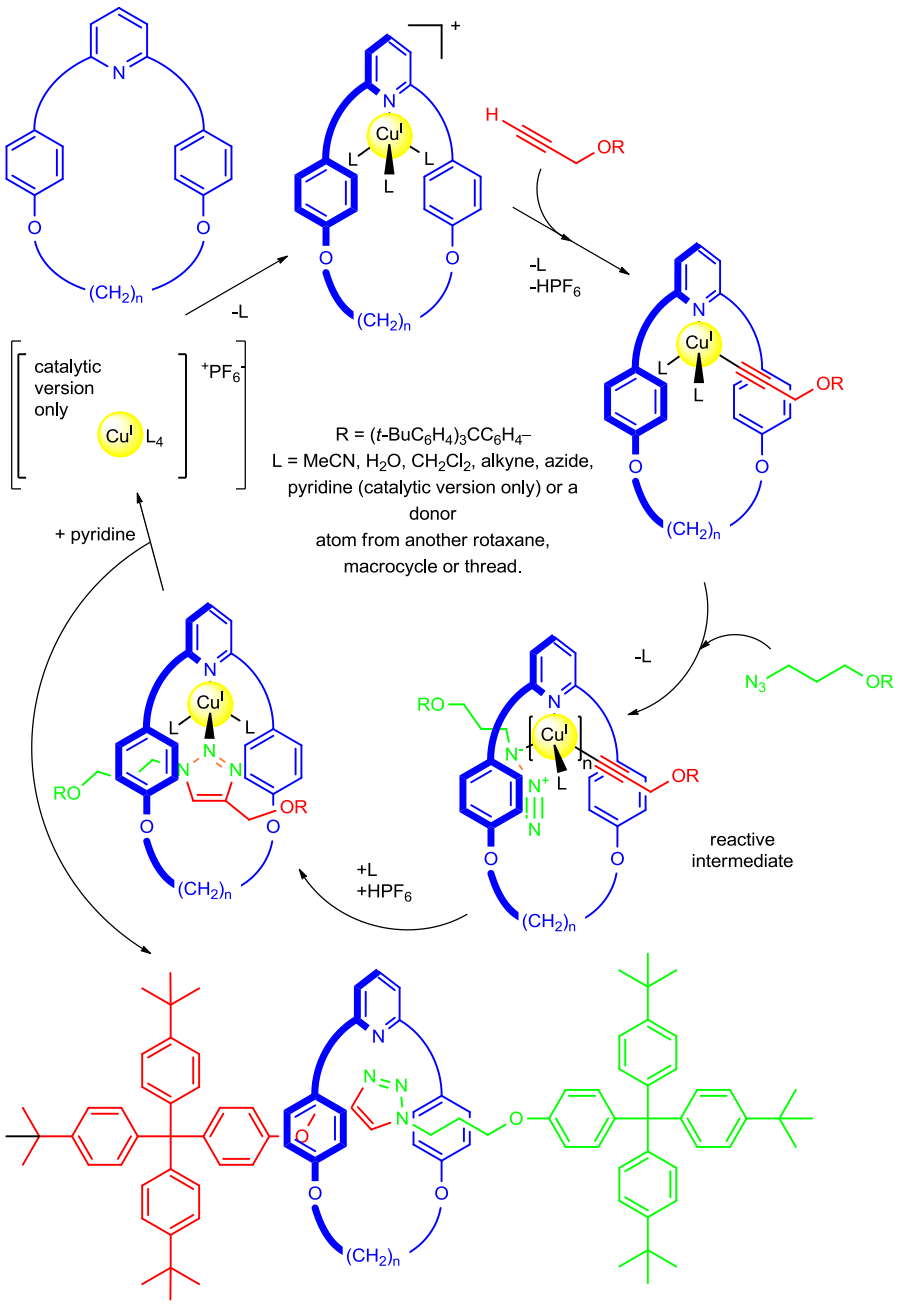
The first active metal template synthesis was reported by the Leigh group in 2006.[62] They utilised a copper(I)-catalysed terminal alkyne-azide 1,3 cycloaddition (CuAAc) to

assemble a [2]rotaxane with the model now extending to other transition metal mediated reactions.

1.5.1 CuAAc Active Metal Template For Rotaxane Synthesis

Despite little knowledge of the mechanism of the CuAAc reaction[63-64] at the time, its mild conditions and high yielding character made it favourable for initial investigations and facilitated the accumulation of proof for the active metal template concept. Furthermore, it was known that the addition of Cu(I) accelerated the reaction rate. As a result, it was anticipated that co-ordination of a tetrahedral Cu(I) ion within the cavity of a monodentate or bidentate macrocycle would enhance co-ordination of an azide and terminal alkyne to the copper, through opposite faces of the macrocycle (Scheme 1.15). The subsequent coupling reaction would then result in the [2]rotaxane being formed.

Leigh and co-workers reported yields of up to 94% for the synthesis of selected [2]rotaxanes in studies conducted on the stoichiometric version of the active metal template strategy and went on to investigate the use of sub-stoichiometric amounts of copper active species. They were able to determine that the metal could in fact turn over, as both the template and as a cycloaddition catalyst, providing that the reaction was conducted in the presence of a competitive ligand (such as pyridine) to recycle the copper which is sequestered by the multidentate rotaxane. Optimisation of the sub-stoichiometric reaction led to yields of 82% of the rotaxane when using just 4 mol% of the Cu(I) catalyst with respect to each half-thread reactant.[62] A later publication reports the generality of the reaction and efforts made to probe mechanistic details.[65] Goldup has since investigated the effect of the size of the macrocycle cavity on the reaction.[66] Leigh *et al.* have also extended the use of the CuAAC 'click' reaction into the active template synthesis of [3]rotaxanes,[67] catenanes[68] and trefoil knots.[69]

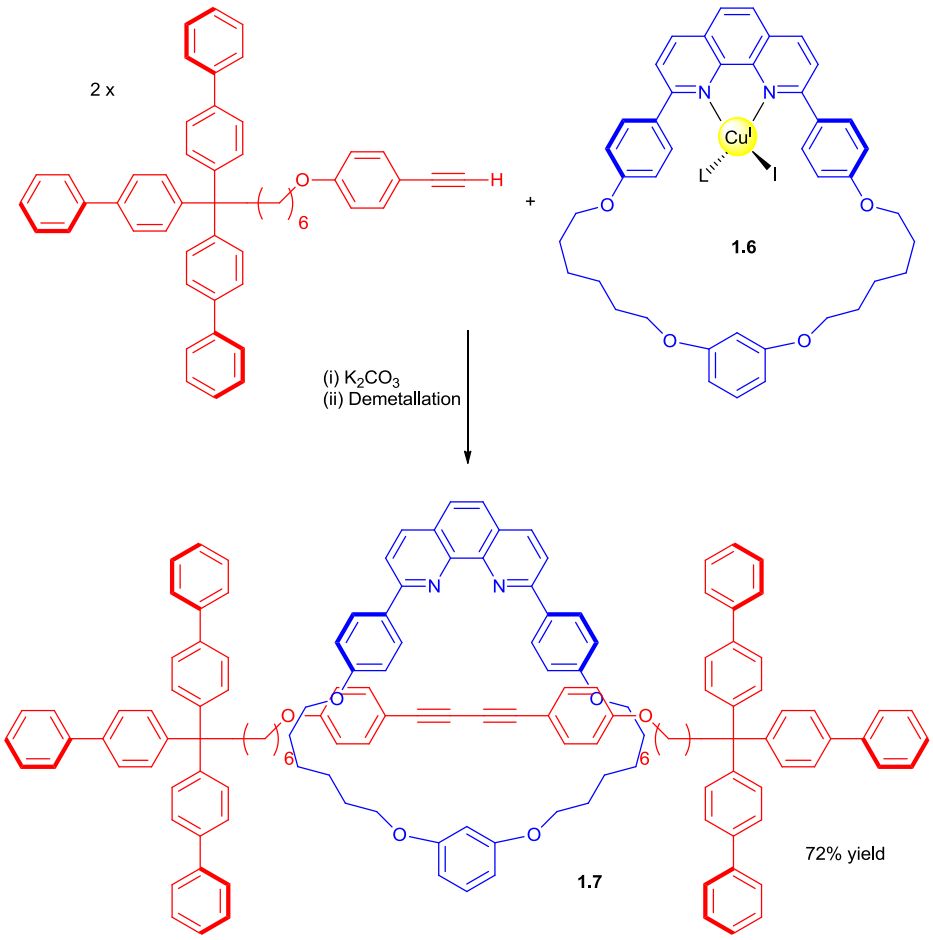


Scheme 1.15 Outline of the CuAAc reaction conducted by Leigh *et al.* to investigate the effect of macrocycle ring size on [2]rotaxane formation.[61]

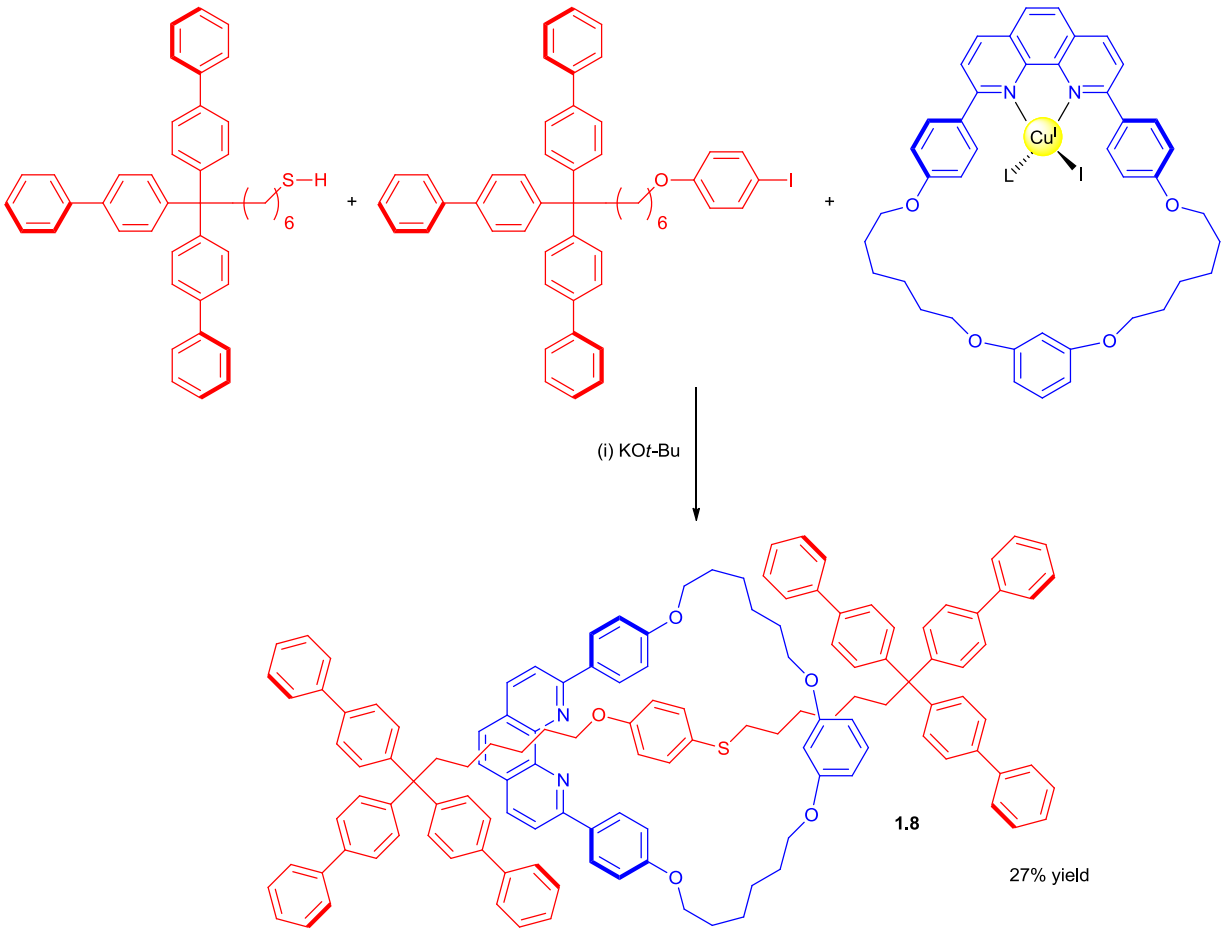
1.5.2 Copper Mediated Oxidative Alkyne-Alkyne Homocoupling

Following on from the success of the CuAAc reaction as a viable method for rotaxane synthesis, other template reactions quickly emerged. One of the first involved the use of Cu-mediated alkyne homocouplings (Glaser-Hay couplings) by Saito and co-workers.[70] Stoichiometric quantities of a Cu(I)-phenanthroline complex **1.6** were used to yield the homocoupled alkyne [2]rotaxane **1.7** in 72% yield (Scheme 1.16). In the same paper, Saito reports the use of the same complex in another stoichiometric active

template reaction, exploiting the copper-mediated Ullman C-S coupling reaction, to give [2]rotaxane **1.8** in a modest 27% yield (Scheme 1.17).



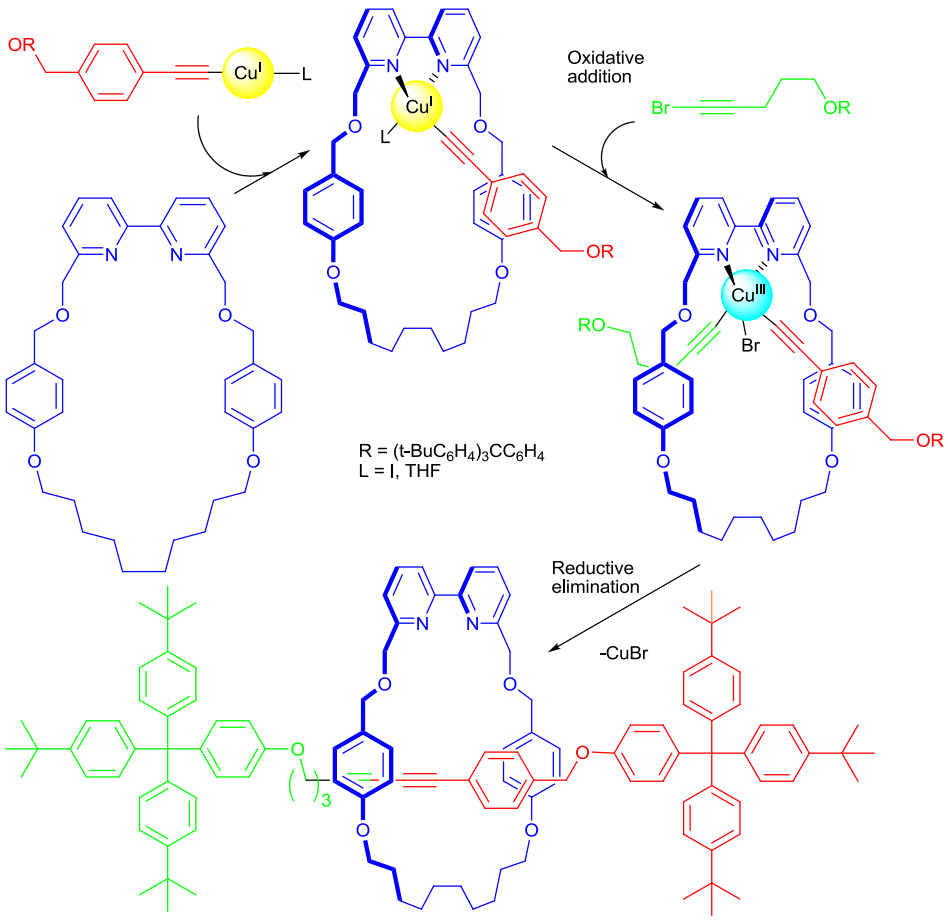
Scheme 1.16 Stoichiometric active template rotaxane synthesis using Glaser homoalkyne couplings[70]



Scheme 1.17 Stoichiometric active template rotaxane synthesis using an Ullman C-S coupling[70]

1.5.3 Copper Mediated Alkyne-Alkyne Heterocoupling

Following on from the successful application of the CuAAc reaction, the Leigh group went on to develop a copper-catalysed alkyne-alkyne heterocoupling active template, based on a modified Cadiot-Chodkiewicz procedure.[71] Crucially, the rotaxane products have unsymmetrical axles and, unlike classical passive synthetic procedures, do not leave strong intercomponent binding motifs in the final product (Scheme 1.18).[61] The group were able to achieve excellent selectivities and high yields with respect to hetero- *vs*. homocoupled products (>98% and up to 85% respectively), making the Cadiot-Chodkiewicz one of the most efficient active templates available to the synthetic chemist to date.

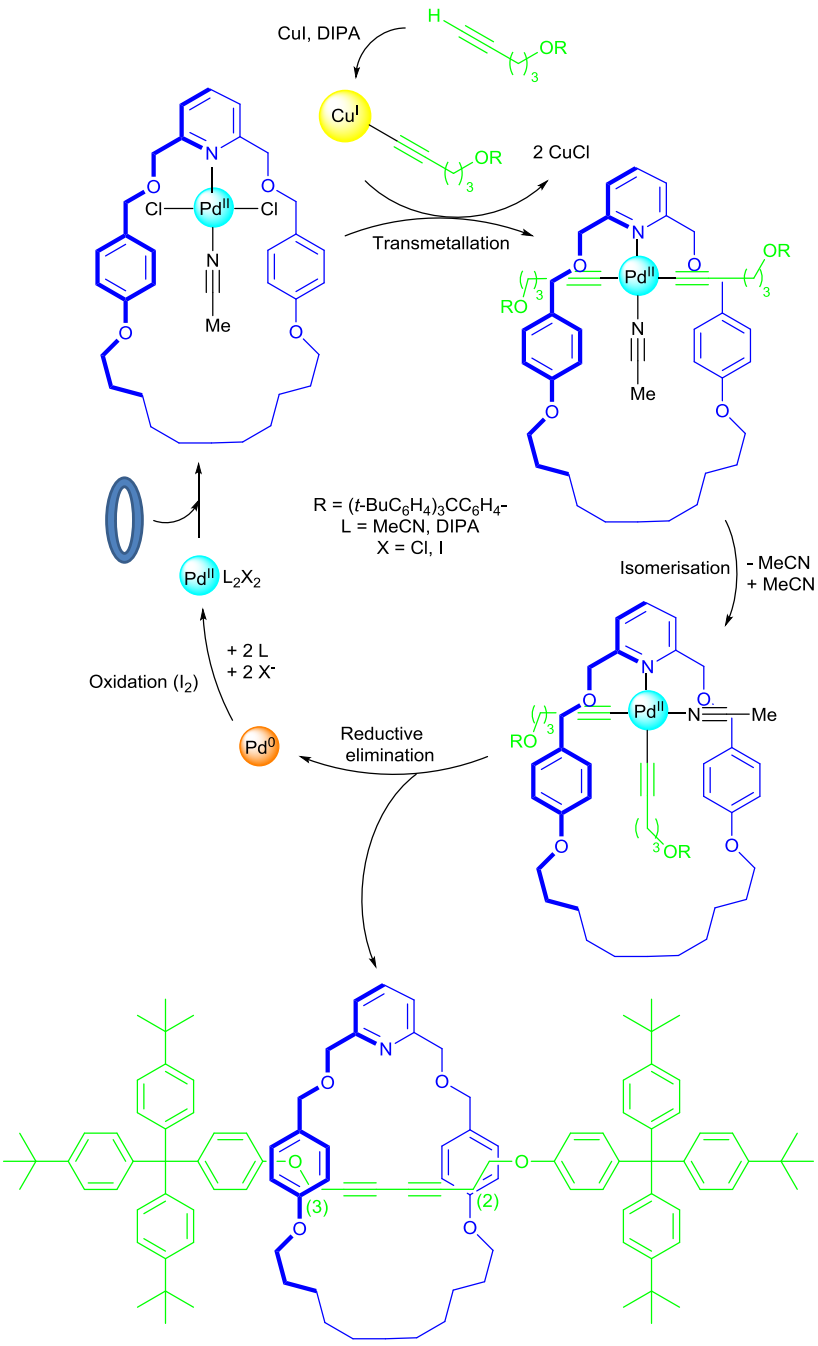


Scheme 1.18 Stoichiometric Cadiot-Chodiewicz (alkyne-alkyne heterocoupling) active template synthesis of a [2]rotaxane.[61, 71]

1.5.4 Palladium(II)-Catalysed Active Metal Template Reactions

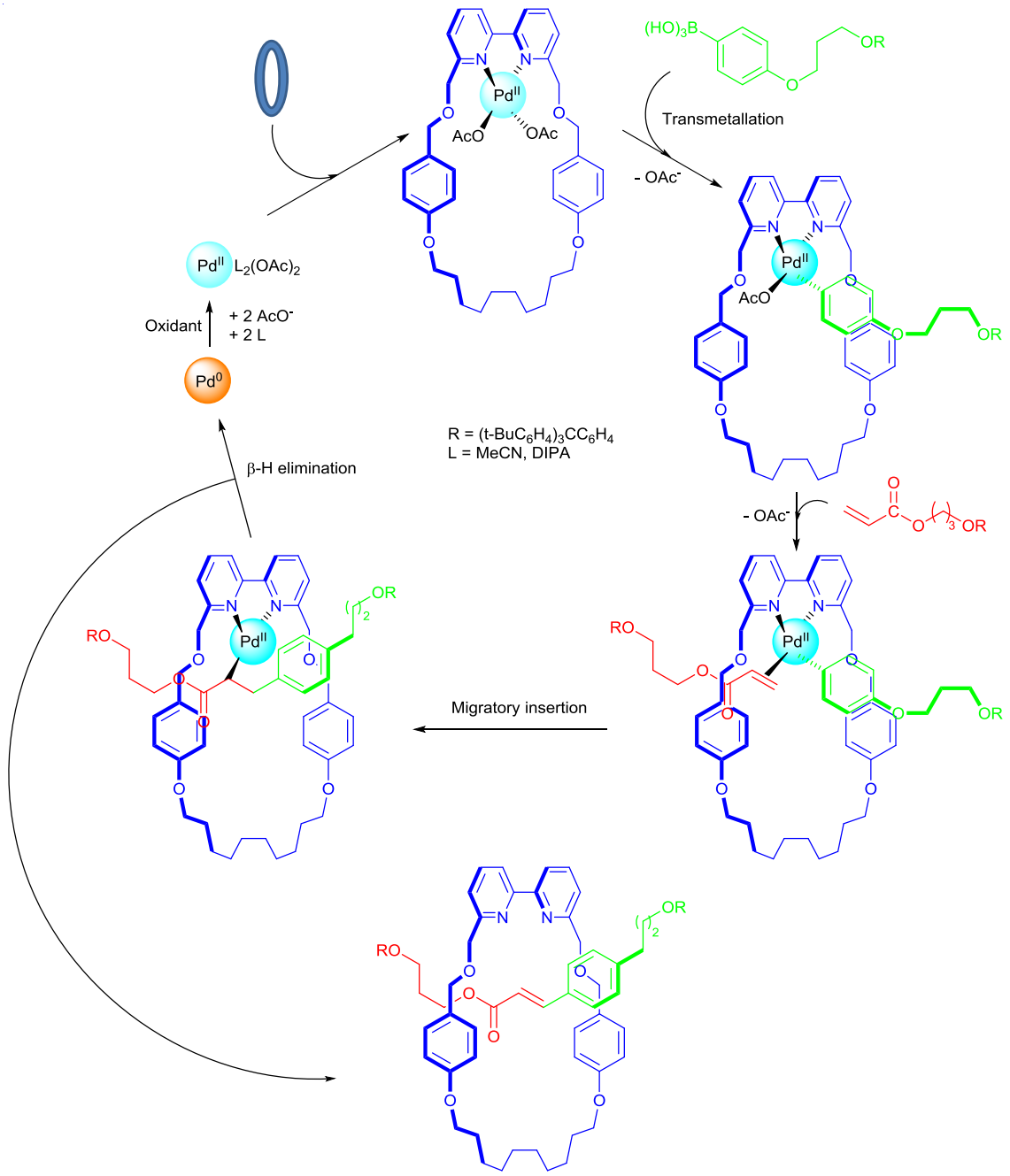
Palladium catalysed cross-coupling reactions are one of the most important and widely used reactions in modern synthetic chemistry for the formation of C-C bonds. With this in mind, Leigh and co-workers extended their interest in the active template methodology to palladium-catalysed reactions, first experimenting with Pd(0) species[72] and, more successfully, with Pd(II) species.[73] Studies found that the demand on template geometry was greatly increased with palladium as the active template, when compared to their earlier work with copper and as a result the group found that attempts to couple together half-threads with Pd(0) yielded only non-interlocked species.[72] Leigh *et al*. postulated that this is due to the markedly different co-ordination requirements for Pd(0) compared to Pd(II), resulting in the metal detaching from the *N*-based macrocyclic ligand at key stages during the reaction. Experimentation with Pd(II) as the active species proved to be far more fruitful because the Pd(II) was ligated much more strongly to the macrocycle throughout the reaction. This, in turn, led to the first Pd-catalysed rotaxane forming active metal template reactions, in both stoichiometric

and catalytic forms, centred around the Pd(II) homocoupling of alkynes (Scheme 1.19).[73-74]



Scheme 1.19 Stoichiometric and sub-stoichiometric active metal template synthesis of [2]rotaxanes using Pd(II)-mediated oxidative homocoupling of terminal alkynes.[61, 73]

In order to extend the practicality and applicability of Pd(II) as the active metal template, the concept was extended to cross-couplings, thus allowing access to rotaxanes with unsymmetrical axles. Leigh and co-workers applied the oxidative Heck Pd(II) cross-coupling reaction to the active metal template synthesis of rotaxanes and found the reaction to be mild, efficient and substrate tolerant (Scheme 1.20).



Scheme 1.20. Catalytic active metal template synthesis of [2]rotaxanes using the oxidative Heck Pd(II) reaction[72]

Recently, Leigh and co-workers have reported the application of the active metal template concept to a multi-component assembly process, whereby successive Pd(II)-mediated Michael additions of α-cyano esters to vinyl ketones were exploited.[75]

1.6 Cyclochirality and Rotaxanes

One of the least exploited features of mechanically interlocked molecular structures, such as rotaxanes, is the phenomenon of *cyclochirality* or *mechanical planar chirality*.[76] The concept of cyclochirality is closely linked to topological chirality but a topologically chiral molecule is defined as one that cannot be deformed to form its mirror image without cutting, whereas a macrocycle on a rotaxane can be pulled apart to allow de-threading and re-threading to confer its mirror image, thus the rotaxane is not topologically chiral but termed cyclochiral. A rotaxane can possess cyclochirality even if both wheel and axle are themselves achiral, made possible if the wheel and axle bear groups which impart directionality. This is shown pictorially in Figure 1.4.

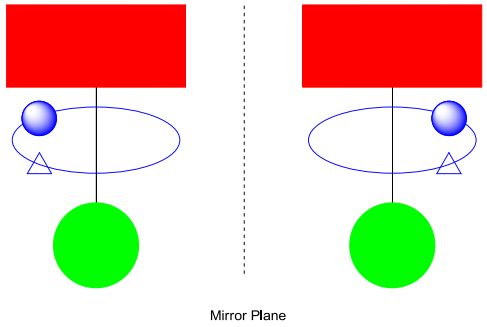


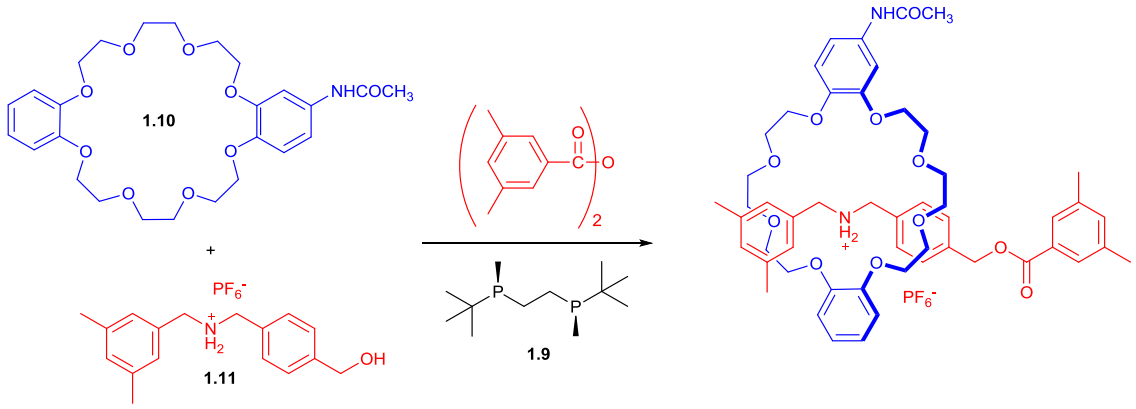
Figure 1.4 Illustration of cyclochirality. Both wheel and axle bear groups which impart directionality.

The synthesis of enantiopure cyclochiral rotaxanes is an area which is beginning to attract more attention. Limited efforts so far have focussed on two main preparatory techniques: (i) preparation of a racemic mixture of the optically active cyclochiral rotaxane, followed by isolation of the desired enantiomer by preparative chiral stationary phase HPLC and (ii) asymmetric preparation of the desired enantiomer.

The first reported preparation of a racemic mixture of pure cyclochiral rotaxanes was reported by Vögtle and co-workers in 1997.[77] The cyclochirality arose from the unsymmetrical distribution of sulfonamide and amide moieties, distributed on the macrocycle wheel, in conjunction with the use of unsymmetrical stopper groups- both of which imparted directionality. The mixture was resolved by chiral HPLC. More recently, Kameta and co-workers also adopted this strategy. They too were able to successfully synthesise and resolve racemic mixtures of selected cyclochiral rotaxanes[78-79] to exploit them as amino acid chiral sensors. However, it was reported that not all of their mixtures could be separated using chiral HPLC and so it was

postulated that the structure (i.e. stopper and chain length) of the axle may be a primary factor influencing the efficiency of the final separation.[78] This perhaps highlights the inherent drawbacks that such an approach affords in that not all racemic mixtures of cyclochiral rotaxanes can be successful resolved. In addition to this, the final yield of a given enantiomer is restricted to a maximum of 50%, limiting the scale to which cyclochiral rotaxanes can be prepared.

Conversely, the application of asymmetric synthesis, whereby only the desired enantiomer is synthesised, does not suffer the same purification and yield drawbacks as the resolution of racemic cyclochiral mixtures approach. Nevertheless, the asymmetric preparation of a cyclochiral rotaxane is extremely challenging and to date only one successful synthesis has been reported,[80] albeit in a 48% yield and, more importantly, only 4.4 % ee. Takata and co-workers employed the chiral trialkylphosphane catalyst **1.9**, with amide substituted crown ether **1.10** as the macrocyclic component and secondary ammonium salt **1.11** as the mono-stoppered axle (Scheme 1.21).



Scheme 1.21 The only reported asymmetric synthesis of a cyclochiral rotaxane to date.[80] The reaction proceeds in 48% yield with a 4.4% ee.

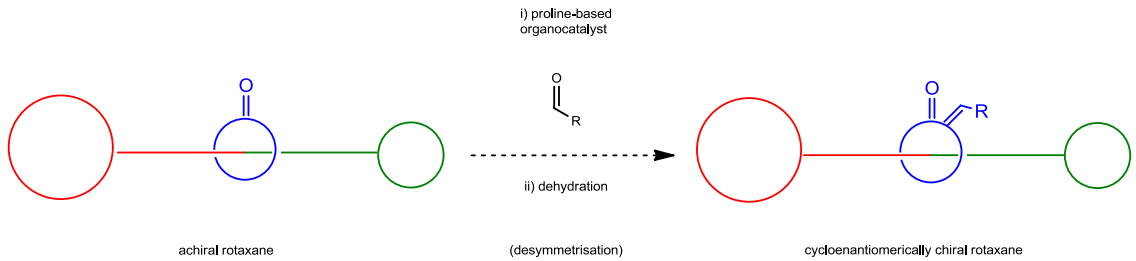
It is clear from these results that the goal of efficiently synthesising and investigating the asymmetric induction properties of cyclochiral rotaxanes, particularly ones with no other form of chirality, remains a major challenge and one which now forms the foundation of this research project.

CHAPTER 2 – STUDIES TOWARDS THE SYNTHESIS OF A CYCLOCHIRAL ROTAXANE

2.1 Results and Discussion

2.1.1 Project Overview

The main goal of this project was to enantioselectively synthesise a cyclochiral rotaxane by the desymmetrisation of an achiral rotaxane. An achiral rotaxane consisting of a symmetrical macrocycle and a thread with sterically different stoppers at either end could potentially be enantioselectively desymmetrised to form a non-symmetrical macrocyclic portion and hence, an optically active, cyclochiral rotaxane. A possible desymmetrisation reaction could be the proline-based organocatalytic direct aldol reaction (Scheme 2.1). Subsequent dehydration of the resulting β-hydroxyketone, to remove residual point chirality, should produce an optically active, purely cyclochiral rotaxane. Should this approach be successful, this would constitute a novel use of desymmetrisation, a unique application of organocatalysis as well as an innovative asymmetric approach to cyclochiral rotaxanes.



Scheme 2.1 Overview of the desymmetrisation of an achiral rotaxane

2.1.2 Design of a Prochiral Rotaxane for Desymmetrisation

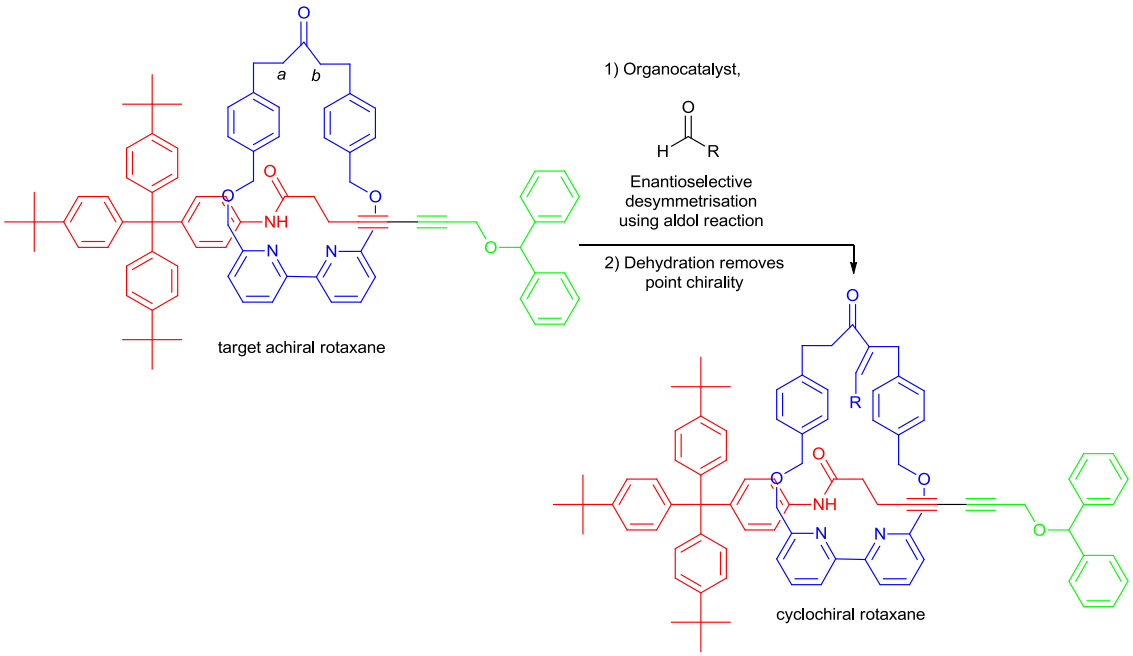
The target rotaxane is shown in Scheme 2.2. It was designed such that one stopper was sterically more bulky than the other so that one face of the macrocycle could be significantly blocked by the bulky stopper [(^{t}BuC$_6$H$_4$)$_3$CC$_6$H$_4$], leaving attack at the opposite face more favourable. Furthermore, it was envisaged that the macrocycle would be positioned predominantly over the amide moiety on the axle, due to the possible H-bonding between the bipyridine *N* and the amide N*H*.[61] It was reasoned that the chiral catalyst selected for the proline-based organocatalytic direct aldol reaction would determine at which carbonyl α-position (*a* or *b*) the reaction with the aldehyde

occurred (favouring the reaction of one enamine intermediate over the other).[81] Simultaneously, the facial selectivity would be controlled by the bulkier stopper. It was our aim to screen a number of readily available proline-organocatalysts.[82]

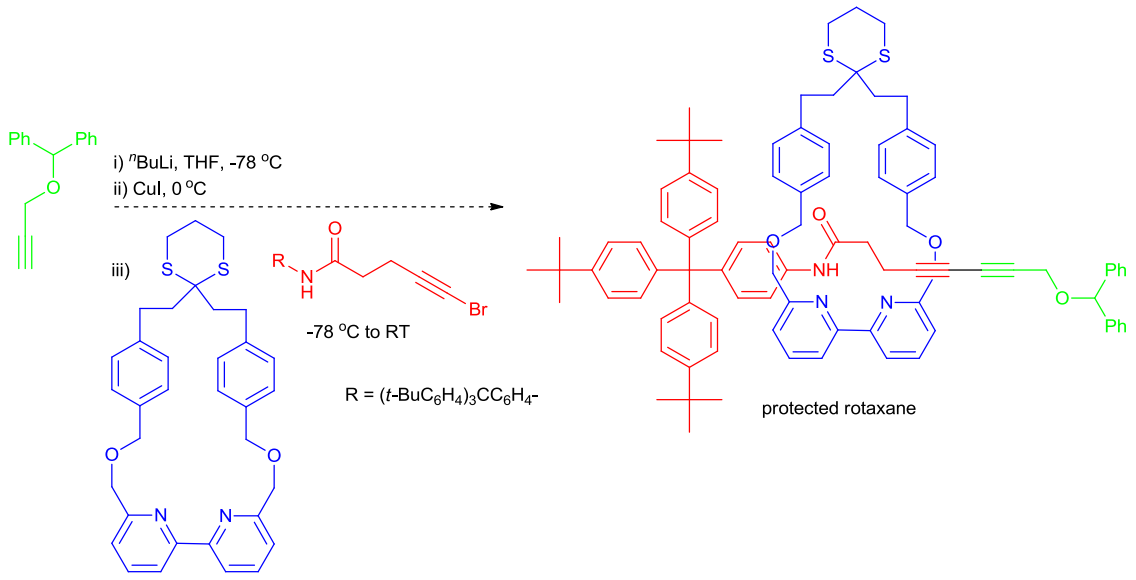
2.1.3 Synthetic overview of the target prochiral rotaxane

It was proposed to prepare the target prochiral rotaxane *via* an active-template Cu-mediated Cadiot-Chodkiewicz type cross-coupling (Scheme 2.3).[71] For preliminary investigations, it was reasoned that the ketone would have to be protected as the 1,3-dithiane due to the presence of strong base. The retrosynthetic plan for the synthesis of the macrocycle is outlined in Scheme 2.4. It was imagined that a Williamson ether synthesis could be employed to form macrocycle **2.1**. Consecutive deprotonation and alkylation of 1,3 dithiane would allow access to synthon **2.2**. A synthetic route towards synthon **2.3**, a bipyridine compound, was known, and involved a transition metal catalysed coupling of bromopyridine.[73]

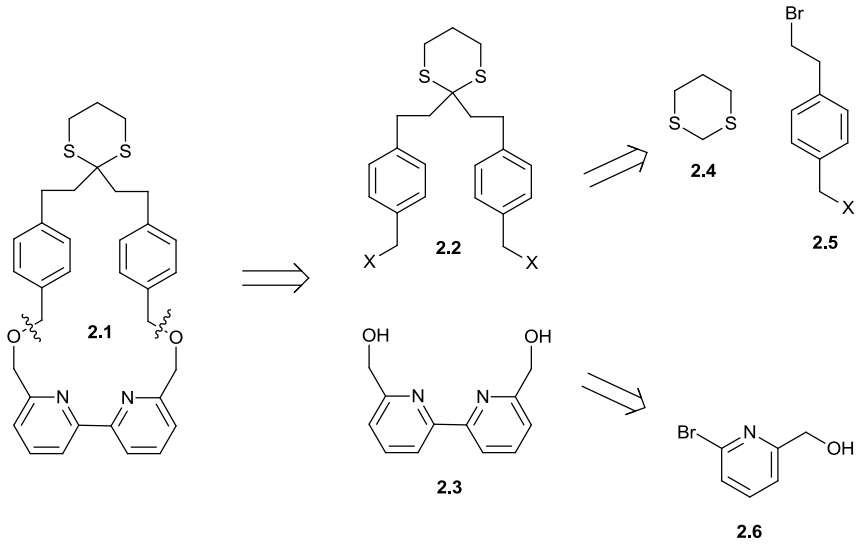
To summarise, the key synthetic objectives at the outset of the project were (i) synthesis of the protected macrocycle; (ii) synthesis of the "half-threads" and prochiral rotaxane and (iii) enantioselective desymmetrisation of the prochiral rotaxane (including screening of organocatalysts and optimisation of reaction conditions).



Scheme 2.2 Design of target achiral rotaxane and resulting cyclochiral rotaxane from desymmetrisation and dehydration



Scheme 2.3. Outline of the Cadiot-Chodkiewicz type cross-coupling reaction, incorporating two "half-threads" and protected macrocycle



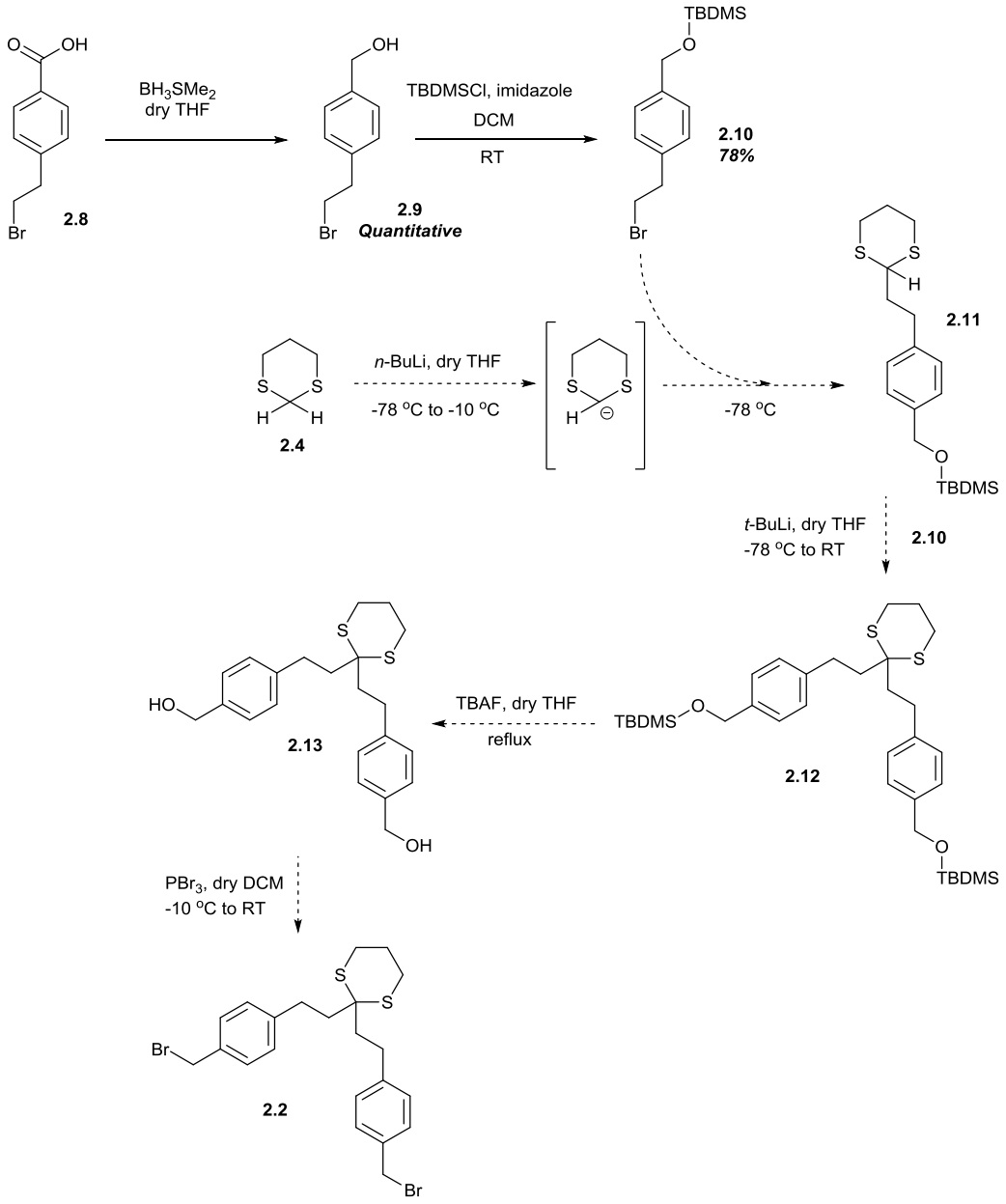
Scheme 2.4. Retrosynthetic plan for the protected macrocycle

2.2 Preparation of Macrocycle 2.1

The primary objective of the project was to successfully synthesise the target macrocycle **2.1** shown in Scheme 2.4. To achieve this, the macrocycle was split into two key synthons, **2.2** and **2.3** to provide two separate synthetic targets. It was postulated that subsequent coupling of each synthon should give the desired product.

Firstly, we turned our attention to the more synthetically challenging synthon **2.2**. The dibromide (**2.2,** where X is bromine) derivative was selected for initial synthetic

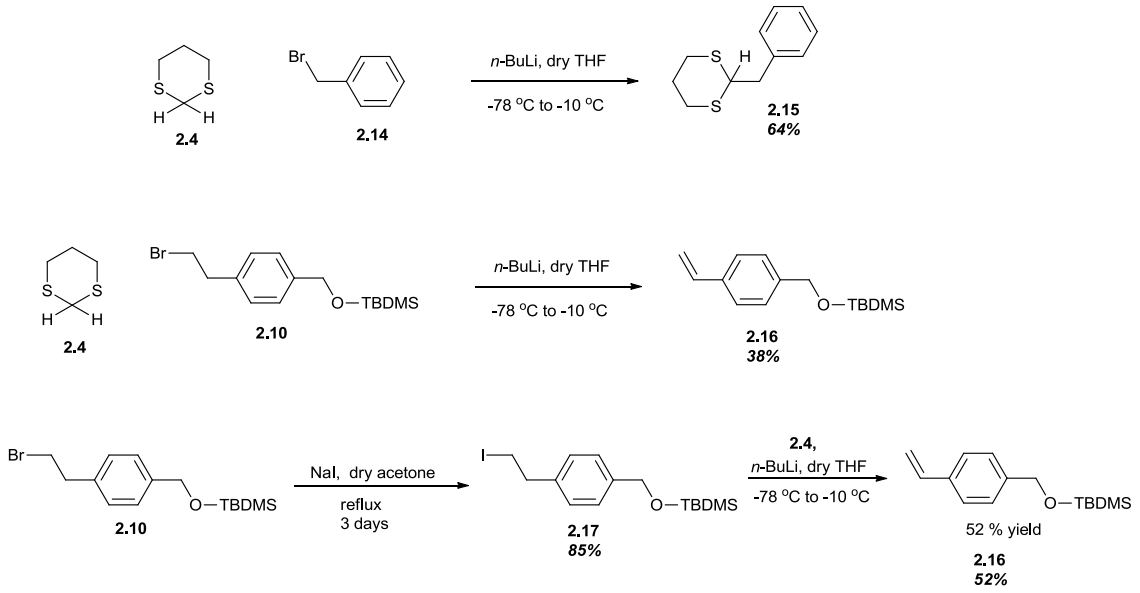
attempts as the bromo leaving groups had already been reported by Leigh *et al.* to be suitable for the final Williamson ether coupling of the macrocycle precursors.[71] With this in mind, the synthetic plan shown in Scheme 2.5 was devised.



Scheme 2.5 Initially proposed synthetic scheme to macrocycle precursor 2.2

The synthesis started from commercially available, yet expensive, 4-(2-bromoethyl)benzoic acid **2.8**, which was successfully reduced to the corresponding primary alcohol **2.9** (quantitative yield) using boron dimethyl sulfide, following the procedure used by Klein.[83] Primary alcohol **2.9** was then protected as the *t*-butyldimethylsilyl ether under standard reaction conditions[84] affording compound **2.10** in 78 % yield after purification by flash column chromatography.

The core success and synthetic value of Scheme 2.5 depended on the result of the sequential deprotonation and S_N2 reaction between readily available 1,3-dithiane **2.4** and our preformed electrophile **2.10**. There is literature precedence that similar coupling reactions lead to moderate to high yields of mono- and di-alkylated dithiane products using both bromide and iodide precursors.[85-86] In order to probe the scope of these reactions, a series of microscale trials were conducted (Scheme 2.6).



Scheme 2.6. Overview of the trial reactions conducted to model the synthesis of mono-alkylated product 2.10. In each case, 1 equivalent of *n*-BuLi and halide was used. Unfortunately, the E2 elimination product was favoured over the desired substitution product when 2.10 was substituted for 2.14.

Firstly, benzyl bromide **2.14** was used instead of our valuable bromide **2.10**. This trial reaction proved successful. The mono-alkylated 1,3 dithiane **2.15** was afforded in 64 % yield when using 1 equivalent of both *n*-butyllithium and benzyl bromide. However, when the same conditions were applied to our bromide **2.10**, NMR revealed that the major product **2.16** (38% yield), resulting from E2 elimination of the bromide and there was only a trace amount of the desired product **2.11**. This outcome had been mechanistically impossible during the initial test reaction due to the position of the bromide in test substrate.

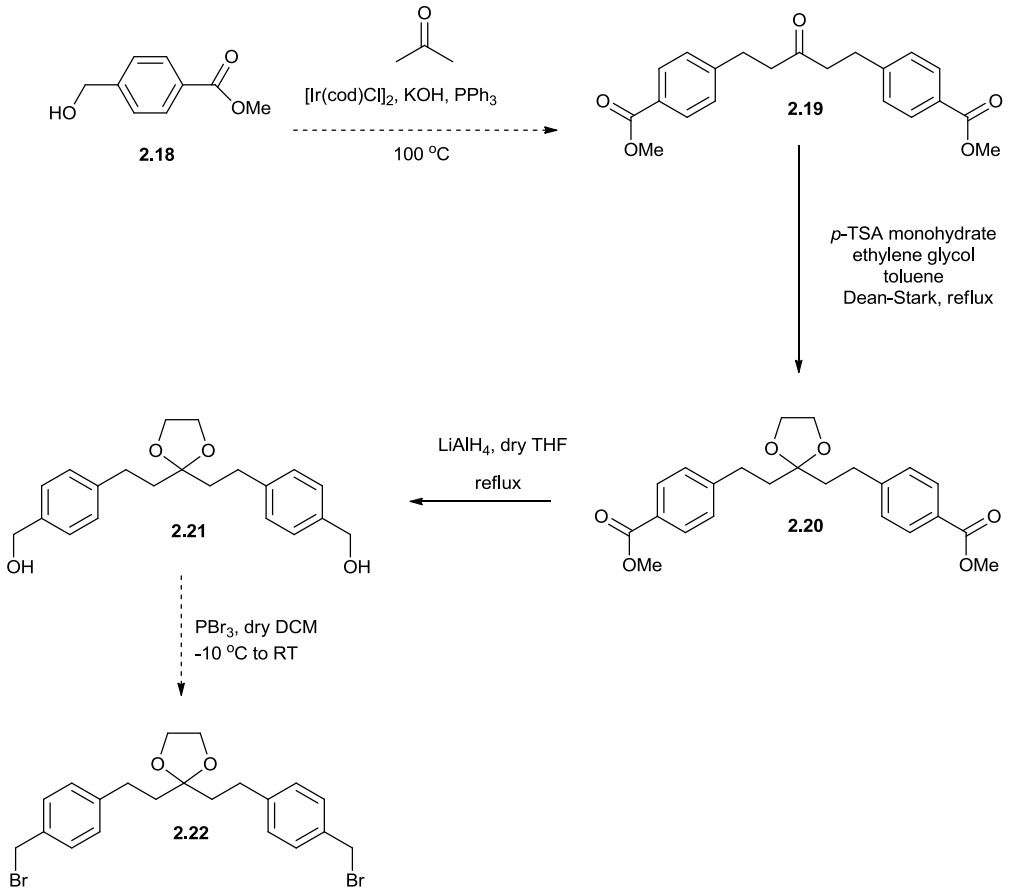
A Finkelstein reaction was then used to convert the bromide **2.10** to the corresponding iodide **2.17** in 85% yield using the procedure of Baughman and co-workers.[87] Iodide **2.17** was then used in the reaction with 1,3-dithiane but again, perhaps as expected, the E2 elimination product **2.16** was afforded (52%) along with unreacted starting material.

In a final attempt to synthesise the mono-alkylated product **2.11**, HMPA was added to the reaction solvent system for each reaction permutation to try to accelerate the substitution reaction.[86] Disappointingly, this too had no significant consequence on the final product in each case. Furthermore, the excess HMPA was difficult to completely remove from the crude product, even with repeated washing of the combined organic layers with water and brine.

After some discussion, it was decided that we would abandon the synthetic route shown in Scheme 2.5 and adopt another approach to our macrocycle precursor due to the inability to form the theoretically more accessible mono-alkylated species **2.11**, when compared to the bis-alkylated dithiane (**2.12**), and the expense and poor availability of starting material **2.8**.

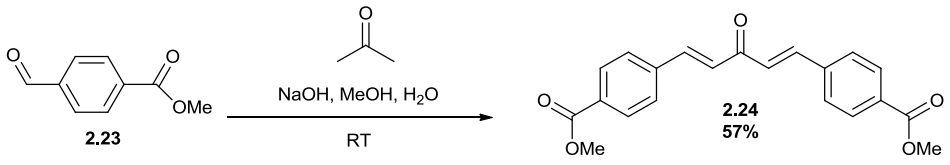
2.3 Synthesis of Macrocycle Precursor 2.22

Without wishing to completely redesign macrocycle **2.1** at this stage, a survey of the literature was conducted to find an alternative route to a viable precursor for macrocycle **2.1**. Ishii and co-workers have reported a solvent free route to α-alkylated ketones from *simple* primary alcohols using an $[Ir(cod)Cl]_2/PPh_3/KOH$ system.[88] Unfortunately, Ishii and co-workers had not reported tests done with an ester group present in the starting material. With this in mind, a novel synthetic route was planned as outlined in Scheme 2.7. Notably, in macrocycle precursor **2.22**, an acetal group was chosen to protect the ketone moiety. Commercially available methyl 4-(hydroxymethyl)benzoate **2.18** was reacted with acetone and the $[Ir(cod)Cl]_2/PPh_3/KOH$ system as detailed by Ishii and co-workers.[88] NMR of the crude reaction mixture revealed hydrolysis of the ester group and none of the desired aldol product **2.19** so another route to this product was sought using milder conditions.



Scheme 2.7 An alternative approach to a viable macrocycle precursor.

Vander Jagt and co-workers have reported the synthesis of a range of chalcone-based analogues which exhibit some similar structural features to our target intermediate **2.19**[89] **(**Scheme 2.8). Subsequent selective reduction of the olefin moieties of **2.24** could then afford access to target **2.19** (Scheme 2.7).



Scheme 2.8 Proposed aldol route to structure 2.24. Subsequent olefin reduction of 2.24 should yield target intermediate 2.19

Therefore, starting from commercially available methyl 4-formyl benzoate **2.23**, an aldol-type reaction was conducted at room temperature to successfully yield intermediate **2.24** in a modest 57% (Scheme 2.8). Initial attempts at this reaction were however low yielding (< 20%) with the formation of a polar material as evident from TLC. Isolation and characterisation of this material was not achieved due to its poor solubility even in more polar organic solvent systems. This was speculated to be an alcohol based by-product resulting from attack of the ester and/or ketone moieties based

on the relative polarity by TLC. However, when the reaction was repeated at high dilution, it was found to proceed satisfactorily with the crude product precipitating from the reaction solvent system.

A literature database search revealed a number of reportedly high yielding and selective methodologies for the reduction of olefins of the type characteristic in structure **2.24** to afford target **2.19**. The first to be investigated was the use of the use of a zinc-copper couple as reported by Sondemgam and co-workers.[90] They reported the olefin reduction of a very similar compound (**2.24** with no ester substituents) in a 95% yield. However, when their experimental procedure was conducted on our derivative **2.24**, there was significant recovery of starting material and no product **2.19** was visible in an NMR spectum recorded from the crude reaction mixture, even after reaction for 5 days. It was thought that the poor reactivity at the two olefin sites of **2.24** may be 2-fold: (a) the presence of the deactivating ester groups attached to the aromatic ring coupled with the extended conjugation throughout the structure; and (b) the preformed zinc-copper couple was not active enough to conduct the reaction.

We then went on to investigate the use of silane-based chemistry to reduce our olefin **2.24**, although the literature precedence for this was again based on experimentation with 1,5-diphenylpenta-1,4-dien-3-one and not structure **2.24**. Hijama and co-workers have reported the use of a dimethylphenylsilane / CuCl / PPh_3 / TBAF system for the reduction of conjugate α,β-unsaturated ketones in moderate to high yields.[91] However, extension of their prescribed procedure to **2.24** did not afford target compound **2.19** with NMR of the crude reaction mixture showing unreacted starting material and what looked to be some silane by-product which was not isolated nor further characterised.

Hayashi and co-workers have also reported the use of silanes (specifically hexamethyldisilane) for the conjugate reduction of enones; however, they also employed allyl palladium chloride dimer as a reaction catalyst.[92] Again, their experimental procedure was extended to structure **2.24** but to no avail with the NMR spectrum of the crude product showing no appreciable amount of target **2.19**. This reaction also afforded a number of uncharacterised side products, visible by TLC of the reaction mixture which smeared upon elution.

Having yet to isolate target **2.19**, we decided to conduct a trial reaction on an ethyl acetate solution of **2.24** using an H-Cube fitted with a 10 % Pd on charcoal catalyst and

1 atm of hydrogen gas for initial investigations. TLC of the product solution revealed two spots under UV (254 nm). NMR of the crude reaction mixture revealed a 4:6 ratio of compound **2.19**, together with alcohol **2.25** (Figure 2.1).

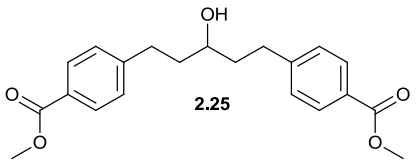


Figure 2.1 60% Alcohol by-product from reaction of 2.24 with 1 atm H_2 and 10 % Pd/C

It became clear that the H-cube could not be used for large scale reactions of this type due to the poor solubility of **2.24** in ethyl acetate and also in ethanol (the preferred solvents for catalytic hydrogenation using an H-Cube). The trial reactions had, however, provided access to compound **2.19** in modest yield and afforded a by-product which could be later re-oxidised to improve the yield of **2.19**. By replicating the H-cube conditions using a H_2 filled balloon, the reaction could be completed in less than 4 hours, importantly without the requirement of large volumes of ethyl acetate to completely dissolve the starting material **2.24**. It was evident that, as the reaction progressed, products **2.19** and **2.25** possessed a far greater solubility in the solvent system than **2.24** and, as a result, the reaction was driven to completion.

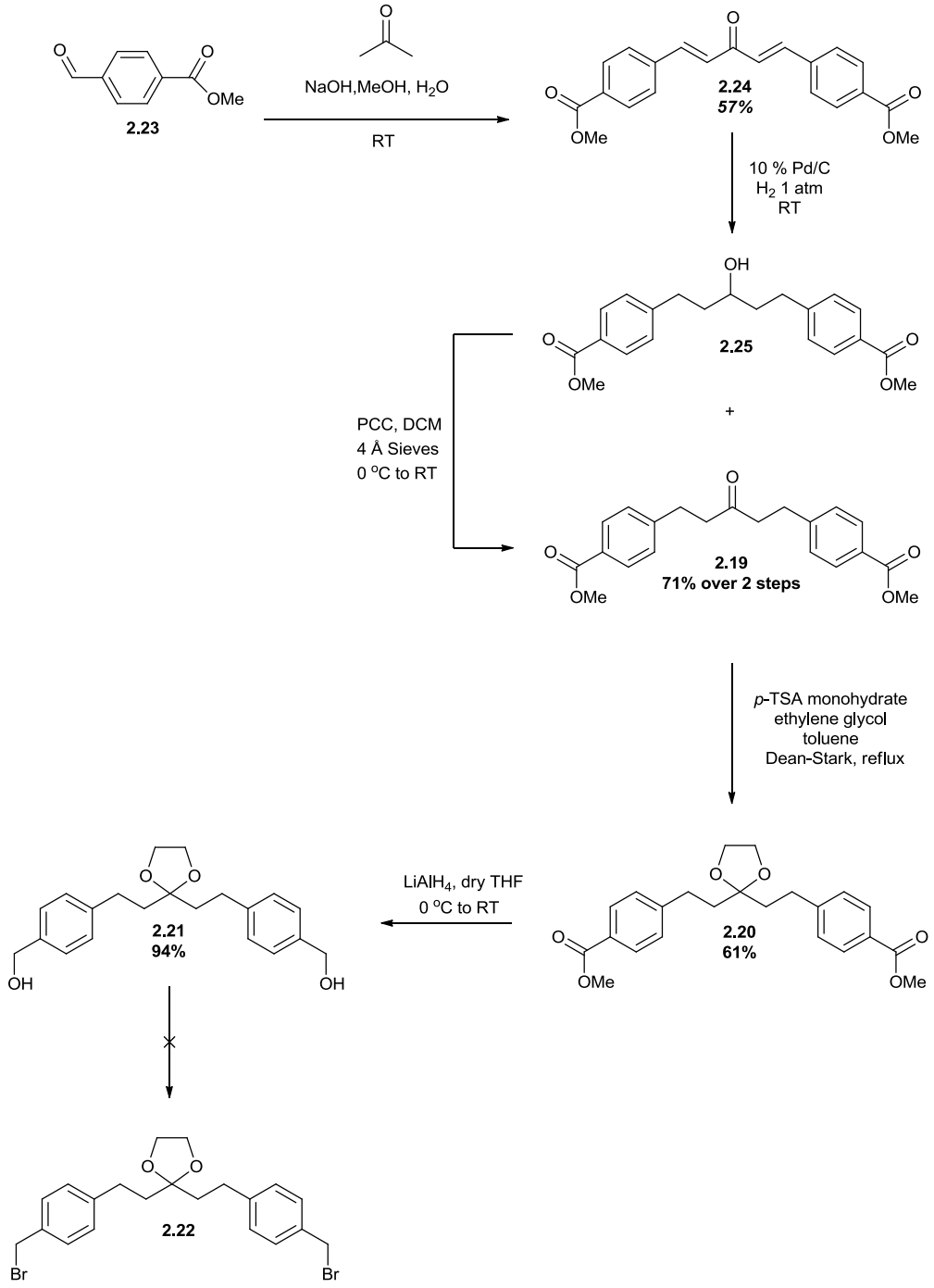
PCC was selected as the oxidation reagent due to its availability and low cost and this proved sufficient for the conversion of alcohol **2.25** to target compound **2.19** under standard conditions. Overall yields of 71% of **2.19** were achieved using this 2 step reduction-oxidation method Scheme 2.9.

Having isolated compound **2.19** (Scheme 2.9), the five membered acetal **2.20** was prepared under standard conditions[84] to protect the base sensitive ketone moiety in **2.19**. Yields of up to 61% of **2.20** were achieved after purification.

The next step in the proposed synthetic plan (Scheme 2.9) was to reduce the ester groups in **2.20** to afford the corresponding diol **2.21**. This was successfully achieved by reduction in THF with $LiAlH_4$. After work-up and purification, the diol **2.21** was isolated in a pleasing 94% yield.

The final step in the synthetic route to the macrocycle precursor involved the conversion of the diol **2.21** to the dibromide **2.22**. A literature database search revealed a number of potential reaction conditions with which to achieve this including the use of HBr gas

and Br_2 or coupling reagents such Br_2/PPh_3. In addition, milder conditions have also been reported, using traditional Mitsunobu type reactions and also with PPh_3 coupled with ethyl tribromoacetate and separately with *N*-bromosaccharin. After several attempts using molecular bromine and the Appel type[87, 93] conditions listed above there was some concern over the stability of the acetal group to the conditions required for bromination of the diol moiety as no dibromide retaining the crucial acetal moiety was detected by crude NMR of the reaction mixtures. Furthermore, it was evident that there was some decomposition on silica, observed after 2D TLC of the crude reaction mixture. After some discussion within the group it was decided that we would significantly re-design the macrocycle in the hope we would find a milder, more efficient synthetic route which negated the need to recycle reaction by-products and would afford stable products which could be subsequently purified by flash column chromatography.

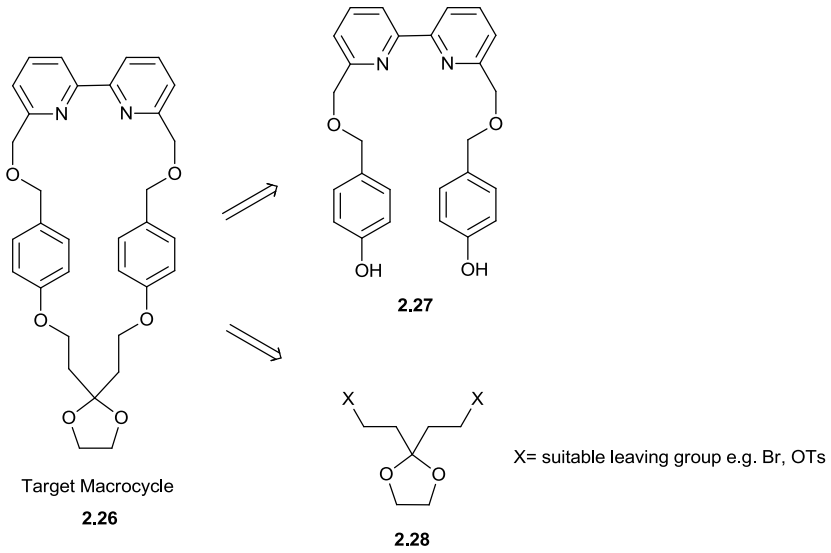


Scheme 2.9 Summary of the conducted route to macrocycle precursor 2.22

2.4 Preparation of Macrocycle 2.26

Macrocycle **2.26** was designed as an alternative to macrocycle **2.1** (Scheme 2.10 and Scheme 2.4 respectively). As before, retrosynthetic analysis shows disconnecting macrocycle **2.26** adjacent to the benzyl position to give rise to a pair of potentially accessible precursor molecules **2.27** and **2.28**. It was envisaged that formation of macrocycle **2.26** could readily proceed *via* a Williamson ether style coupling of

diphenol **2.27** and acetal precursor **2.28** providing suitable pendant leaving groups were chosen for **2.28**.

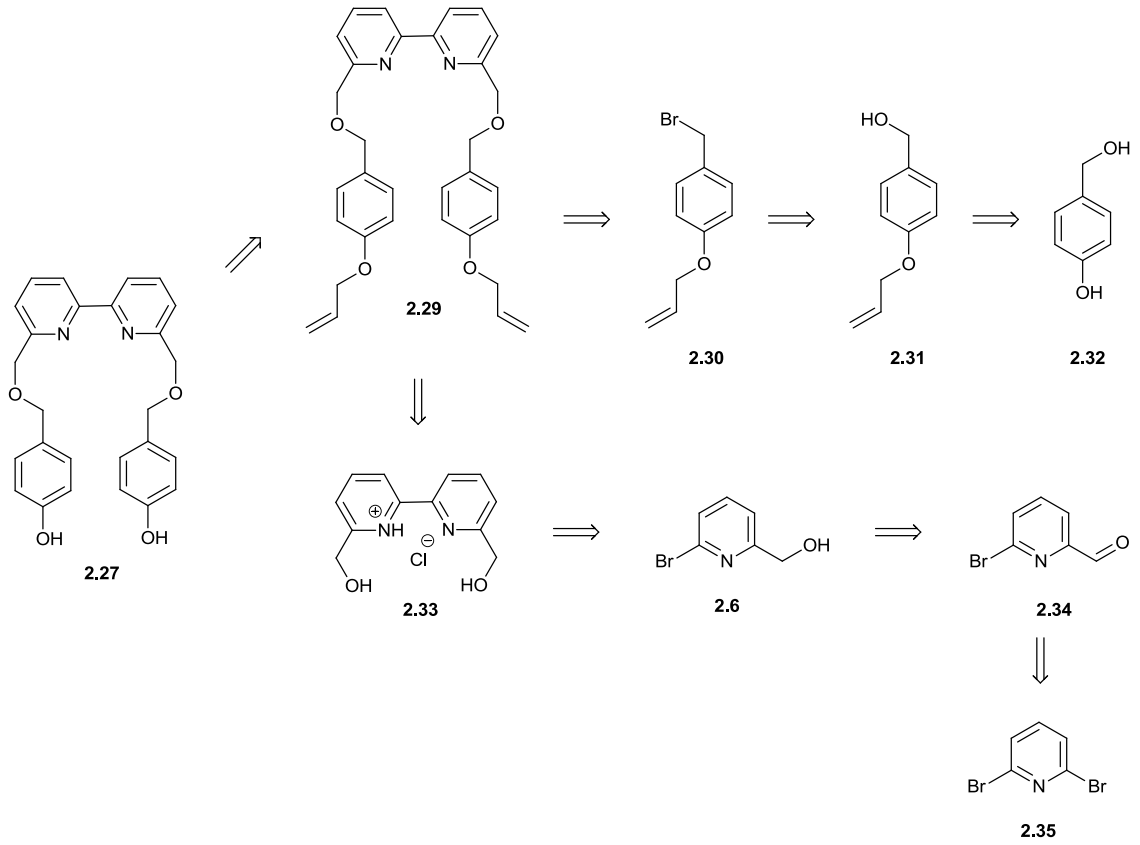


Scheme 2.10 Retrosynthetic Approach to Macrocycle 2.26

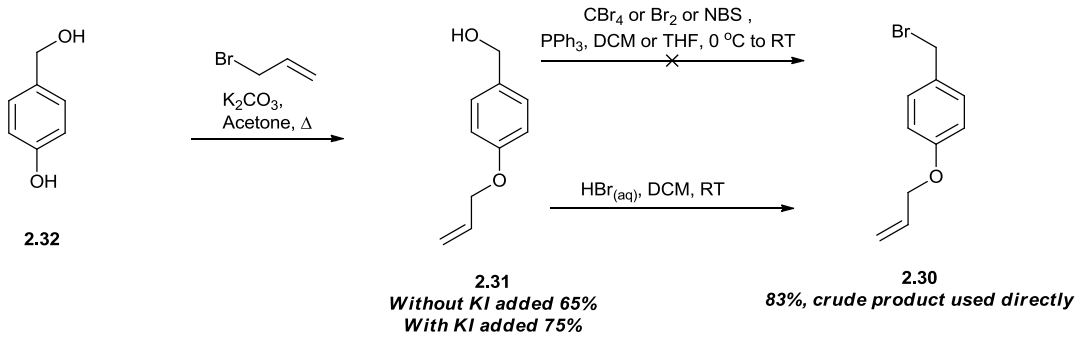
2.5 Synthesis of Macrocycle Precursor 2.27

Macrocycle precursor **2.27** is a known compound and has previously been synthesised by Leigh and co-workers.[65] Following their literature precedence, the retrosynthetic approach show in Scheme 2.11 was undertaken. Diphenol **2.27** can be accessed by deprotection of the corresponding allyl-protected diphenol **2.29**, which in turn can be prepared by reacting bipyridine salt **2.33** and benzyl bromide analogue **2.30**. The benzyl bromide derivative **2.30** can be synthesised from commercially available 4-hydroxybenzyl alcohol **2.32** in two steps; protection of the phenolic hydroxyl moiety followed by halogenation at the benzylic alcohol. Synthesis of bipyridine salt **2.33** can be achieved in three steps starting from commercially available 2,6-dibromo pyridine **2.35** *via* successive formylation, reduction and homocoupling steps or directly from commercially available alcohol **2.6**.

4-Hydroxybenzyl alcohol **2.32** underwent alkylation with allyl bromide in the presence of K_2CO_3 in refluxing acetone to afford ether **2.31** in 65% yield. By exploiting the relative insolubility of KBr in acetone, compared to KI, the reaction yield was later improved to 75% by addition of KI as a Finkelstein reagent (Scheme 2.12). This is thought to improve the efficacy of the leaving group (iodide *v*. bromide) and also form an additional driving force for the reaction to occur through precipitation of the insoluble KBr salt reaction by-product.



Scheme 2.11 Retrosynthetic Approach to Macrocycle Precursor 2.24



Scheme 2.12 Synthesis of benzyl bromide 2.30

With protected alcohol **2.31** in hand and following literature precedent by Leigh[65] and Nakayama,[94] we set out to prepare bromide **2.30** using a variety of Appel-type conditions employing molecular bromine, tetrabromomethane and *N*-bromosuccinimide to find the optimal conditions. In each case, the progress of the reaction and formation of the bromide was difficult to follow as the major product streaked upon TLC of the crude reaction mixture. However, a polar, highly UV active product, was visible by TLC after *ca*. 30 minutes indicating the formation of triphenylphosphine oxide which implied that the reaction had progressed as expected. Upon 2D TLC of the crude

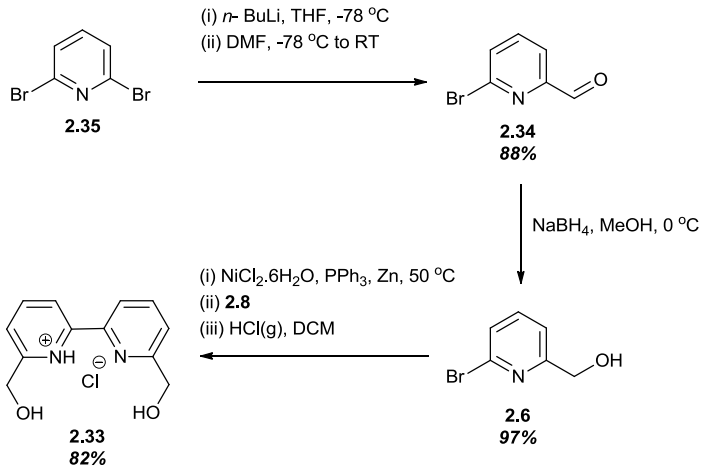
reaction mixture, it was discovered that the desired product was not stable on silica. This made multi-gram separation of product **2.30** difficult from the excess triphenylphosphine reagent and triphenylphosphine oxide by-product. Therefore, it was decided to look for alternative strategy to **2.30**.

After some informal discussion with Dr. Stephen Goldup (at Queen Mary University of London, who worked on the original synthesis)[65] we were able to confirm that benzyl bromide **2.30** was indeed unstable on silica and, furthermore, discovered it possessed a relatively short shelf-life and should be used directly in further experimentation to prevent excessive decomposition (the lachrymatory decomposition product mixture was found to be acidic, presumably due to the liberation of HBr).

Pleasingly, it was found that bromide **2.30** could be synthesised in sufficiently high purity (as evidenced by NMR) by reaction of **2.31** with excess aqueous HBr in dichloromethane and immediately concentrated *in vacuo*. The crude reaction product was then reconstituted in fresh DCM/H_2O and washed copiously with a saturated solution of K_2CO_3, water and brine. Subsequent drying over $MgSO_4$ and careful concentration *in vacuo* (low water bath temperature) afforded **2.30** in 83% yield without the requirement for further purification. The product was stored at -20 ^oC, under argon, to prolong stability but best results were obtained when used immediately in the next reaction.

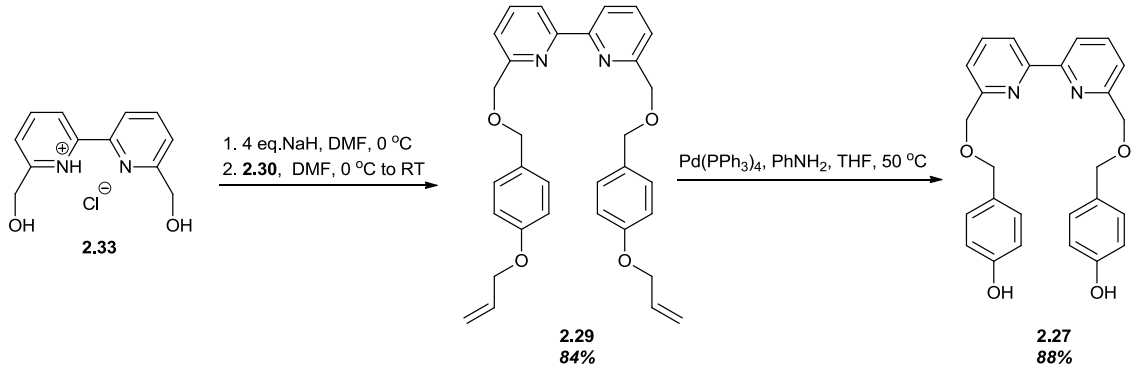
Commercially available 2,6-dibromo pyridine **2.35** underwent formylation in the presence of *n*-butyl lithium and dimethylformamide in THF to afford aldehyde **2.34** in 88% yield (Scheme 2.13). A routine $NaBH_4$ reduction of the resulting aldehyde moiety furnished the corresponding primary alcohol **2.6** in 97% yield. Bipyridine salt **2.33** was synthesised *via* a nickel catalysed homo cross-coupling of **2.6**, followed by precipitation of the HCl salt (82% yield). To probe the most effective reaction conditions as a viable route towards the target compound **2.33**, initial test reactions were conducted following literature precedence.[73] It is noteworthy that Leigh *et al.* bubbled HCl gas from a canister through a DCM solution of their crude reaction mixture to precipitate salt **2.33**. It seemed sensible to explore the option of using a much safer method for precipitation of the target salt, and it was pleasing to find that reaction of a dichloromethane / methanol solution of our crude reaction product, with acetyl chloride, precipitated the pure salt **2.33**.[95] Alternatively, HCl gas was generated *in situ* by dropwise addition of concentrated sulphuric acid onto calcium chloride and the resulting gas bubbled through a DCM solution of the crude reaction product. Zinc dust was selected over granular

zinc to enhance the reaction surface area and yield, however we found that using the dust, unactivated, gave poor final yields (≤ 32 %) of salt **2.33** (presumably due to an oxide layer present on the surface of the metal which inhibits formation of the organozinc intermediate). Activating the zinc dust before use by sequential washing with 1M HCl, distilled water, acetone and, finally, diethyl ether afforded far better yields of the salt **2.33** (82%).



Scheme 2.13 Synthesis of bipyridine 2.33

Having synthesised key intermediates **2.30** and **2.33**, our attention turned to the coupling these molecules together to afford macrocycle precursor **2.29** (Scheme 2.16).

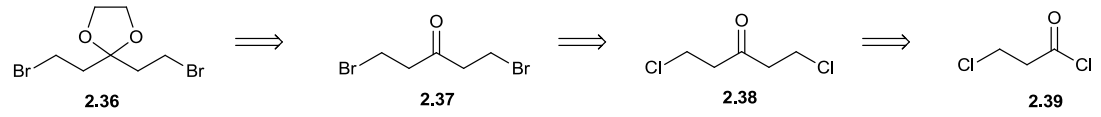


Scheme 2.14 Synthesis of 2.3 and macrocycle precursor 2.2

Bipyridine salt **2.33** readily underwent reaction with bromide **2.30** in the presence of NaH at room temperature to afford allyl intermediate **2.29** in high yield (84%). This was then treated with tetrakis(triphenylphosphine)palladium and aniline in THF at 50°C to afford macrocycle precursor **2.27** in 88% yield.

2.6 Synthesis of Macrocycle Precursor 2.28

With a high yielding route to several grams of macrocycle precursor **2.27** established, we began to address the synthesis of the accompanying macrocycle precursor **2.28**, which despite its relatively small size, in comparison to **2.27**, gave rise to several synthetic challenges. Firstly, in order for the final macrocycle to be symmetrical, there had to be an odd number of methylene units in the alkyl chain and the key carbonyl moiety (at which future desymmetrisation chemistry would occur) must be located in the centre, to retain symmetry in the target prochiral rotaxane intermediate. Secondly, this carbonyl group required protection during the rotaxane forming reaction, after which, the protecting group had to be able to be removed using mild reaction conditions, to unmask the carbonyl function for subsequent desymmetrisation. In addition to these design features, the precursor had to bear leaving groups suitable for macrocycle forming reactions *via* an ether synthesis and which must be installed under mild conditions so as to protect the carbonyl protecting group. With these critical design features in mind, the target **2.36** was chosen, the retrosynthetic pathway to which is shown in Scheme 2.15.



- 5 methylene units in alkyl chain
- Centrally located masked carbonyl
- Suitable leaving groups for ether synthesis

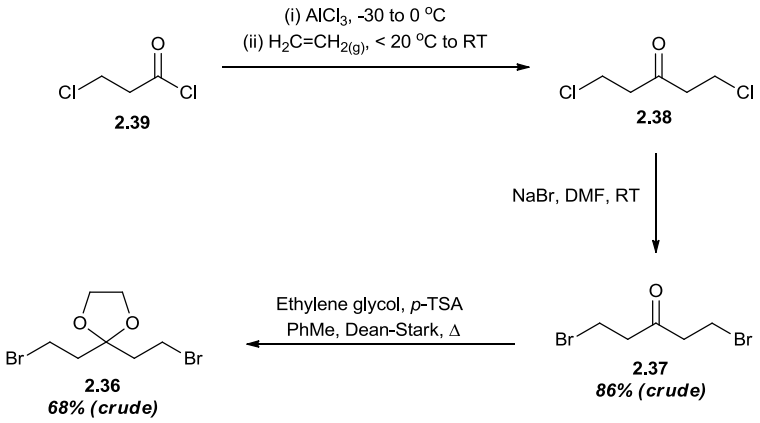
Scheme 2.15 Retrosynthetic approach to 2.36

It was envisaged that acetal protected dibromide **2.36** could be accessed from commercially available 3-chloropropionyl chloride **2.39** in three steps using an aliphatic Friedel-Crafts reaction, a Finkelstein reaction and finally preparation of the acetal protected dibromide **2.36** using typical Dean-Stark conditions.

Following a literature precedent[96] for the formation of **2.38**, **2.39** underwent an aliphatic Friedel-Crafts in the presence of $AlCl_3$ and ethylene gas to afford a thick black syrup, **2.38** (Scheme 2.16). Upon attempts to purify this compound by chromatography, either on silica or florisil, or by distillation the product readily decomposed. This was confirmed by streaking of the product on each stationary phase and by liberation of acidic fumes (assumed to be HCl) upon distillation. Furthermore, upon standing and subsequent storage, the crude compound appeared to be particularly sensitive to light

and temperature, which were again confirmed by the observation of acidic fumes being liberated from the compound storage vessel. For this reason **2.38** was used directly, in its crude form, for conversion to the corresponding dibromide **2.37** using NaBr in DMF. Bearing in mind the isolation problems experienced with **2.38**, it was decided not to attempt to purify **2.37** as it was postulated that the rate of decomposition could perhaps be accelerated due to the increased efficacy of the bromide leaving group compared to the chloride. A tentative crude yield of 86% was achieved for the synthesis of **2.37**.

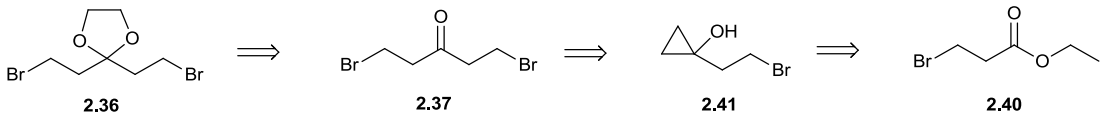
With a crude product mixture of **2.37** in hand, attempts were made to protect the central carbonyl moiety as the 1,3-dioxolane using well established Dean-Stark methodology in the presence of ethylene glycol and a *p*-toluenesulfonic acid catalyst. Crude NMR revealed that the reaction had proceeded as expected (tentative crude yield of **2.36** was 68%). However, there was some concern that the tosic acid catalyst had catalysed decomposition of the some of the bromide functionality further, resulting in a complex reaction mixture. Due to the difficulty of purification at each stage during the synthesis of **2.36** it was decided to abandon this approach to macrocycle precursor **2.36** and look for an alternative route which may afford fewer by-products and require a lesser degree of purification.



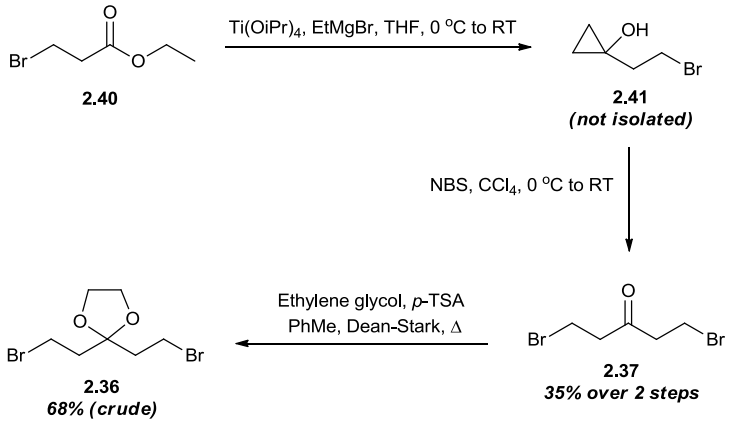
Scheme 2.16 Synthesis of 2.36 from 2.39

After examination of related literature, an interesting 'one-pot' modified Kulinkovich reaction drew our attention. Kündig and co-workers[97] have reported a procedure in which commercially available ethyl 3-bromopropanoate **2.40** is converted to dibromo ketone **2.37** *via* cyclopropane intermediate **2.41**. Furthermore, they claimed to have been able to purify **2.37** *via* vacuum distillation, contrary to what we were able to achieve whilst trying to purify the related dichloro ketone **2.38**. It was hoped that by implementing Kündig's approach we could directly access an appreciable quantity of

product **2.37**, negating the necessity for any chlorine/bromine halogen exchange step. This would also afford the possibility of having pure **2.37** prior to protecting the carbonyl group with an acetal moiety and ultimately provide a cleaner end product mixture (due to fewer stages being taken forward for reaction as complex crude mixtures). This alternative retrosynthetic route to **2.36** is presented in Scheme 2.17.



Scheme 2.17 Retrosynthetic approach to 2.36 from 2.40



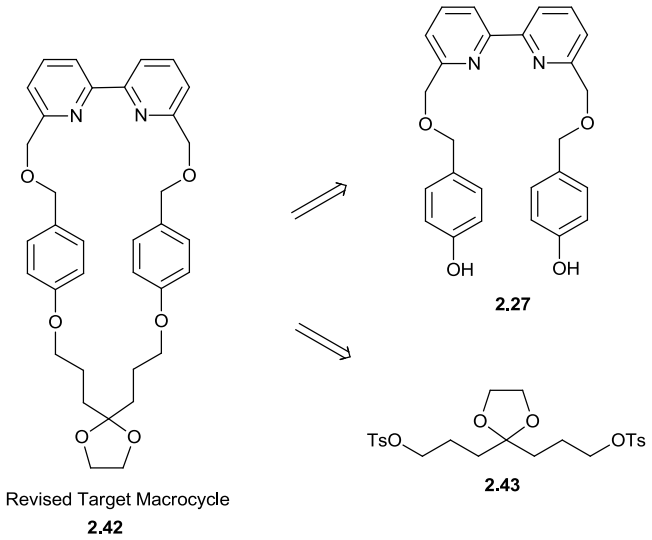
Scheme 2.18 Synthesis of 2.11a from 2.15

It was quickly discovered that successful synthesis (Scheme 2.18) and purification of **2.37** was particularly challenging and time consuming. Firstly, the literature prescribed vacuum distillation step for isolation of dibromo ketone **2.37** was found to require particular care and diligence. The boiling point of each fraction distillate, observed on an internal thermometer appeared very similar which made isolation of uncontaminated distillates extremely challenging. Furthermore, overheating of the reaction mixture vessel resulted in immediate formation of a viscous black residue (not characterised) and liberated an acidic gas (assumed to be HBr). After several attempts *ca*. 0.4 g of **2.37** was isolated in 35% yield over 2 steps. However, the yield was thought to have been severely impacted by collecting only fractions that were deemed 'clean' visually during the distillation process. Unfortunately, contaminated fractions could not be recycled and redistilled due to the stability of the product. With minimal delay, dibromo ketone **2.37** was again subjected to the same Dean-Stark conditions as above to install the carbonyl protecting acetal group. A crude product mixture (68% yield) was found to be comprised mainly of **2.36** but, again, there was indication of several low

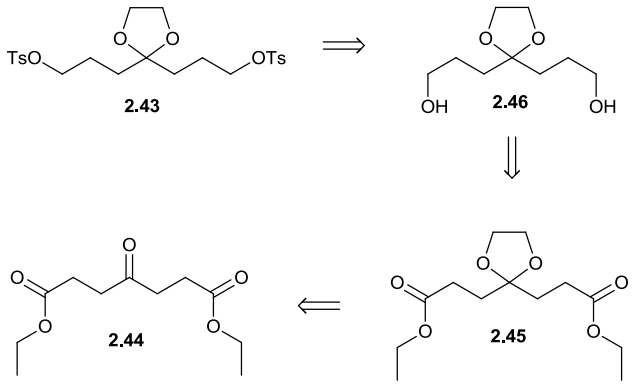
level reaction by-products which afforded a complex ^{1}H NMR spectrum and prohibited further characterisation.

2.7 Preparation of Macrocycle Precursor 2.43

Due to the difficulty inherent in the purification of a moderate to high yield of **2.36**, coupled with the instability observed when handling and storing the above dihalogens (whether as the ketone or as the acetal) we moved to redesign this portion of the macrocycle so as to avoid the use of halogens as leaving groups. Somewhat constricted by the necessity for symmetry in the macrocycle, the new precursor again had to comprise an odd number of carbon linkers in the alkyl chain and bear a carbonyl group on the central carbon atom. A survey of suitable, commercially available, starting materials which would meet our requirements and which lacked the presence of any halogen on the alkyl chains was conducted. Any starting material had to permit rapid modification to allow ether synthesis with precursor **2.27** and, unsurprisingly, very few commercial candidates were found. Diester **2.44** (Scheme 2.20) was found to be the most promising starting point as it had a centrally located carbonyl, was symmetrical and access to pendant leaving groups was thought to be routine. Instead of employing dihalogen leaving groups for our macrocylisation step, we decided to attempt to make the ditosylate **2.43** (Scheme 2.19). It was anticipated that this would be more stable than the dihalogen analogues synthesised previously and afford a solid rather than oils, which could permit purification by recrystallisation when conducted at scale. In using diester **2.43** rather than **2.36**, the size of the target macrocycle precursor, and, thus, new macrocycle **2.42 (**Scheme 2.19**)** would be expanded by 2 carbon units (one on each side of the central carbonyl) and it was unknown at this stage whether this increase in ring size and flexibility would support rotaxane formation. No computational modelling could be conducted prior to synthesis to investigate this; however, by building a Corey-Pauling-Kolten (CPK) model,[98] we were able to visualise that the ring which this precursor might afford. Although flexible, it was reasoned that it may be able to support rotaxane formation without the macrocycle 'dethreading'.

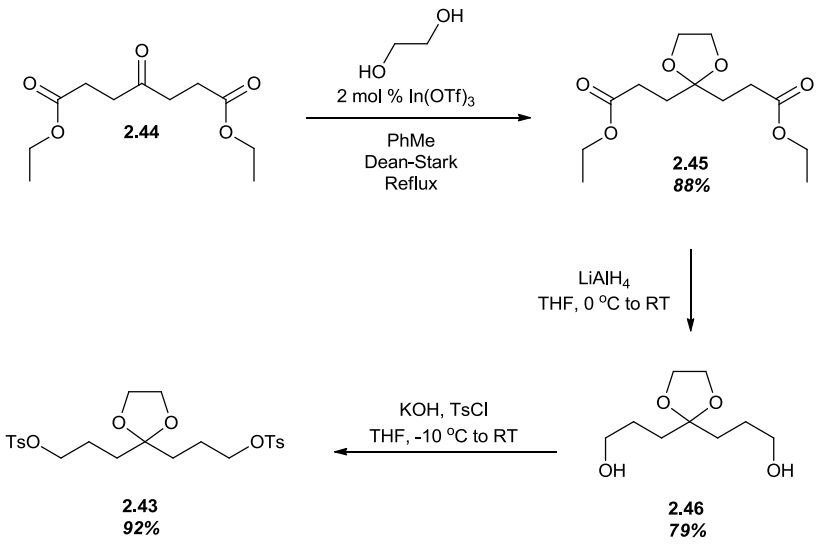


Scheme 2.19 Structure of revised macrocycle structure 2.42 and precursor 2.43



Scheme 2.20 Retrosynthetic approach to 2.18

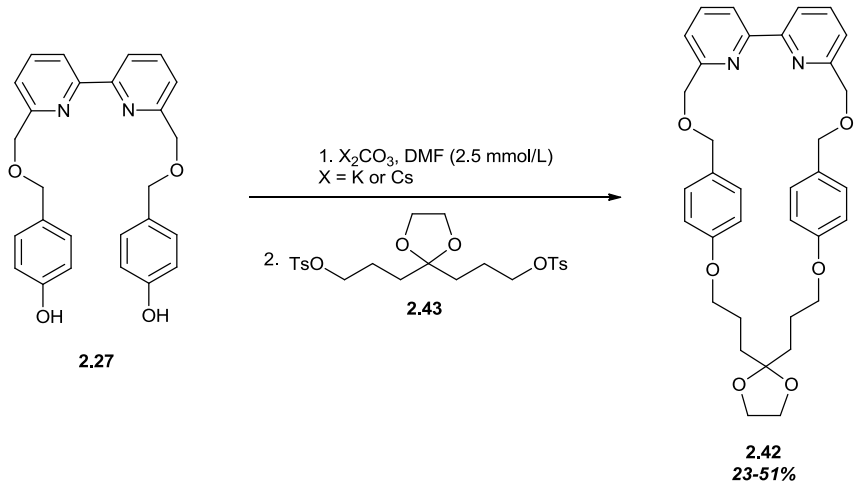
For the initial ketone protection step to form **2.45** from **2.44** an alternative catalyst to *p*-TsOH was sought to prevent acid catalysed hydrolysis of the ester groups. Gregg and co-workers[99] have demonstrated the use of catalytic indium triflate for the acetal protection of a wide range of alehydes and unreactive ketones possessing acid sensitive functionality. By employing similar reaction conditions for our system and a Dean-Stark apparatus for the azeotropic removal of water, acetal disester **2.45** was isolated in 88% yield (Scheme 2.21). The ester moieties were then routinely reduced to the corresponding diol using excess $LiAlH_4$ in THF to afford **2.46** in 79% yield. Finally, ditosylate **2.43** was isolated in high yield (92%) by reaction of diol **2.46** with KOH and tosyl chloride in THF. Pleasingly, following aqueous work-up, the crude product crystallised as a colourless solid and it was readily purified by recrystallisation from methanol/hexane. No decomposition of **2.43** was noted upon standing.



Scheme 2.21 Synthesis of macrocycle precursor 2.18 from 2.21

2.8 Synthesis of Macrocycle 2.42

Having successfully isolated macrocycle precursors **2.27** and **2.43** (Scheme 2.19), our attention turned to the coupling of these precursors to form the symmetrical macrocycle **2.42** *via* a Williamson ether synthesis. Following a modified literature procedure by Leigh and co-workers, diphenol precursor **2.27** and ditosylate **2.43** were reacted with K_2CO_3 in DMF at 65 ^oC. In order to reduce the formation of undesired oligomers, reactions were carried out at high dilution (2.5 mmol/L). Using K_2CO_3, a modest yield of 23% of macrocycle **2.42** was achieved. We then found that by switching the base to Cs_2CO_3 and warming the reaction to 80 ^oC, the yield could be further improved to 51% (Scheme 2.22). This was thought to be due to the 'caesium effect' whereby the larger size of caesium *vs*. potassium affords increased solubility in anhydrous DMF.[100] Furthermore, the use of caesium carbonates has been reported to suppress intermolecular substitution which would lead to unwanted oligomers compared to the competing intramolecular pathway required to obtain the macrocycle.[100]

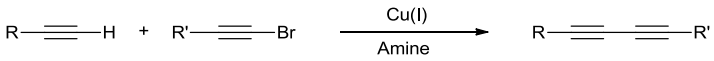


Scheme 2.22 Williamson ether synthesis of 2.17

2.9 Cadiot-Chodkiewicz Heterocoupling Reaction

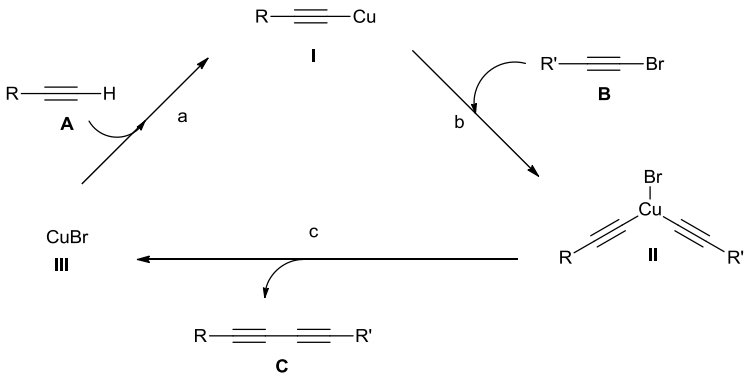
2.9.1 Introduction

The Cadiot-Chodkiewicz reaction affords non-symmetrical diynes *via* the copper-mediated coupling of acetylenes and bromoacetylenes in the presence of an amine (Scheme 2.23). The reaction can tolerate a wide range of functional groups including amines,[101] alcohols,[102] epoxides,[103] esters,[104] amides,[104] carboxylic acids,[105] disulfides[106] and transition metal complexes.[107]



Scheme 2.23 Cadiot-Chodkiewicz coupling of acetylene and bromoacetylene

The proposed reaction mechanism of the Cadiot-Chodkiewicz reaction is shown in (Scheme 2.24). The first step of the reaction is the formation of the reactive intermediate, the copper-acetylide **I** (a, Scheme 2.24). Oxidative addition of the bromoalkyne **B** to copper-acetylide **I** then forms a Cu(III) species **II** (b, Scheme 2.24). The dialkyne product **C** is formed *via* a reductive elimination, which also regenerates the Cu(I) catalyst **III** (c, Scheme 2.24).



Scheme 2.24 Proposed mechanism of the Cadiot-Chodkiewicz heterocoupling reaction. a) Ligand exchange. b) Oxidative addition. c) Reductive elimination.

2.9.2 Cadiot-Chodkiewicz in Supramolecular Chemistry

The application of the Cadiot-Chodkiewicz reaction in the total synthesis of natural products containing polyacetylene functionality has been well documented[103-104, 108] and this has been extended into the field of supramolecular chemistry. Bunz and co-workers have applied this reaction to the synthesis of a range of cyclynes with 'butterfly' topologies such as the one shown in Figure 2.2.[109]

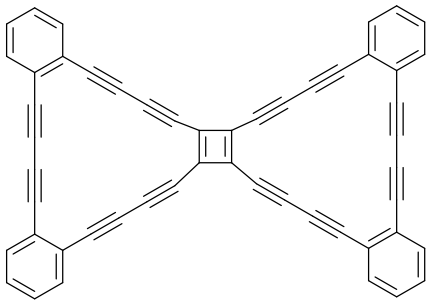


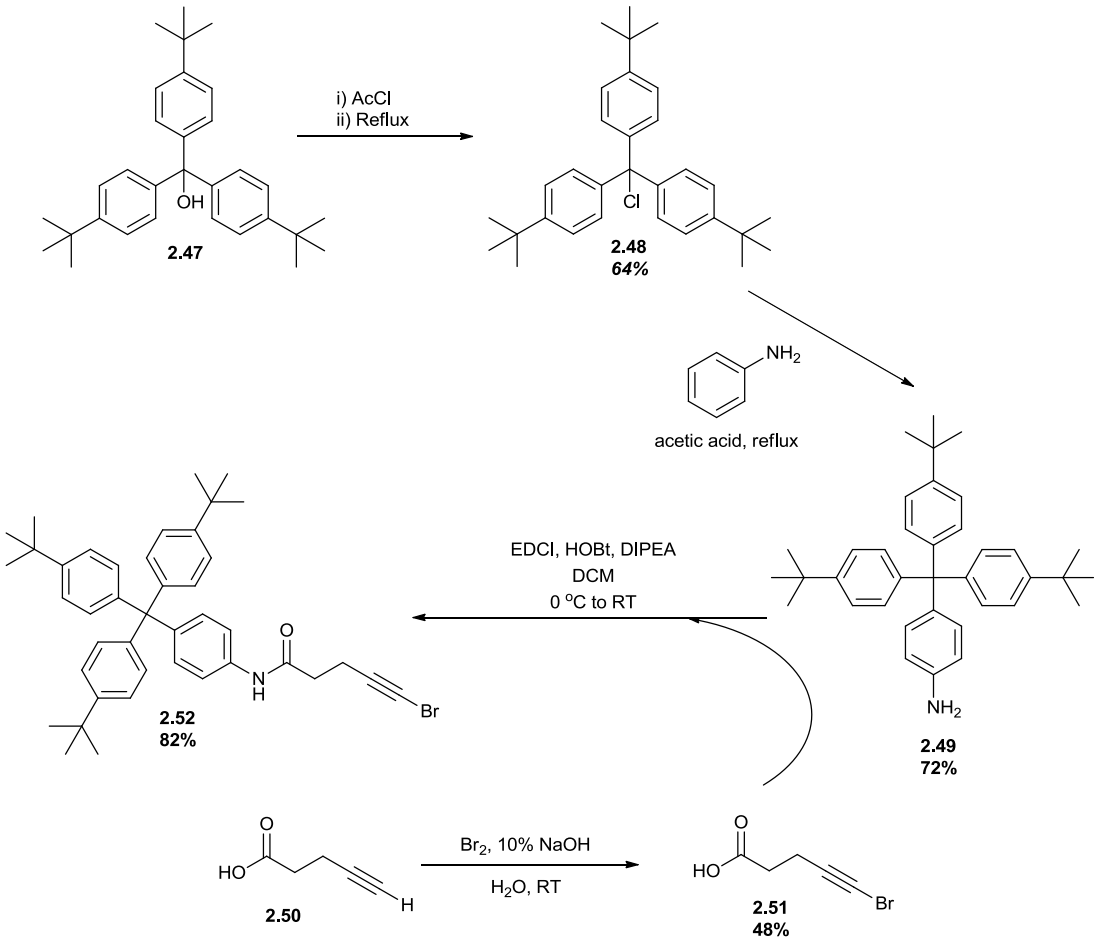
Figure 2.2 Cyclyne with 'butterfly' topology[109]

Leigh and co-workers have used a Cadiot-Chodkiewicz reaction in their active metal synthesis of rotaxanes and catenanes.[68, 71] Furthermore they have shown macrocycles containing the bipyridine motif to be excellent ligands for the active copper species. They found that, despite standard 'one-pot' conditions providing them with rotaxane, they experienced poor selectivity between the hetero-coupled and homo-coupled alkyne tread. To address this issue they developed a modified procedure whereby a copper-acetylide reactive intermediate was preformed using *n*-butyl lithium before addition of the bromoacetylene. This led to greater than 98% selectivity of the desired rotaxane in 84% yield (see Scheme 1.18).[71] It is active template syntheses of this type, where the Cadiot-Chodkiewicz heterocoupling reaction is used in conjunction with a use of a

macrocycle ligand containing a bipyridine moiety, which form the basis for the trials conducted as part our work.

2.9.3 Synthesis of Stoppers for the Cadiot-Chodkiewiz Reaction

Although the stoppers developed by Leigh *et al.* for the Cadiot-Chodkiewicz formation of rotaxanes are different (Scheme 1.18) and do produce a non-symmetric thread, they are not structurally dissimilar, with only the length of the carbon chain between the ether group and the acetylene linker differing on each side. Critically, for our desymmetrisation application, facial selectivity for the approach of the organocatalyst is reliant on one side of the target [2]rotaxane being sterically more accessible than the other. In order to emphasise this on any rotaxane produced, a pair of half-threads with significantly different stopper groups were designed for use in our Cadiot-Chodkiewicz trial reactions.

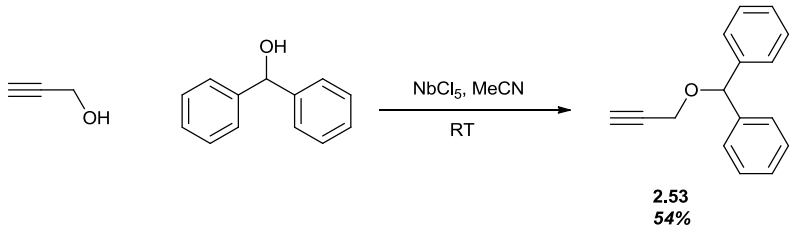


Scheme 2.25 Synthetic route to half-thread 2.52

Half-thread **2.52** (Scheme 2.25) was selected as a suitable bromoalkyne stopper as it bore significant steric bulk in the form of the three *t*-butyl phenyl rings. Furthermore, it was envisaged that the amide proton could hydrogen bond with the bipy moiety present

in the macrocycle. Binding of the macrocycle close to **2.52** (the sterically more demanding of the two half-threads), should result in one face of the macrocycle being relatively resistant to approach by the organocatalyst which we planned to use for the future desymmetrisation step.

Starting from alcohol **2.47**, conversion to the amine **2.49** was achieved in two steps by refluxing in acetyl chloride to afford the chloride **2.48** (64% yield), then refluxing in aniline (72% yield).[110] Commercially available terminal alkyne **2.50** was converted to the corresponding bromoalkyne **2.51** by reaction with sodium hypobromite (formed *in situ* by reacting bromine and NaOH) in 48% yield.[111] With **2.49** and **2.51** in hand, an EDCI promoted coupling reaction[112] afforded half-thread **2.52** in 82% yield (Scheme 2.25).



2.53
54%

Scheme 2.26 Synthesis of alkyne half thread 2.53[113]

Half-thread **2.53** (Scheme 2.26) was chosen as the least sterically demanding half-thread for our Cadiot-Chodkiewicz reaction. Whilst biphenyl stopper **2.53** is large enough to prevent de-threading of any rotaxane produced, it was postulated that with this stopper installed on the rotaxane, approach of the desymmetrisation organocatalyst would occur preferentially at the face bearing stopper **2.53** over stopper **2.52**. Synthesis of half-thread **2.53** was achieved in 54% yield following a literature procedure by Yadav and co-workers.[113]

2.10 Cadiot-Chodkiewicz Reaction Results

With macrocycle **2.42** and stoppers **2.52** and **2.53** in hand, we then moved to synthesise our target [2]rotaxane **2.54** using a Cadiot-Chodkiewicz reaction (Table 2.1).

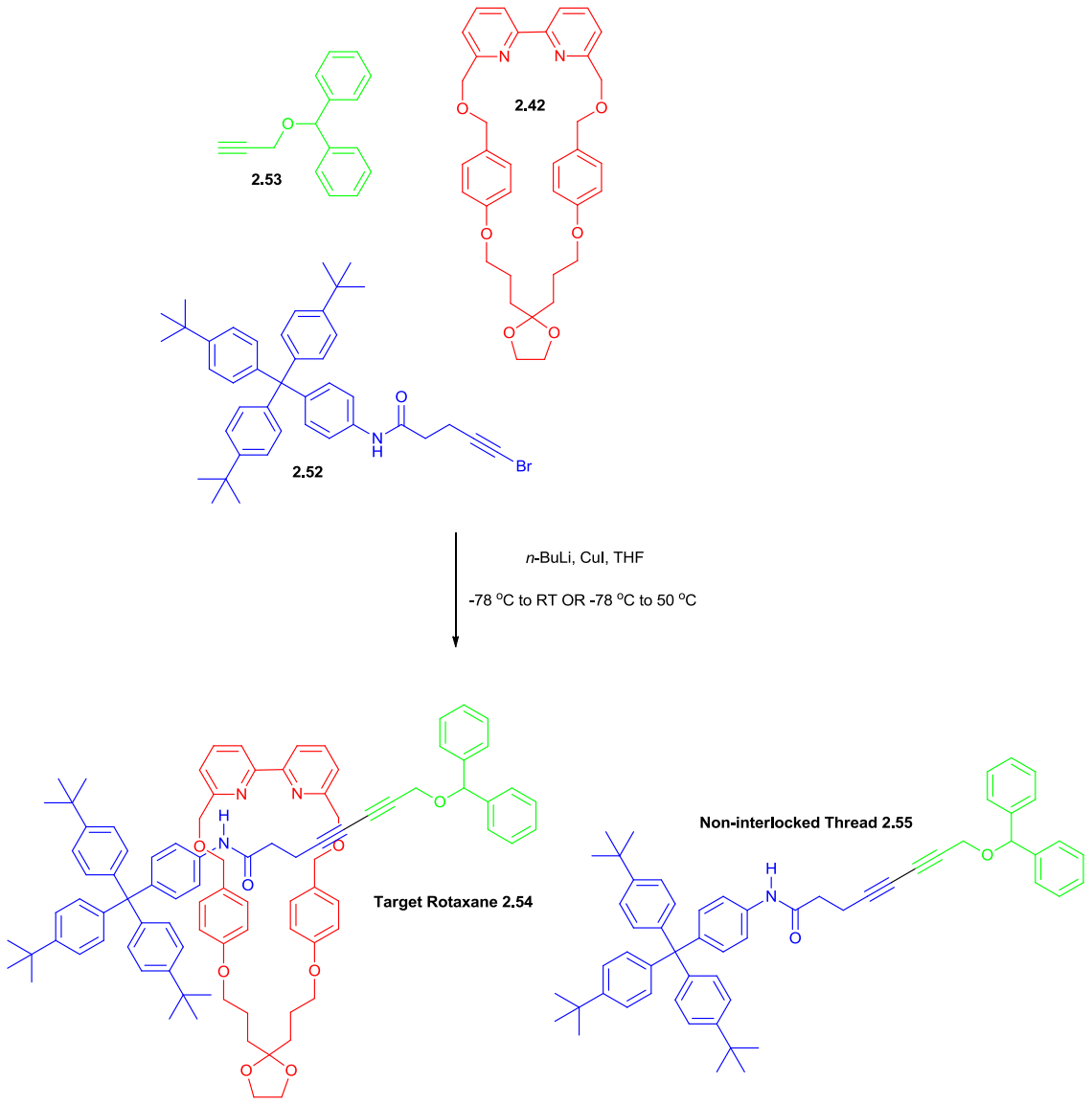
Following conditions developed by Leigh and co-workers,[68, 71] the copper acetylide species was formed first by reacting alkyne **2.53** with *n*-butyl lithium in THF, before introduction of the copper iodide catalyst. To the resulting copper acetylide was added the bromoalkyne **2.52** and the macrocycle (Method A, Table 2.1) and the reaction left stirring under N_2 for the time specified. After 24 hours (entry 1, Table 2.1) ^{1}H NMR of

the reaction mixture revealed 26% conversion to the non-interlocked thread **2.55**, and unreacted starting material and no [2]rotaxane **2.54** evident. The reaction was then repeated and left for 5 days in an attempt to improve the conversion from starting material (entry 2, Table 2.1 55% conversion to non-interlocked thread). Again, no rotaxane was observed. By warming the reaction to 50 ^{o}C, the conversion from alkyne to non-interlocked thread was further improved to 62% but unfortunately no rotaxane could be detected by ^{1}H NMR of the reaction mixture (entry 3, Table 2.1). With evidence that the coupling reaction was progressing and could perhaps be optimised to improve conversion later, we focused our attention on attempting to direct the coupling reaction through the macrocycle cavity rather than *exo* to the macrocycle. The order of addition of the starting materials was changed (Method B, Table 2.1) as follows: Firstly, the copper iodide catalyst was stirred with macrocycle in THF to attempt to ligate the copper within the macrocycle cavity *before* formation of the copper acetylide. Next, alkyne **2.53** was deprotonated with *n*-butyl lithium before the two solutions were mixed and bromoalkyne **2.52** added. After reaction for 5 days the conversion of alkyne **2.53** to non-interlocked thread **2.55** was 32%, with no rotaxane observed (entry 4). In each case, a significant amount of starting material remained.

2.11 Conclusion

The Cadiot-Chodkiewicz heterocoupling of acetylenes was investigated as a possible route to a [2]rotaxane which could be taken forward for subsequent desymmetrisation. Unfortunately in our trials, ^{1}H NMR of the product mixture revealed the reaction to be incompatible with the use of bipy macrocycle **2.42** and only non-interlocked heterocoupled thread and starting material were observed after up to 5 days reaction. Furthermore, changing the order of addition of the reaction starting materials did not afford any rotaxane nor did the addition. It is postulated that this may be due to the puckering effect the acetal group has on the macrocycle conformation (seen when a theoretical CPK model is constructed). The effect of this is two fold: firstly, the macrocycle cavity size is constricted and the bipy moiety becomes twisted such the ring nitrogens are *exo* with respect to the macrocycle cavity which may explain why only non-interlocked thread was found and no rotaxane. After some informal discussion with Dr. Stephen Goldup (Queen Mary University of London, who worked on the original project) is was muted that the macrocycle ring size is critical to the reaction outcome. With little time to develop a range of macrocycles with varying ring size with

which to further probe the reaction suitability, it was decided to look towards the CuAAC active metal template approach to form a rotaxane.



Entry	Method[a]	Temp. (°C)	Time	Conv. of 2.53 to 2.55[b]	Rotaxane Observed[b]
1	A	RT	24 h	26%	No
2	A	RT	5 days	55%	No
3	A	50	5 days	62%	No
4	B	50	5 days	32%	No

[a] Method A: *n*-BuLi (1 eq.), **2.53** (1 eq.), THF, -78 °C → 0 °C, 30 min; CuI (1 eq.), 0 °C→ RT, 15 min; **2.52** (1.1 eq.), **2.42** (1 eq.), THF, -78 °C → RT. Method B: Pre-stir CuI (1 eq.), **2.42** (1 eq.), THF, 0 °C→RT (**I**); *n*-BuLi (1 eq.), **2.53,** THF, -78 °C → 0 °C (1 eq.) (**II**); Combine products **I** and **II, 2.52**, THF, 0 °C→RT. [b] Determined by ^{1}H NMR analysis of the reaction mixture.

Table 2.1 Summary of Cadiot-Chodkiewicz reaction results

2.12 CuAAC 'Click' Reaction

2.12.1 Introduction

The term 'Click' chemistry was first defined by Sharpless and co-workers as a synthetic strategy in which reaction building blocks are joined in a stereoselective, high yielding, non toxic reaction.[114] Perhaps the most prevalent example of 'click' methodology is the Cu(I)-catalysed azide-alkyne cycloaddition (CuAAC) reaction, independently reported by Sharpless[64] and Meldal[63] in 2002. Over 1000 research publications, including several reviews on the CuAAC 'click' reaction demonstrate the use of a wide range of copper(I) catalysts and a variety of solvents, including DCM, THF, DMF and DMSO.[115-119]

2.12.2 CuAAC 'Click' Reaction in Supramolecular Chemistry

The CuAAC 'click' reaction has also been widely used in the field of supramolecular chemistry; recently in the synthesis of macrocycles,[120-121] 3-point star molecules[122] and molecular knots.[69] Independently, Sauvage and Stoddart have pioneered the use of the CuAAC 'click' reaction in the template synthesis of rotaxanes with Sauvage utilising a copper template[123] and Stoddart employing a π-acceptor/π-donor template.[124] A number of examples of the passive template synthesis of rotaxanes and catenanes using the CuAAC 'click' reaction can be found in the literature.[125-129]

Leigh and co-workers pioneered the CuAAC 'click' reaction in the active template synthesis of rotaxanes (see Scheme 1.15).[61] The metal centre has a dual role, acting as both the reaction template and as a catalyst for the rotaxane-forming reaction. Leigh and co-workers have also investigated other pyridine-based macrocycles in the CuAAC 'click' active template synthesis of rotaxanes and have gone on to extend the use of the CuAAC 'click' reaction to the active template synthesis of [3]rotaxanes,[67] catenanes and trefoil knots.[69]

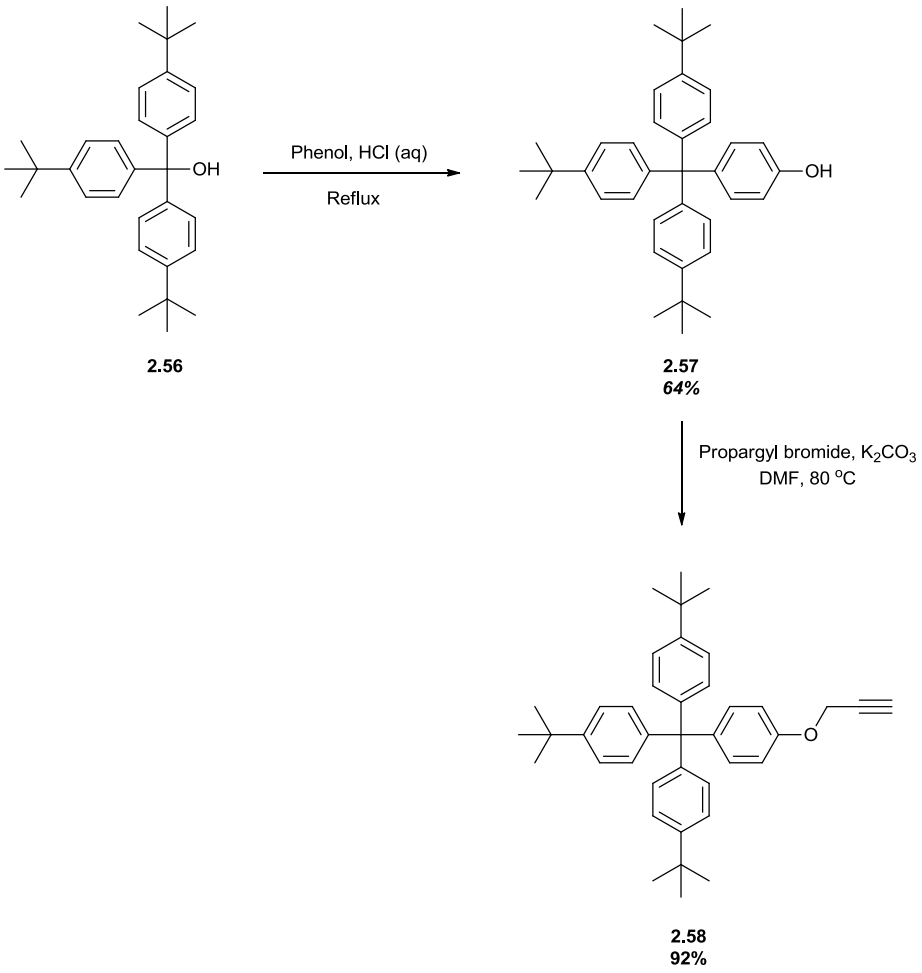
2.12.3 Investigation of the use of the CuAAC 'Click' Reaction for Rotaxane Formation

With a reliable route to macrocycle **2.42** in hand, and as our attempts to employ the Cadiot-Chodkiewicz reaction towards a rotaxane had yielded only non-interlocked thread, it was hypothesised that in the time remaining the CuAAC 'click' reaction could

provide an alternative reaction pathway for access to a rotaxane. In addition, around this time in our project, Goldup and co-workers had just published their investigations on the effect of macrocyclic ring size on the formation of the rotaxanes by employing the CuAAC 'click' reaction.[66] Importantly, they were able to demonstrate that the size of the macrocycle cavity is a major contributory factor in the yield of the corresponding rotaxane. By varying the size of the alkyl chain present in their bipy-based macrocycles, by just two methylene linkers, and screening the optimal reaction temperatures, yields were reported to vary by up to as much as 80%, clearly indicating the importance of ring size and conformation of the reaction outcome. We were interested to find out if our macrocycle could form a rotaxane using the same conditions Goldup's group had developed for formation of their rotaxanes.[65] Interestingly, our macrocycle has 7 carbons between the phenolic oxygens, a ring size untested by the Goldup group. We postulated whether this ring size might afford a yield lying between that achieved by Goldup using both hexyl- and octyl- carbon linked macrocycles. In addition, we wanted to investigate experimentally if the acetal group present on our macrocycle could serve to pucker the macrocycle and result in a smaller ring cavity as indicated theoretically by our CPK model. Access to suitable stoppered 'half-threads' which we could use to probe the suitability of our macrocycle in rotaxane forming reactions are known[62] and could be synthesised quickly.

2.12.4 Synthesis of Suitable Rotaxane Stoppers for a CuAAC 'click' Reaction

Our initial aim was to synthesise a pair of 'stoppered half-threads', the first containing a terminal alkyne moiety and the second, an azide moiety, which could react *via* a copper (I) mediated cycloaddition (through the cavity of our macrocycle) to form a rotaxane (Scheme 2.27 and Scheme 2.28).



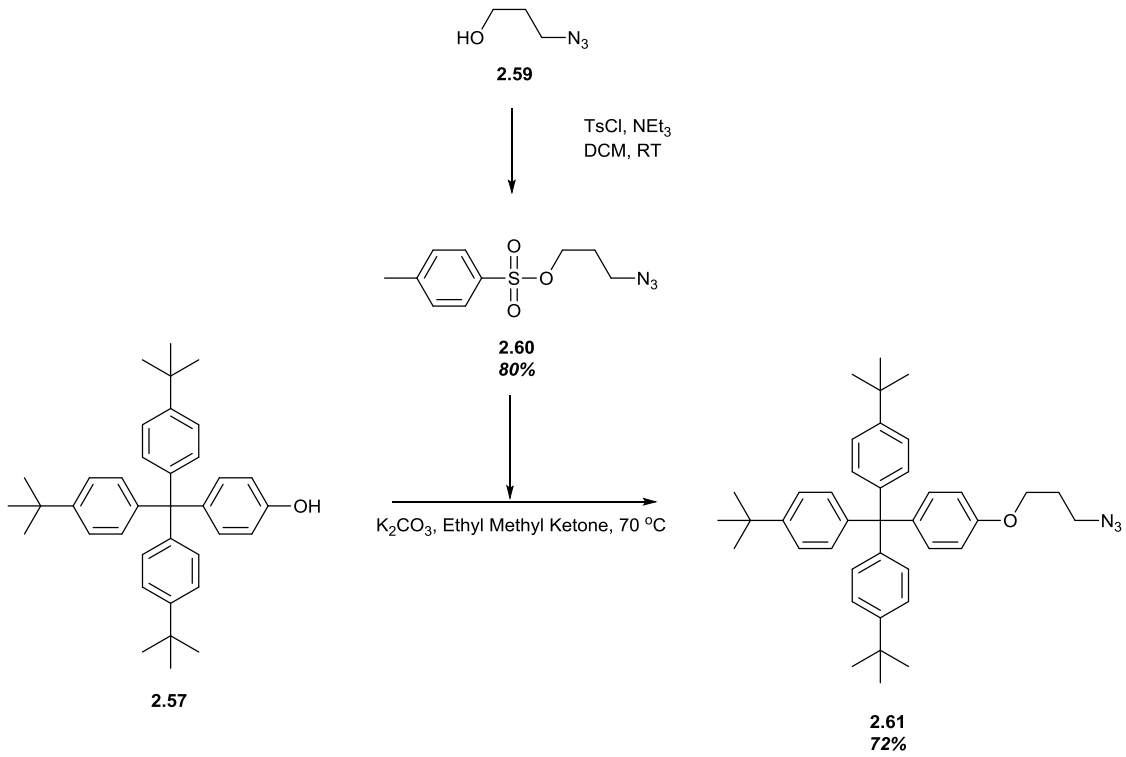
2.56

2.57
64%

2.58
92%

Scheme 2.27 Synthesis of alkyne half thread 2.58

Following a literature precedent by Leigh and co-workers[62], tris(4-*tert*-butylphenyl)methanol **2.56**, which was available within our group, was reacted with phenol in the presence of an HCl catalyst to afford 4-[tris(4-*tert*-butylphenyl)methyl]phenol **2.57** in 64% yield. This was then taken forward and a phenolic propargyl group installed by reaction of **2.57** in DMF, with commercially available propargyl bromide in the presence of potassium carbonate. The synthesis of the target alkyne half-thread **2.58** was achieved in 92% yield (Scheme 2.27).



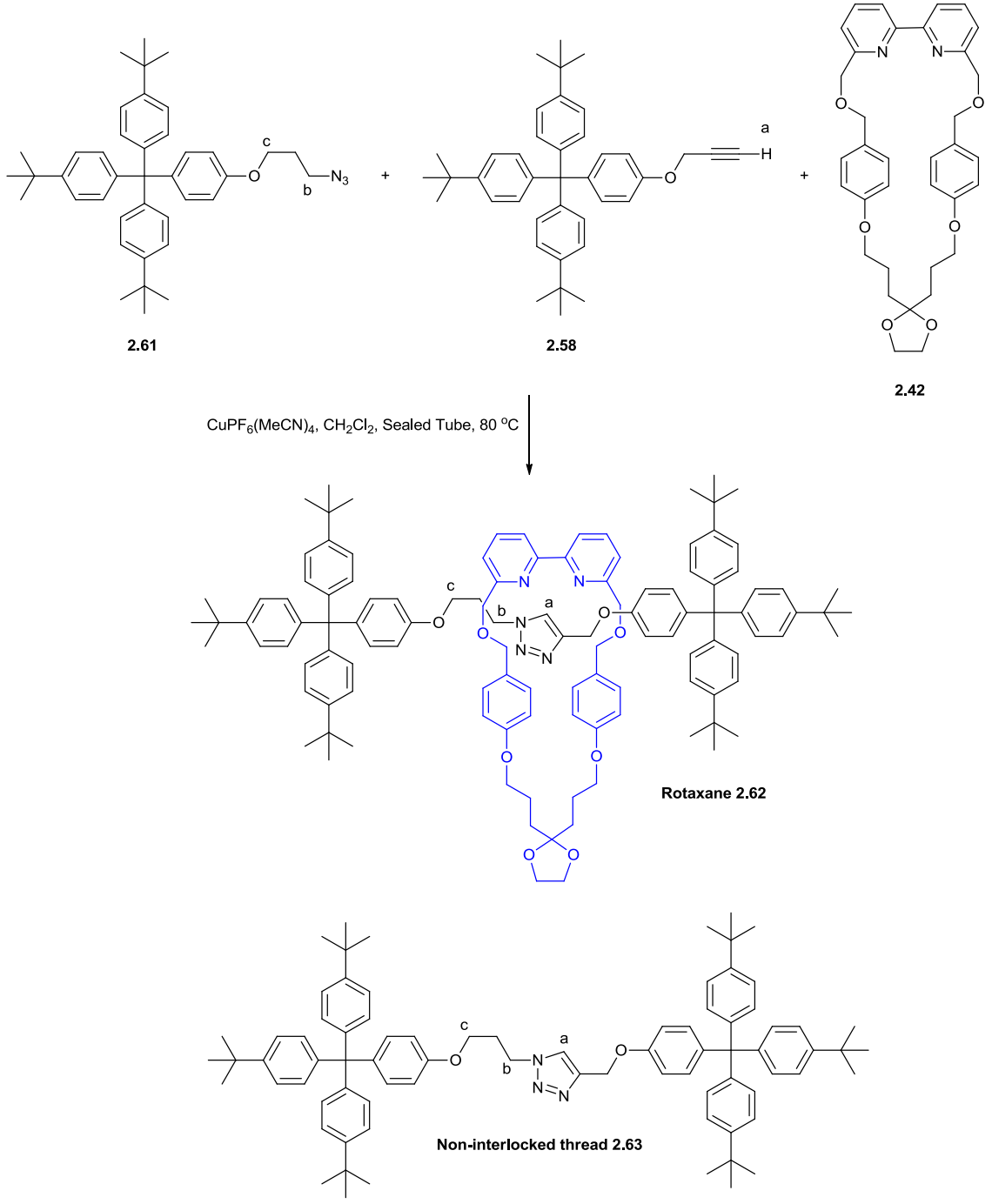
Scheme 2.28 Synthesis of azide half thread 2.62

Our attention then turned to the synthesis of the azide half-thread **2.61**.[62] Starting from commercially available 3-azidopropan-1-ol **2.59**, reaction with tosyl chloride and triethylamine in DCM afforded azide **2.60** in 80% yield. Having installed a more favourable leaving group (tosyl *vs*. hydroxyl), **2.60** was then coupled to 4-[tris(4-*tert*-butylphenyl)methyl]phenol **2.57** by reaction with potassium carbonate in butanone. A 72% yield of target azide half-thread **2.61** was achieved.

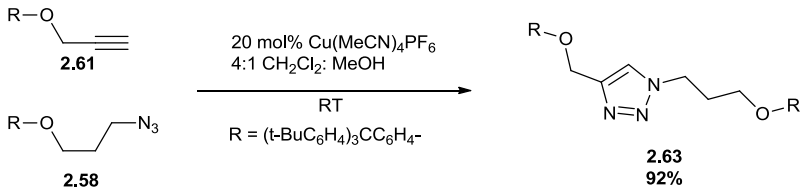
2.13 CuAAC Reaction Results

Having synthesised macrocycle **2.42**, alkyne **2.58**, azide **2.61** and following a literature precedent by Goldup and co-workers[66], we next attempted a rotaxane-forming reaction using the CuAAC active metal template methodology (Scheme 2.29). The reaction protocol was simple, whereby 1 equivalent of macrocycle **2.42**, alkyne **2.58** and azide **2.61** were combined with 0.9 equivalents of $CuPF_6.(MeCN)_4$ in CH_2Cl_2 in a sealed microwave tube and left to stir at 80 ^oC under N_2 for 24 hours (a microwave was not used). Despite several attempts to purify the product mixture by column chromatography, only partial purification of the main product was achieved due to co-elution and streaking of the reaction components on silica (tentative yield, 58%). To determine whether the [2]rotaxane had formed, non-interlocked thread was synthesised following a literature precedent by Leigh[130] in 92% yield (Scheme 2.30). The ^1H NMR

spectrum for the non-interlocked thread was stacked against the ^{1}H NMR spectrum recorded for the semi-purified product mixture and those of half threads **2.58, 2.61** and macrocycle **2.42**. The diagnostic protons, indicated a,b and c (Scheme 2.29 and Figure 2.3), show significant chemical shift due to the shielding effect the macrocycle cavity has on the thread when comparing the region of interest in the [2]rotaxane **2.62** (in the reaction mixture) with non-interlocked **2.63** thread, alkyne **2.58** and azide **2.61**.



Scheme 2.29 CuAAC active metal template synthesis of [2]rotaxane 2.62 and non-interlocked thread 2.63



Scheme 2.30 Synthesis of non-interlocked thread 2.63[130]

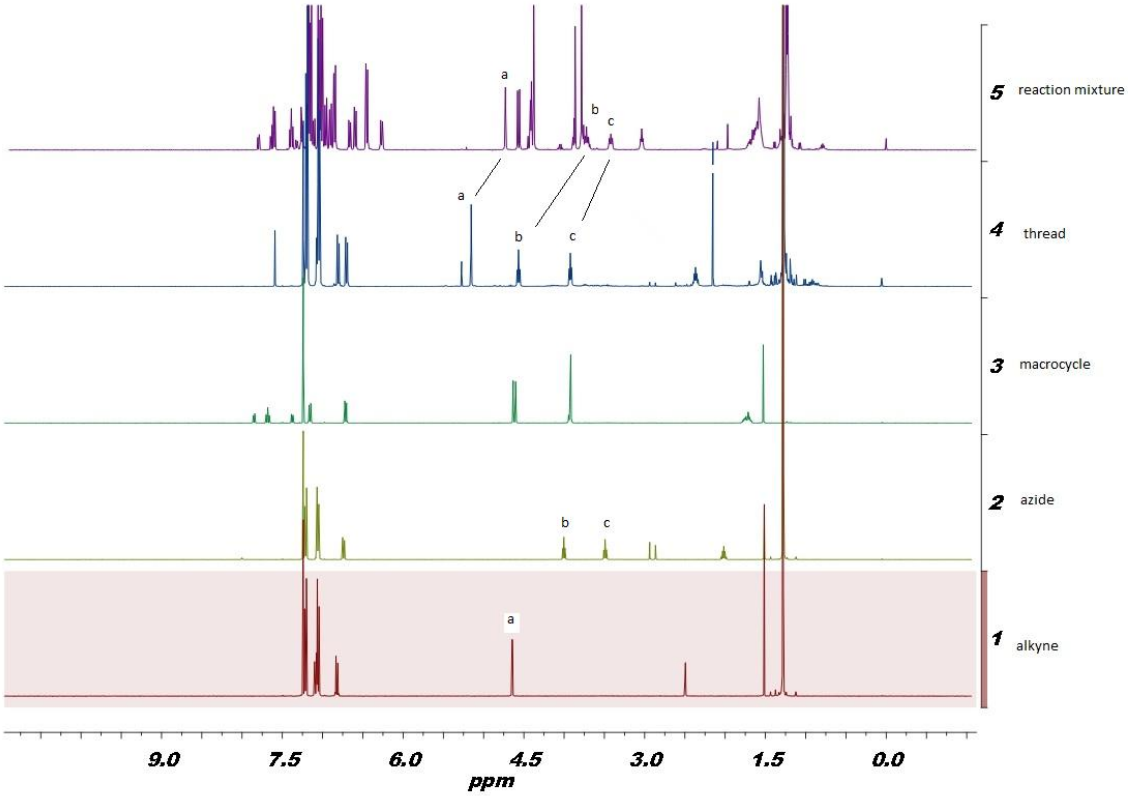


Figure 2.3 Stacked ^{1}H NMR plot showing crude reaction mixture (5), non-interlocked thread 2.63 (4), macrocycle 2.42 (3), alkyne 2.58 (1) and azide 2.61 (2). The 3 diagnostic chemical shifts indicating formation of the [2]rotaxane are labelled a,b and c.

2.14 Conclusion

Macrocycle **2.42** was successfully synthesised. The Cadiot-Chodkiewicz active metal template method using **2.42, 2.53** and **2.54** produced only non-interlocked thread instead of rotaxane. Therefore, we were unable to proceed with our original desymmetrisation approach to a cyclochiral rotaxane. The CuAAC was evaluated for the formation of a [2]rotaxane using macrocycle **2.42**, alkyne **2.58** and azide **2.61**. Despite being unable to isolate the [2]rotaxane **2.62**, ^{1}H NMR indicated formation of the [2]rotaxane in the crude reaction mixture through observation of chemical shift

corresponding to the aliphatic CH_2 groups present on the azide and C-H on the alkyne, compared to the non-interlocked thread species and half-threads. It has now been demonstrated that reactions of this type are extremely sensitive to macrocycle ring size;[66] therefore in future it may be necessary to further optimise the structure of the ring in order to maximise rotaxane yield.

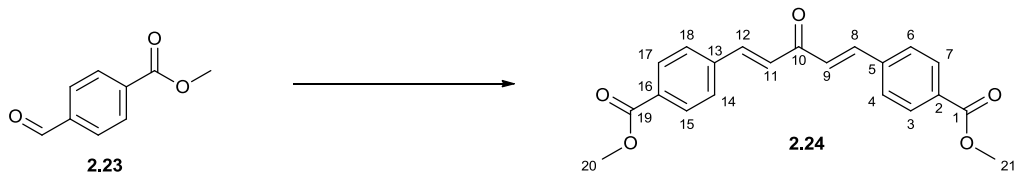
Due to the lack of time to redesign and synthesise a new macrocycle, we decided to concentrate our efforts on an alternative approach to a cyclochiral rotaxane, which was already underway in the Lee Group. The work towards this alternative approach is presented in Chapter 3.

2.15 Experimental

General Information

^{1}H NMR spectra were recorded on Bruker AV 300 and AV 400 spectrometers at 200 and 400 MHz respectively and referenced to residual solvent. ^{13}C NMR spectra were recorded using the same spectrometers at 75 and 100 MHz respectively. Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks (e.g. $CDCl_3$ at δ_H 7.26). *J* values are given in Hz and s, d, dd, t, q, quint and m abbreviations correspond to singlet, doublet, doublet of doublet, triplet, quartet, quintet and multiplet. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat to a diamond/ZnSe plate. Melting points were recorded on a Stuart Scientific SMP10 and are uncorrected. Flash column chromatography was carried out using Matrix silica gel 60 from Fisher Chemicals and TLC was performed using Merck silica gel 60 F254 pre-coated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$ or aqueous acidic ammonium molybdate as appropriate. Unless otherwise stated, reagents and solvents were purchased from commercial sources and used with no further purification. Pet. ether refers to petroleum ether which distils in the range 40 – 60 °C.

Dimethyl 4,4'-((1*E*,4*E*)-3-oxopenta-1,4-diene-1,5-diyl)dibenzoate 2.24

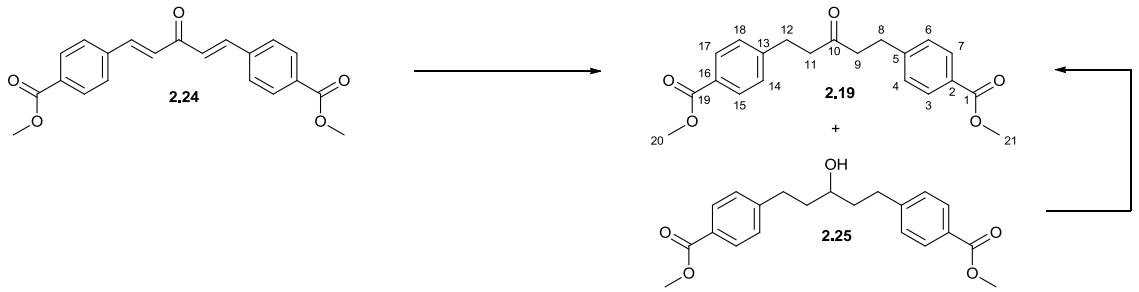


To a solution of methyl 4-formylbenzoate **2.23** (20.0 g, 122 mmol) in methanol (500 mL) under a nitrogen atmosphere was added acetone (4.5 mL , 61 mmol) at 0 ^{o}C. A 1.5 M aqueous solution of sodium hydroxide was then prepared by adding NaOH (6.60 g , 165 mmol) to a 1:1 solution of water-methanol (110 mL) and subsequently added dropwise over 2 hours with constant stirring. The solution was allowed to warm to room temperature after which a thick yellow precipitate formed. After 12 hours the reaction was complete (monitored by TLC) and the precipitate filtered and washed thoroughly with methanol until the filtrate was colourless. Recrystallisation of the

crude product from boiling xylene followed by washing of the resulting solid with methanol yielded the title compound **2.24** (12.0 g, 57 %) as a yellow solid.

Mp 219-222 ^{o}C; R_f 0.28 (3:1 petroleum ether-ethyl acetate) viewed: UV (254 nm) or $KMnO_4$ dip; ν_{max} /cm^{-1} 3447 (C=C), 1717 br (C=O), 1652 (C=C), 1594 (Ar C=C), 1436 (Ar C=C), 1412 (C-H), 1314 (C-H), 1281 (=C-O-C); δ_H (400 MHz, $CDCl_3$) 8.06 (4 H, d, *J* 8.3, H-3, H-7, H-15, H-17), 7.73 (2 H, d, *J* 16.0, H-8, H-12), 7.65 (4 H, d, *J* 8.2, H-4, H-6, H-14, H-18), 7.12 (2 H, d, *J* 16.0, H-9, H-11), 3.92 (6 H, s, H-20, H-21); δ_C (100 MHz, $CDCl_3$) 188.5 (C-10), 166.6 (C-1, C-19), 142.5 (C-8, C-12), 139.1 (C-5, C-13), 131.9 (C-2, C-16), 130.4 (C-4, C-6, C-14, C-18), 128.5 (C-3, C-7, C-15, C-17), 127.4 (C-9, C-11), 52.5 (C-20, C-21); Found (ESI): $[M+H]^+$ 351.1230, $C_{21}H_{19}O_5$ requires 351.1227.

Dimethyl 4,4'-(3-oxopentane-1,5-diyl)dibenzoate 2.19

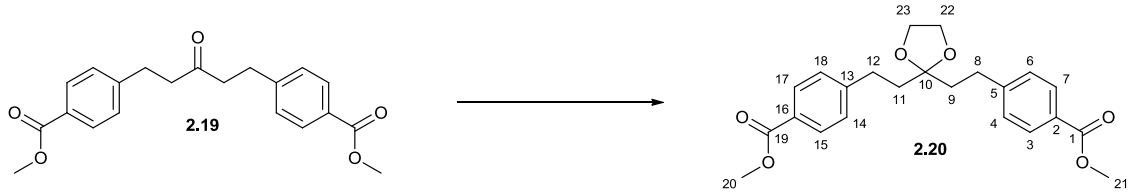


To a two-necked round-bottomed flask, equipped with a 3-way gas tap and stirrer bar, was suspended 4,4'-((1*E*,4*E*)-3-oxopenta-1,4-diene-1,5-diyl)dibenzoate **2.24** (10.0 g, 29 mmol) in ethyl acetate (300 mL) under a nitrogen atmosphere at room temperature. 10 % palladium on charcoal (0.70 g, 7% w/w) was then added in one portion and the reaction left to stir for 10 minutes. The reaction vessel was then evacuated and immediately purged with hydrogen gas from a balloon and left to stir at room temperature until all of the starting material had been consumed (monitored by TLC). After 4 hours, the reaction vessel was purged with nitrogen gas and the exhausted catalyst removed by filtration over a pad of celite. The filtrate was concentrated under reduced pressure to yield an off-white crude mixture of the title compound **2.19** and dimethyl 4,4'-(3-hydroxypentane-1,5-diyl)dibenzoate **2.25**. The crude mixture was subsequently dissolved in dry dichloromethane (100 mL) and cooled to 0 ^{o}C before pyridinium chlorochromate (4.00 g, 19 mmol) and 4 Å molecular sieves (1 g) were added. The reaction was left to stir at 0 ^{o}C for 2 hours before allowing the reaction to warm to room temperature. Consumption of the more polar alcohol by-product was monitored by careful TLC analysis and upon completion of the reaction after 4 hours the molecular sieves were removed by filtration and the filtrate passed through a pad of florisil. The residue was washed with ethyl acetate and the filtrate concentrated *in vacuo* to yield a pale brown solid which, after purification by column chromatography (petroleum ether-ethyl acetate 6:1 to 3:1), gave the title compound **2.19** (7.20 g, 71 %) as a white solid.

Mp 106-109 ^{o}C; R_f 0.34 (3:1 petroleum ether-ethyl acetate) viewed: UV (254 nm) or $KMnO_4$ dip; ν_{max} /cm^{-1} 2952 (C-H), 2890 (C-H), 1734 (C=O), 1706 (C=O), 1608 (Ar C=C), 1433 (C-H), 1287 (=C-O-C); δ_H (200 MHz, $CDCl_3$) 7.90 (4 H, d, *J* 8.5, H-3, H-7, H-15, H-17), 7.18 (4 H, d, *J* 8.5, H-4, H-6, H-14, H-18), 3.87 (6 H, s, H-20, H-21), 2.90 (4 H, t, *J* 7.0, H-8, H-12), 2.70 (4 H, t, *J* 7.0, H-9, H-11); δ_C (50 MHz, $CDCl_3$) 208.2 (C-10), 167.2 (C-1, C-19), 146.6 (C-5, C-13), 130.0 (C-4, C-6, C-14, C-18), 128.6

(C-3, C-7, C-15, C-17), 128.3 (C-2, C-16), 52.2 (C-20, C-21), 44.1 (C-9, C-11), 29.7 (C-8, C-12) ; Found (ESI): $[M+H]^+$ 355.1542, $C_{21}H_{23}O_5$ requires 355.1540.

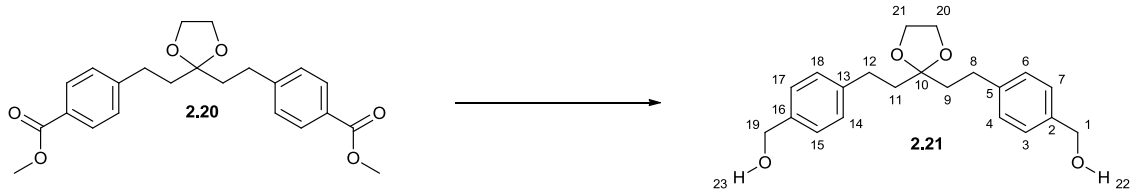
Dimethyl 4,4'-(2,2'-(1,3-dioxolane-2,2-diyl)bis(ethane-2,1-diyl))dibenzoate 2.20



To a solution of dimethyl 4,4'-(3-oxopentane-1,5-diyl)dibenzoate **2.19** (5.00 g, 14 mmol) in dry toluene (50 mL) under a nitrogen atmosphere was added *p*-toluenesulfonic acid monohydrate (133 mg, 0.7 mmol) and ethylene glycol (4 mL, 72 mmol). The reaction was stirred at reflux for 24 hours whilst a Dean-Stark apparatus was used to collect the water produced by reflux. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (petroleum ether-ethyl acetate 3:1) to give the title compound **2.20** (3.40 g, 61%) as a white solid.

Mp 103-104 ^{o}C; R_f 0.43 (3:1 petroleum ether-ethyl acetate) viewed: UV (254 nm) or $KMnO_4$ dip; ν_{max} /cm^{-1} 2996 (C-H), 2953 (C-H), 2890 (C-H), 1705 (C=O), 1608 (Ar C=C), 1573 (Ar C=C), 1433 (C-H), 1287 (=C-O-C), 1183 (C-O), 1107 (C-O); δ_H (200 MHz, $CDCl_3$) 7.93 (4 H, d, *J* 8.4, H-3, H-7, H-15, H-17), 7.23 (4 H, d, *J* 8.4, H-4, H-6, H-14, H-18), 4.00 (4 H, s, H-22, H-23), 3.87 (6 H, s, H-20, H-21), 2.81 – 2.68 (4 H, m, H-8, H-12), 2.04 – 1.89 (4 H, m, H-9, H-11); δ_C (50 MHz, $CDCl_3$) 167.3 (C-1, C-19), 147.8 (C-5, C-13), 130.0 (C-4, C-6, C-14, C-18), 128.5 (C-3, C-7, C-15, C-17), 128.0 (C-2, C-16), 110.8 (C-10), 65.5 (C-22, C-23), 52.2 (C-20, C-21), 39.1 (C-9, C-11), 30.3 (C-8, C-12); Found (ESI): $[M+NH_4]^+$ 416.2069, $C_{23}H_{30}O_6N_1$ requires 416.2068.

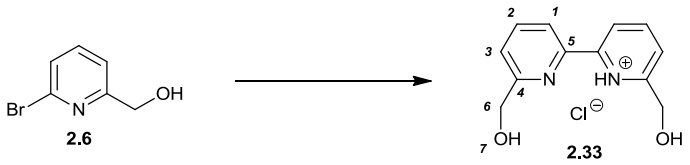
(4,4'-(2,2'-(1,3-Dioxolane-2,2-diyl)bis(ethane-2,1-diyl))bis(4,1-phenylene))dimethanol 2.21



To lithium aluminium hydride (0.75 g, 20 mmol) suspended in dry THF (50 mL) under a nitrogen atmosphere at 0 ^{o}C was added dropwise a solution of dimethyl 4,4'-(2,2'-(1,3-dioxolane-2,2-diyl)bis(ethane-2,1-diyl))dibenzoate **2.20** (2.60 g, 7 mmol) in dry THF (10 mL). The reaction was stirred at 0 ^{o}C for 2 hours before being allowed to warm to room temperature. Formation of the diol was monitored by TLC and after 4 hours the reaction was quenched by careful sequential addition of water (0.75 mL), 15% $NaOH_{(aq)}$ (0.75 mL) and water (2.25 mL) and the solution stirred a further 30 minutes. The resulting precipitate was filtered and the filtrate dried over anhydrous sodium sulphate before being concentrated *in vacuo* to yield a crude white solid. Purification by column chromatography (petroleum ether-ethyl acetate 4:1 to 1:1) gave the title compound **2.21** as a white solid (2.10 g, 94 %).

Mp 96-98 ^{o}C; R_f 0.25 (1:1 petroleum ether-ethyl acetate) viewed: UV (254 nm) or $KMnO_4$ dip; ν_{max} /cm^{-1} 3338 br (O-H), 2950 (C-H), 2874 (C-H), 1133 (C-O-C), 1013 (C-OH); δ (200 MHz, $CDCl_3$) 7.25 (4 H, d, *J* 8.3, H-3, H-7, H-15, H-17), 7.15 (4 H, d, *J* 8.2, H-4, H-6, H-14, H-18), 4.60 (4 H, s, H-1, H-19), 3.99 (4 H, s, H-20, H-21), 2.77 – 2.58 (4 H, m, H-8, H-12), 2.14 (2 H, s, H-22, H-23), 2.02 – 1.82 (4 H, m, H-9, H-11); δ (50 MHz, $CDCl_3$) 141.7 (C-5, C-13), 138.6 (C-2, C-16), 128.7 (C-4, C-6, C-14, C-18), 127.4 (C-3, C-7, C-15, C-17), 111.1 (C-10), 65.4 (C-1, C19), 65.2 (C-20, C-21), 39.4 (C-9, C-11), 29.9 (C-8, C-12); Found (ESI): $[M+NH_4]^+$ 360.2173, $C_{21}H_{30}O_4N_1$ requires 360.2169.

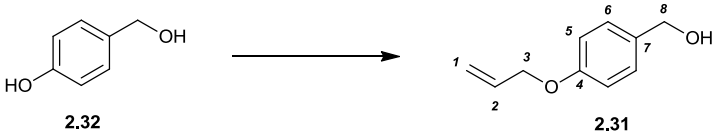
2-(Hydroxymethyl)-6-(6-(hydroxymethyl)pyridin-2-yl)pyridinium chloride 2.33[73]



Zinc powder (2.00 g, 31 mmol) was activated by washing consecutively with 1M $HCl_{(aq)}$ (20 mL), distilled water (25 mL), acetone (25 mL), diethyl ether (25 mL) and then dried under reduced pressure. To a solution of PPh_3 (22.3 g, 85 mmol) and $NiCl_2$ (2.76 g, 21 mmol) in anhydrous DMF (100 mL) was added activated zinc (1.39 g, 21 mmol) and the resulting green suspension stirred for 1 hour at 50 ^oC. (6-Bromo-pyridin2-yl)-methanol **2.6** (4.00 g, 21 mmol) was added to the resulting deep red solution and the reaction mixture stirred for 3 hours (monitored by TLC). Upon completion of the reaction, the solution was allowed to cool to room temperature and poured onto a saturated solution of EDTA in 1:1 NH_3/H_2O (125 mL) and subsequently extracted with $CHCl_3$/IPA [3:1] (4 x 250 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was then dissolved in dichloromethane (100 mL) and cooled 0 ^oC. HCl gas was generated by dropwise addition of sulphuric acid onto fused calcium chloride and the resulting gas, passed through a Dreschel bottle (to prevent suck-back), bubbled through the DCM solution of the reaction product for 30 minutes and allowed to warm to ambient temperature. The resulting hydrochloride salt was removed by vacuum filtration to afford the title compound **2.33** (1.54 g, 82% yield) as an off-white solid.

Mp 207-209 ^oC (lit. 208-212 ^oC); ν_{max} /cm^{-1} 3326 (N-H), 3156 (N-H), 3066 (Ar C=C), 3009 (C-H), 2941 (C-H), 1611 (C-H), 1591 (C-H), 1446 (C-H); δ (200 MHz,) 8.35 (2 H, d, *J* 7.7, H-1), 8.13 (2 H, t, *J* 7.8, H-2), 7.69 (2 H, d, *J* 7.7, H-3), 4.75 (4 H, s, H-6); δ_C (100 MHz, $(CD_3)_2SO$) 161.3 (C-4), 152.40 (C-2), 138.9 (C-1), 121.3 (C-5), 119.4 (C-3), 63.8 (C-6).

4-(Allyloxy)phenyl methanol 2.31[73, 131]

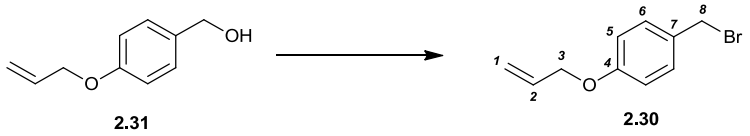


2.32 **2.31**

K_2CO_3 (10.0 g, 0.07 mol) was added to a solution of 4-hydroxybenzyl alcohol **2.32** (1.80 g, 14.5 mmol) in anhydrous acetone (20 mL). Allyl bromide (1.3 mL, 14.6 mmol) was then added and the reaction mixture heated at reflux for 20 h. After cooling to RT, the reaction mixture was concentrated *in vacuo* and the product reconstituted in CH_2Cl_2 (60 mL). H_2O (50 mL) was added and the phases separated. The aqueous phase was re-extracted with CH_2Cl_2 (2 x 60 mL) and the combined organic extracts were washed with H_2O (2 x 100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (pet ether-EtOAc, 10:1) to give the title compound **2.31** (1.79 g, 75% yield) as a colourless oil.

R_f 0.65 (EtOAc); Mp 84-86 ºC [lit.[73] mp 86-90 °C]; δ_H (400 MHz, $CDCl_3$) 7.15 (2 H, d, *J* 8.5, H-5), 6.91 (2 H, d, *J* 8.5, H-6), 5.96 (1H, ddt, *J* 17.1, 10.5, 5.7, H-2), 5.40 (1H, dd, *J* 17.1, 1.2, H-1), 5.29 (1H, dd, *J* 10.5, 1.2, H-1), 4.52 (2 H, d, *J* 5.7, H-3), 4.20 (2H, s, H-8); δ_C (101 MHz, $CDCl_3$) 153.4 (C-4), 133.7 (C-7), 128.8 (C-2), 126.2 (C-6), 118.3 (C-1), 114.5 (C-5), 69.1 (C-3), 63.2 (C-8); Low Resolution ESI-MS (MeOH) *m/z* = 165.1 $[M+H]^+$.

1-(Allyloxy)-4-(bromomethyl)benzene 2.30[73]

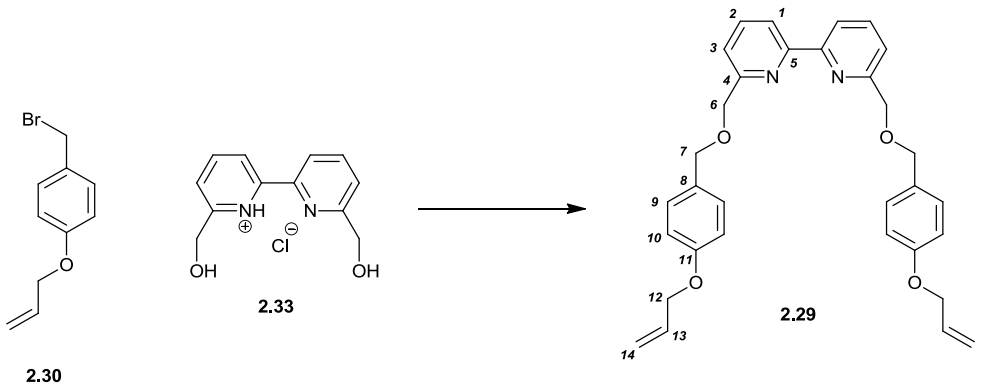


2.31 2.30

Allylic ether **2.31** (12.0 g, 74 mmol) was dissolved in CH_2Cl_2 (100 mL) and $HBr_{(aq)}$ (48%, 100 mL) was added. The mixture was then immediately concentrated under reduced pressure to near dryness. The residue was partitioned between CH_2Cl_2 (200 mL) and H_2O (200 mL) and the phases separated. The organic phase was washed with saturated $K_2CO_{3(aq)}$ (200 mL), H_2O (200 mL), brine (200 mL), then dried ($MgSO_4$) before being concentrated *in vacuo* to give bromide **2.30** (13.7 g, 83% yield) as a pale brown gum, which was used without delay and with no further purification.

R_f 0.41(smear) (EtOAc: Pet. Ether 2:8); δ_H (400 MHz, $CDCl_3$) 7.40 (2 H, d, *J* 8.5, H-5), 6.85 (2 H, d, *J* 8.5, H-6), 6.10 (1H, ddt, *J* 17.1, 10.5, 5.7, H-2), 5.45 (1H, dd, *J* 17.1, 1.2, H-1), 5.35 (1H, dd, *J* 10.5, 1.2, H-1), 4.52 (2 H, d, *J* 5.7, H-3), 4.20 (2H, s, H-8). δ_C (75 MHz, $CDCl_3$) 154.4 (C-4), 134.8 (C-7), 129.9 (C-2), 127.2 (C-6), 119.3 (C-1), 114.6 (C-5), 69.1 (C-3), 37.4 (C-8).

6,6'-Bis((4-(allyloxy)benzyloxy)methyl)-2,2'-bipyridine 2.29[73]

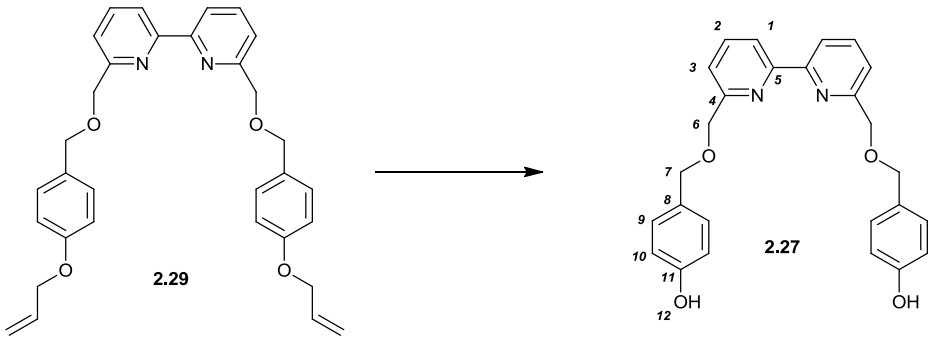


2.30 **2.33** **2.29**

To a suspension of 2-(hydroxymethyl)-6-(6-hydroxymethylpyridin-2-yl)pyridinium chloride **2.33** (2.00 g, 7.91 mmol) in anhydrous DMF (40 mL) at 0 ^{o}C was added NaH (60% dispersion in mineral oil, 1.27 g, 31.7 mmol) and the mixture stirred until effervescence ceased. 1-(Allyloxy)-4-(bromomethyl)benzene **2.30** (5.38 g, 23.7 mmol) was added in one portion and the mixture warmed to room temperature with stirring over 20 h. The reaction mixture was partitioned between H_2O (200 mL) and $CHCl_3$/IPA (3:1, 200 mL) and the layers separated. The aqueous phase was extracted with $CHCl_3$/IPA (3:1, 3 x 150 mL), the combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. Column chromatography (gradient elution: 1. DCM, 2. acetone-DCM, 2:98) afforded the title compound **2.29** as an off-white solid (3.38 g, 84% yield).

Mp 84-86 ºC [lit.[73] mp 86-90 °C]; δ_H (400 MHz, $CDCl_3$) 8.26 (2 H, d, *J* 7.8, H-1), 7.81 (2 H, t, *J* 7.8, H-2), 7.50 (2 H, d, *J* 7.7, H-3), 7.34 (4 H, d, *J* 8.6, H-10), 6.89 (4 H, d, *J* 8.6, H-9), 6.05 (2 H, ddt, *J* 17.1, 10.5, 5.3, H-13), 5.41 (2 H, ddt, *J* = 17.1, 1.6, 1.6, H-14), 5.28 (2 H, ddt, *J* 10.5, 1.4, 1.2, H-14), 4.74 (4 H, s, H-6), 4.61 (4 H, s, H-7), 4.54 (4 H, dt, *J* 5.3, 1.5, H-12); δ_C (101 MHz, $CDCl_3$) 158.3 (C-4), 158.2 (C-11), 155.4 (C-2), 137.4 (C-13), 133.2 (C-8), 130.3 (C-9), 129.4 (C-1), 121.2 (C-5), 119.7 (C-3), 117.7 (C-14), 114.6 (C-10), 73.0 (C-6), 72.5 (C-7), 68.8 (C-12); Found (ESI): $[M+H]^+$ 509.2430, $C_{32}H_{33}N_2O_4$ requires 509.2435.

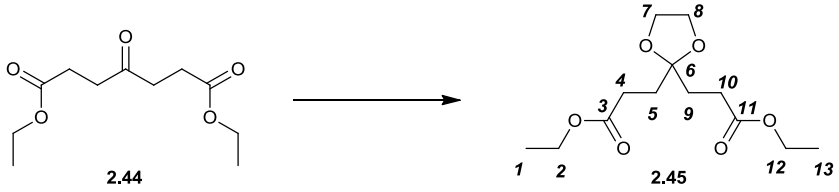
4,4'-(2,2'-Bipyridine-6,6'-diylbis(methylene))bis(oxy)bis(methylene)diphenol 2.2[73]



To a solution of 6,6'-bis((4-(allyloxy)benzyloxy)methyl)-2,2'-bipyridine **2.29** (1.50 g, 2.95 mmol) in anhydrous THF (5 mL) was added aniline (0.549 g, 5.90 mmol) then $Pd(PPh_3)_4$ (0.137 g, 0.12 mmol) and the reaction mixture stirred at 50 ^oC for 8 h. The mixture was then poured into H_2O (60 mL) and extracted with $CHCl_3$/IPA (3:1; 3 x 60 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure. Column chromatography (gradient elution: 1. CH_2Cl_2, 2. MeOH-CH_2Cl_2, 1:99, 3. MeOH-CH_2Cl_2, 2:98, 4. MeOH-CH_2Cl_2, 3:97) afforded the title compound **2.27** (1.11 g, 88% yield) as a pale yellow oil which crystallised upon standing.

Mp 124-127 ºC [lit.[73] mp 128-130 °C]; δ_H (400 MHz, CD_3OD) 8.20 (2 H, d, *J* 7.8, H-1), 7.85 (2 H, t, *J* 7.7 Hz, H-2), 7.56 (2 H, d, *J* = 7.7, H-3), 7.23 (4 H, d, *J* 8.6, H-10), 6.80 (4 H, d, *J* 8.6, H-9), 4.90 (2 H, s, OH), 4.67 (s, 4H, H-6), 4.54 (s, 4H, H-7); δ_C (101 MHz, CD_3OD) 159.5 (C-4), 158.4 (C-11), 156.6 (C-2), 138.8 (C-8), 130.9 (C-9), 130.1 (C-1), 122.9 (C-5), 121.3 (C-3), 116.1 (C-10), 73.9 (C-6), 73.5 (C-7); Found (ESI): $[M+H]^+$ 429.1801, $C_{26}H_{25}N_2O_4$ requires 429.1808

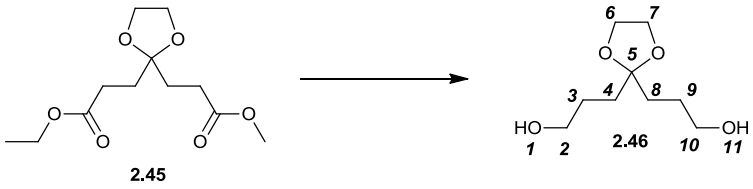
Diethyl 3,3'-(1,3-dioxolane-2,2-diyl)dipropanoate 2.45[132]



A solution of diethyl 4-oxopimelate (15.0 g, 65.1 mmol) and ethylene glycol (6.06 g, 97.7 mmol) in toluene (300 mL) was stirred before indium triflate (0.731 g, 1.30 mmol) was added to the solution. A Dean-Stark apparatus was used for the azeotropic removal of water and the reaction mixture heated at reflux for 18 hrs before being cooled to room temperature. The solvent was then removed *in vacuo* to afford a crude yellow oil product which was subsequently dissolved in EtOAc (150 mL). The resulting solution then washed consecutively with saturated $NaHCO_3$ (100 mL), H_2O (100 mL) and brine (100 mL) before being dried over Na_2SO_4 and concentrated *in vacuo*. The resulting pale yellow oil was purified by flash chromatography (gradient elution: Pet. Ether: EtOAc 15:1 to 6:1 *v*/*v*) to afford the title compound **2.20** (14.9 g, 88% yield) as a colourless oil.

ν_{max} /cm^{-1} 3001 (CH), 2974 (CH), 2932 (CH), 2810 (CH) 2801 (CH), 1726 (C=O), 1380 (C-H), 1420 (C-H), 1264 (C-O), 1213 (C-O); δ_H (300 MHz, $CDCl_3$) 4.11 (4 H, q, *J* 7.1, H-2, H-12), 3.92 (4 H, s, H-7, H-8), 2.40-2.31 (4 H, m, H-4, H-10), 2.00-1.91 (4 H, m, H-5, H-9), 1.28-1.20 (6 H, m, H-1, H-13); δ_C (75 MHz, $CDCl_3$) 173.4 (C-3, C-11), 110.1 (C-6), 65.1 (C-7, C-8), 60.3 (C-2, C-12), 32.4 (C-4, C-10), 28.9 (C-5, C-9), 14.2 (C-1, C-13).

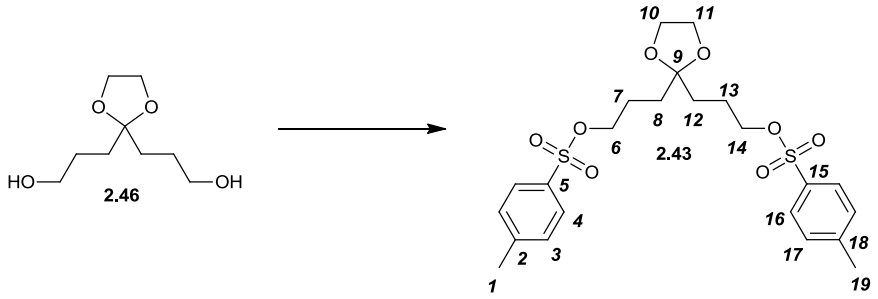
3,3'-(1,3-Dioxolane-2,2-diyl)bis(propan-1-ol) 2.46[132]



$LiAlH_4$ (2.34 g, 61.5 mmol) was added portionwise to a stirring solution of diethyl 3,3'-(1,3-dioxolane-2,2-diyl)dipropanoate **2.20** (4.00 g, 15.4 mmol) in dry THF (150 mL) at 0 ^oC. The reaction was then stirred for 18 hrs at room temperature. The reaction was quenched by careful consecutive addition of 3 mL H_2O, 3 mL of 15% NaOH, followed by 9 mL of H_2O at 0 ^oC. The resulting solution was stirred for 1 hr at room temperature then filtered through a pad of Celite™. The residue was washed with THF (30 mL) before the filtrate was concentrated *in vacuo*. The residue obtained was dissolved in DCM (75 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford crude product. Purification by flash chromatography (gradient elution: Pet. Ether: EtOAc 9:1 to 1:1 *v*/*v*) gave the title compound **2.19** (2.31 g, 79% yield) as a colourless oil.

ν_{max} /cm^{-1} 3279 br (OH), 3010 (CH), 2951 (CH), 2845 (CH), 2837 (CH), 1364 (C-H), 1401 (C-H), 1264 (C-O), 1213 (C-OH); δ_H (300 MHz, $CDCl_3$) 3.90 (4 H, s, H-6, H-7), 3.55 (4 H, t, *J* 6.1, H-2, H-10), 2.95 (2 H, s, H-1, H-11), 1.62-1.71 (4 H, m, H-4, H-8), 1.51-1.62 (4 H, m, H-3, H-9); δ_C (75 MHz, $CDCl_3$) 111.8 (C-5), 65.2 (C-6, C-7), 63.3 (C-2, C-10), 33.8 (C-4, C-8), 27.3 (C-3, C-9).

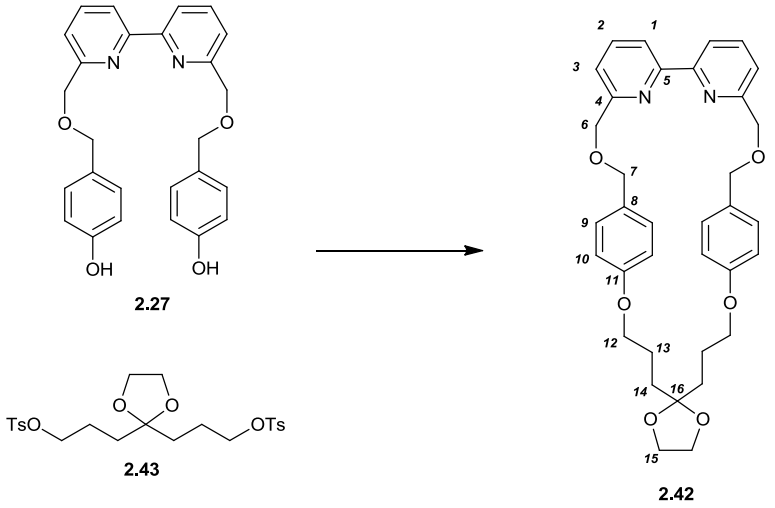
2,2-Bis(3-tosyloxypropyl)-1,3-dioxolane 2.43[133]



A solution of **38** (1.73 g, 9.07 mmol) in dry THF (20 mL) was cooled to -10 ^{o}C under an N_2 atmosphere, TsCl (4.35 g, 22.8 mmol) and powdered KOH (5.1 g, 90.9 mmol) were then added over portion wise over 20 mins. The reaction was allowed to stir for 30 mins before being allowed to reach 0 ^{o}C and left to stir for 18 hrs. The solution was then added to an ice/water mixture and diluted with EtOAc (50 mL), the solution were then washed 3 times with EtOAc (100 mL). The organics were then washed with brine and dried with $MgSO_4$. The solvent was then removed *in vacuo* to afford a crude solid product, the crude product was then recrystallised from hot MeOH and triturated using hexane to yield (2.97 g, 5.97 mmol, 66%) of pure crystalline macrocycle precursor **44**.

Mp 154-156 °C (decomposes) [lit. mp 158-160 °C]; R_f 0.32 (5:1 petrol ether-ethyl acetate) viewed: UV (254 nm); δ_H (300 MHz, $CDCl_3$) 7.76 (4 H, d, *J* 8.3, H-14, H-16), 7.32 (4 H, d, *J* 8.0, H-3, H-17), 4.00 (4 H, t, *J* 6.3, H-6, H-14), 3.82 (4 H, s, H-10, H-11), 2.43 (6 H, s, H-1, H-19), 1.61-1.69 (4 H, m, H-8,H-12), 1.53-1.58 (4 H, m, H-7, H-13); δ_C (75 MHz, $CDCl_3$) 145.0 (C-5, C-15), 133.4 (C-2, C-18), 130.1 (C-3, C-17), 128.1 (C-4, C-16), 110.6 (C-9), 70.7 (C-6, C-14), 65.2 (C-10, C-11), 33.1 (C-8, C-12), 23.6 (C-1, C-19), 21.9 (C-7, C-13).

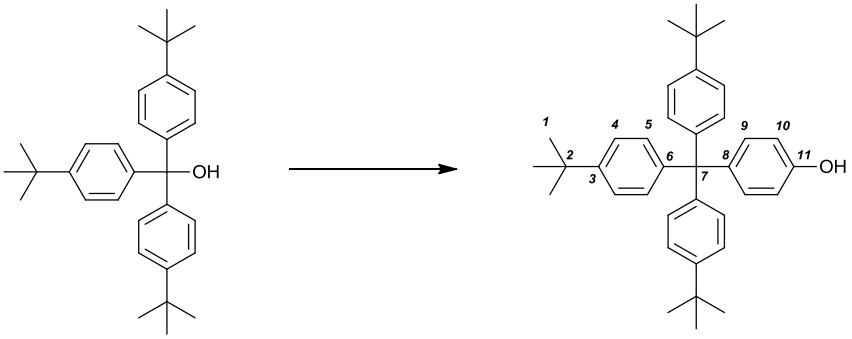
Macrocycle 2.42



To a solution of 4,4'-(2,2'-bipyridine-6,6'-diylbis(methylene))bis(oxy)bis(methylene) diphenol **2.27** (2.00 g, 4.67 mmol) in anhydrous DMF (1.9 L) was added Cs_2CO_3 (7.61 g, 23.35 mmol) then (1,3-dioxolane-2,2-diyl)bis(propane-3,1-diyl)bis(4-methylbenzenesulfonate) **2.43** (2.33 g, 4.67 mmol) and the reaction mixture stirred at 80 ^oC for 72 h. The reaction mixture was then concentrated to *ca*. 500 mL *in vacuo* and 500 mL of EtOAc/H_2O 1:1 *v/v* added. The resulting layers were separated and the acqueous phase extracted thrice with EtOAc (250 mL). The combined organic extracts were washed with brine (twice, 250 mL) and dried ($MgSO_4$) and the solvent removed under reduced pressure. Column chromatography (gradient elution: 1. CH_2Cl_2, 2. MeOH-CH_2Cl_2, 0.5:99 *v*/*v*, 3. MeOH-CH_2Cl_2, 1:99 *v*/*v*) afforded the title compound **2.42** (1.39 g, 51% yield) as an off-white solid.

Mp 108-110 °C; δ_H (400 MHz, $CDCl_3$) 7.88 (2 H, d, *J* 7.7, H-1), 7.70 (2 H, t, *J* 7.8, H-2), 7.40 (2 H, d, *J* 7.7, H-3), 7.20 – 7.11 (4 H, m, H-9), 6.75 – 6.68 (4 H, m, H-10), 4.63 (4 H, s, H-6), 4.61 (4 H, s, H-7), 3.97 – 3.89 (8 H, m, H-12, H-15), 1.79 – 1.66 (8 H, m, H-13, H-14); δ_C (101 MHz, $CDCl_3$) 159.0 (C-11), 158.6 (C-4), 137.5 (C-2) , 130.3 (C-9), 130.0 (C-8), 121.5 (C-1), 120.5 (C-3), 114.9 (C-10), 111.5 (C-5), 77.4 (C-16), 73.0 (C-6), 72.1 (C-7), 68.1 (C-12), 65.2 (C-15), 33.6 (C-14), 23.6 (C-13); Found (ESI): $[M+H]^+$ 583.2794, $C_{35}H_{39}N_2O_6$ requires 583.2802.

4-(Tris(4-*tert*-butylphenyl)methyl)phenol 2.57[66]

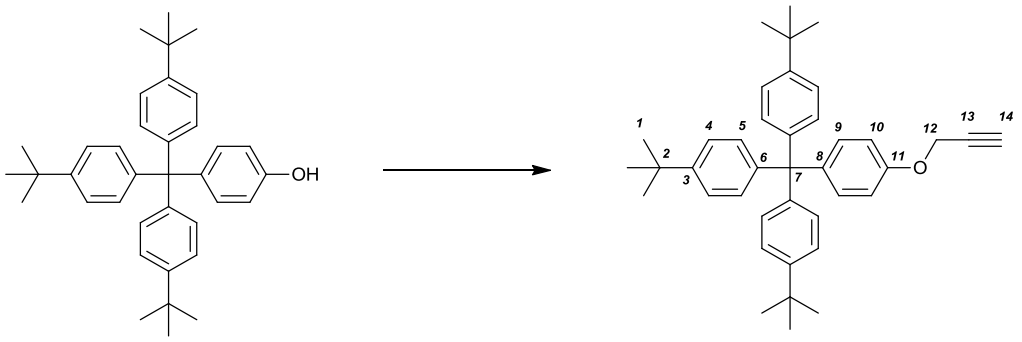


2.56 **2.57**

Tris(4-*tert*-butylphenyl)methanol **2.56** (6.5 g, 15.2 mmol) was added to phenol (14.3 g, 152 mmol) and the mixture warmed to 60 °C. Hydrochloric acid (35% aq., 1 mL) was added and the resulting mixture heated to reflux for 18 hours. The reaction was cooled to ambient temperature and the solid extracted with ethyl acetate (150 mL) and toluene (150 mL). The combined organic layers were washed with 0.5M KOH (aq) (400 mL), 1M HCl (aq) (50 mL) and brine (150 mL). The combined aqueous layers were then extracted with DCM (100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was recrystallised from methanol/hexane to afford the title compound **2.57** (4.90 g, 64% yield) as a colourless solid.

Mp 298-300 °C [lit. mp 304-306 °C]; R_f 0.51 (9:1 petrol ether-ethyl acetate) viewed: UV (254 nm); ν_{max} /cm^{-1} 3461 br. (OH), 2940 (Ar CH), 1615 (Ar C=C), 1589 (Ar C=C), 1502 (Ar C=C), 1458 (Ar C=C), 1358 (C-O), 1229 (C-O); δH (400 MHz, $CDCl_3$) 7.25 (6 H, d, *J* 8.6 H-5), 7.11 (2 H, d, *J* 8.9 H-9), 6.90 (6 H, d, *J* 8.6 H-4), 6.80 (d, 2H, *J* 8.9, H-10) 1.33 (27 H, s, H-1); δC (75 MHz, $CDCl_3$) 153.2 (C-11), 148.3 (C-3), 144.1 (C-6), 139.8 (C-8), 132.4 (C-9), 130.7 (C-5), 124.0 (C-4), 113.9 (C-10), 63.0 (C-7), 34.3 (C-2), 31.4 (C-1); Found (ESI): $[M+NH_4]^+$ 522.3727, $C_{37}H_{48}NO$ requires 522.3730.

4,4',4''-((4-(Prop-2-yn-1-yloxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) 2.58[66]

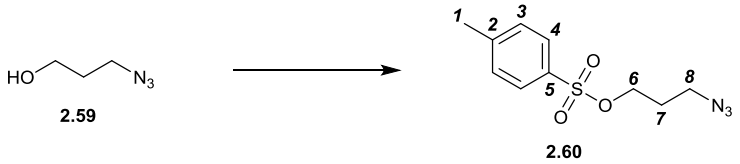


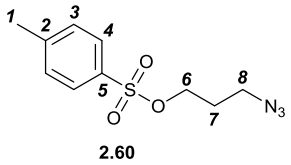
2.57 **2.58**

To a stirring solution of 4-[tris-(4-*tert*-butyl-phenyl)-methyl]-phenol **2.57** (2.40 g, 4.5 mmol) and propargyl bromide (80 % solution in toluene, 0.75 mL, 6.75 mmol) in DMF (45 mL) was added potassium carbonate (3.12 g, 22.5 mmol). The reaction mixture was heated at 80°C for 18 h before being cooled to ambient temperature and concentration under reduced pressure. Water (45 mL) was added to the reaction mixture and extracted thrice with EtOAc (40 mL). The resulting residue was recrystallised from chloroform/ acetonitrile to give the title compound **2.58** as a colourless solid. (2.25 g, 92% yield).

m.p. 262-263°C (decomposes) [lit. m.p.[66] 267-269 °C, decomposes]; ν_{max} /cm^{-1}, 2959 (Ar CH), 2940 (CH), 2901 (CH), 2867 (CH), 2216 (C≡C), 1615 (Ar C=C), 1589 (Ar C=C), 1502 (Ar C=C), 1458 (Ar C=C), 1360 (C-O), 1229 (C-O); δH (400 MHz, $CDCl_3$) 7.23 (6 H, d, *J* 8.6, H-5), 7.11 (2 H, d, *J* 8.9, H-9), 7.07 (6H, d, *J* 8.6, H-4), 6.84 (2H, d, *J* 8.9, H-10), 4.66 (2H, d, *J* 2.4, H-12), 2.62 (1H, t, *J* 2.4, H-14), 1.30 (27 H, s, H-1); δC (101 MHz, $CDCl_3$) 155.2 (C-11), 148.2 (C-3), 144.3 (C-6), 140.6 (C-8), 132.5 (C-9), 130.7 (C-5), 123.9(C-4), 113.1 (C-10), 78.9 (C-13), 75.4 (C-14), 63.2 (C-7), 55.8 (C-12), 34.1 (C-2), 31.2 (C-1).

3-Azidopropyl tosylate 2.60[66]

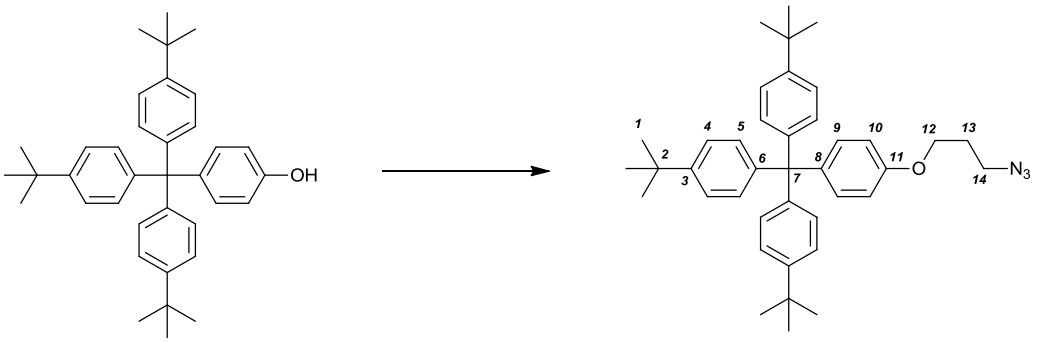




A solution of 3-azido-propan-1-ol **2.59** (1.50 g, 14.8 mmol) and triethylamine (3.03 g, 30.0 mmol) in DCM (125 mL) was cooled to 0°C. *p*-Toluenesulfonyl chloride (3.11 g, 16.3 mmol) was slowly added and the solution allowed to warm and stir at ambient temperature for 24 hours. The reaction was quenched by addition of water (50 mL) and the organic layer separated, dried over $MgSO_4$ and concentrated *in* vacuo to afford an oil was purified by column chromatography (gradient elution: pet. ether: DCM 10:1 to 1:1 *v*/*v*) to give the title compound **2.60** as a colourless oil (3.02 g, 80% yield).

δH (400 MHz, $CDCl_3$) 7.80 (2 H, d, *J* 8.0, H-4), 7.32 (2 H, d, *J* 8.0, H-3), 4.10 (2 H, t, *J* 6.5, H-6), 3.72 (2 H, t, *J* 6.3, H-8), 2.45 (3H, s, H-1), 1.82-1.93 (2H, m, H-7); δC (101 MHz, $CDCl_3$) 145.0 (C-5), 132.5 (C-2), 130.0 (C-3), 127.7 (C-4), 67.1 (C-6), 47.1 (C-8), 28.3 (C-7), 21.7 (C-1). Found (ESI): $[M+H]^+$ 256.0747, $C_{10}H_{14}N_3O_3S$ requires 256.0750.

4,4',4''-((4-(3-Azidopropoxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) 2.61[66]

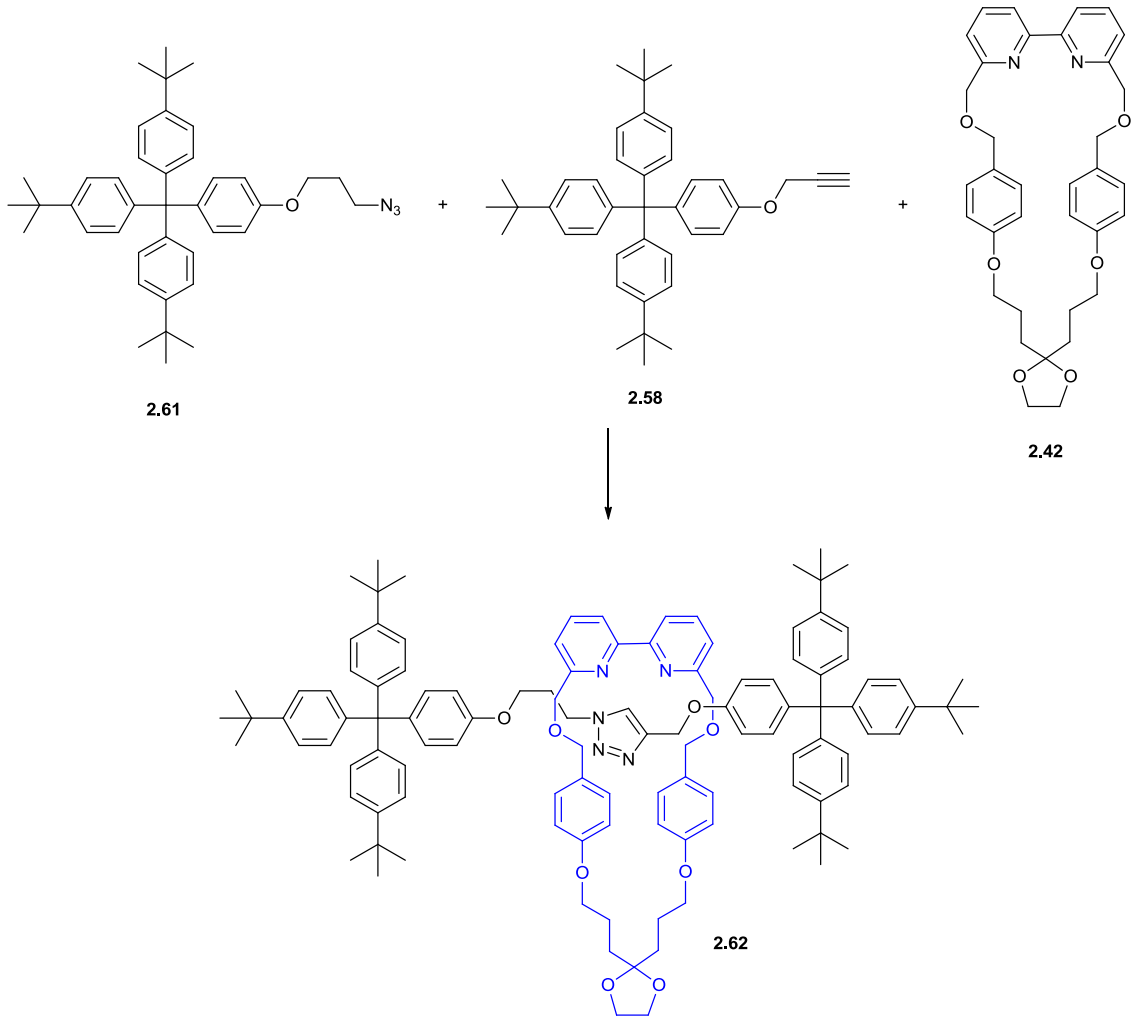


2.57 **2.61**

Potassium carbonate (1.00g, 7.2 mmol) was added to a stirring solution of 4-[tris-(4-*tert*-butyl-phenyl)-methyl]-phenol **2.57** (0.78 g, 1.55 mmol) and 3-azidopropyl tosylate **2.60** (395 mg, 1.55 mmol) in ethyl methyl ketone (20 mL). The resulting suspension was heated at 70°C for 18 h. Once cooled, the solution was filtered through a pad of Celite™ and concentrated *in vacuo*. The resulting residue was purified by column chromatography (pet. ether: DCM 8:2 *v/v*) to afford the title compound **2.61** as a colourless solid (0.66 g, 72% yield).

m.p. 210-212 °C [lit. m.p.[66] 212-214 °C]; δH (400 MHz, $CDCl_3$) 7.31 (6 H, d, *J* 8.6, H-5), 7.11 (2 H, d, *J* 8.9, H-9), 7.07 (6H, d, *J* 8.6, H-4), 6.81 (2H, d, *J* 8.9, H-10), 4.00 (2H, t, *J* 5.99, H-14), 3.51 (2 H, t, *J* 6.66, H-12), 1.99-2.05 (2 H, m, H-13), 1.30 (27 H, s, H-1); δC (101 MHz, $CDCl_3$) 156.0 (C-11), 148.2 (C-3), 144.0 (C-6), 139.9 (C-8), 132.1 (C-9), 130.5 (C-5), 124.1 (C-4), 112.5 (C-10), 64.2 (C-12), 62.9 (C-7), 48.1 (C-14), 34.3 (C-2), 31.4 (C-1), 28.8 (C-13). Found (ESI): $[M+H]^+$ 588.3952, $C_{40}H_{50}N_3O$ requires 588.3948.

General Experimental Procedure for the Attempted CuAAC Active Metal Template Synthesis of Rotaxane 2.62



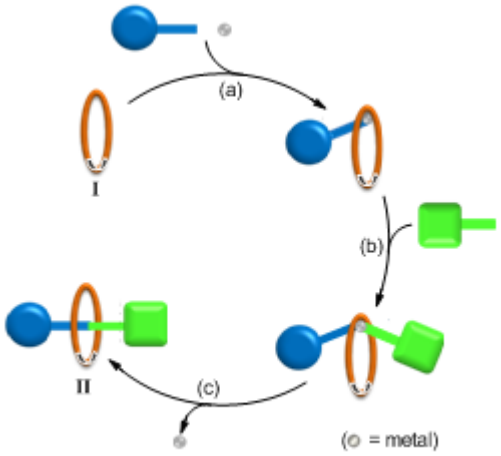
Macrocycle **2.42** (14 mg, 0.025 mmol, 1 eq.), $CuPF_6.(MeCN)_4$ (8.4 mg, 0.0225 mmol, 0.9 eq.), azide **2.58** (14 mg, 0.025 mmol, 1 eq.) and alkyne **2.61** (14 mg, 0.025 mmol, 1 eq.) were combined in CH_2Cl_2 (2.5 mL) in a sealed microwave tube which was then purged with N_2 and then heated at 80 °C for 72 h. The reaction mixture was subsequently diluted with fresh CH_2Cl_2 (50 mL) and washed with a saturated solution of EDTA in 17.5% aqueous NH_3 (50 mL). The aqueous phase was extracted twice with CH_2Cl_2 (50 mL), the organic extracts dried (Na_2SO_4) and the solvent removed under reduced pressure. Chromatography (gradient elution: 1. CH_2Cl_2, 2. MeOH-CH_2Cl_2, 0.5:99 *v*/*v*, 3. MeOH-CH_2Cl_2, 4:96 *v*/*v*) afforded a crude mixture containing [2]rotaxane product **2.62** and macrocycle **2.42**. See Figure 2.3 for stacked ^{1}H NMR.

CHAPTER 3 – STUDIES TOWARDS THE SYNTHESIS OF A C_1-SYMMETRIC BOX MACROCYCLE FOR USE IN THE ACTIVE METAL TEMPLATE SYNTHESIS OF A CYCLOCHIRAL ROTAXANE

3.1 Background

This chapter presents work conducted in collaboration with Pauline Glen. The work centres around access to planar chiral rotaxanes *via* an alternative approach to that presented in chapter 2.

The asymmetric active-template method to form planar chiral rotaxanes proposed is illustrated in Scheme 3.1. By utilising a cross-coupling reaction between two different half-threads with a macrocycle that lacks any element of symmetry (i.e. C_1-symmetric), with the faces of the metal-macrocycle complex being designed to be sterically distinct (e.g. by having point chirality), the approach of the first fragment should be selectively from the less sterically hindered face of the macrocycle. Approach of the second fragment from the opposite face followed by the metal-catalysed bond formation to form the [2]rotaxanes, should lead to an optically active, cyclochiral rotaxane. By then removing the point chirality within the macrocycle, the resulting rotaxane should then be left solely with cyclochirality.



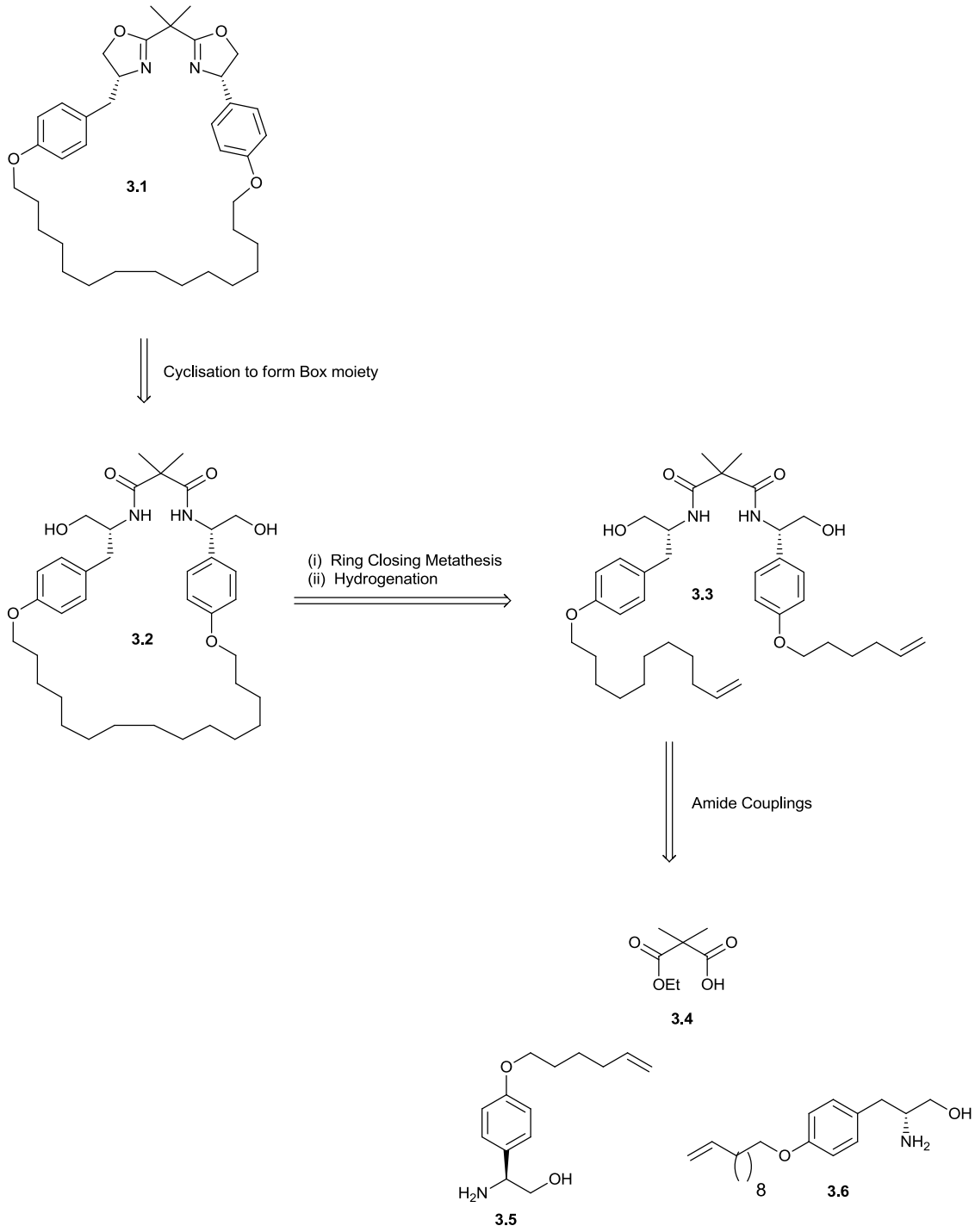
Scheme 3.1 Proposed asymmetric active-metal template for rotaxanes formation. (a) approach of 1st fragment to less sterically hindered face of asymmetric macrocycle I. (b) approach of 2nd fragment to opposite face. (c) covalent bond-forming step and demetallation to furnish chiral rotaxanes II.

The initial aim was to synthesise a suitable C_1-symmetric macrocycle with sterically different faces, which could ligate metal catalysed coupling reactions and whose point chirality could be removed after a rotaxane forming step. With these specifications in mind, bis(oxazoline) (Box) macrocycle **3.1**[134-136] was selected as suitable candidate macrocycle which could then be taken forward for use in rotaxane-forming reactions. The retrosynthetic disconnections required for the synthesis of macrocycle **3.1** are shown in Scheme 3.2. The ring closing metathesis/hydrogenation of precursor **3.3** was identified as the key macrocyclisation step, followed by cyclisation of **3.2** to the bis-oxazoline. The unsymmetrical fragment **3.3** would be assembled through successive amide couplings of dimethyl malonic acid monoethylester **3.4** with amino alcohols **3.5** and **3.6**.

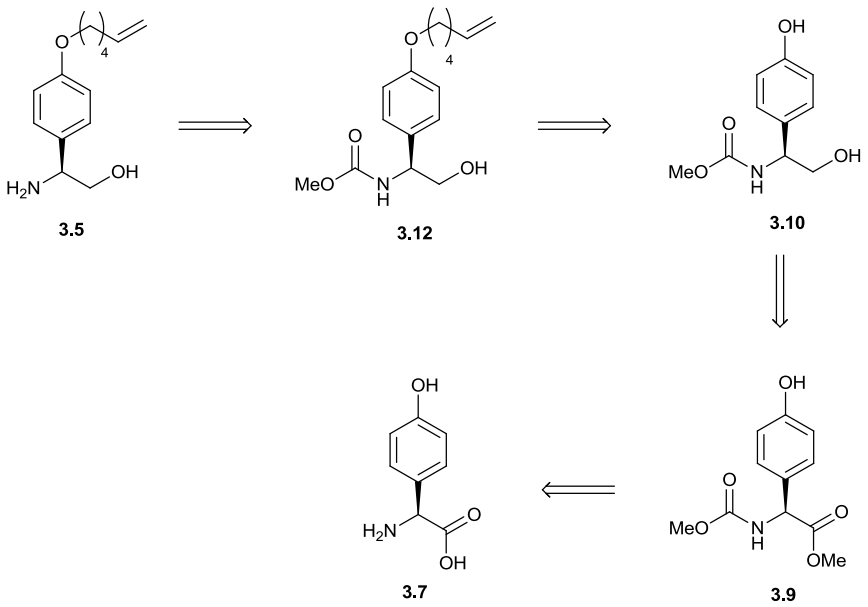
A pre-established small scale synthetic route, developed by Pauline Glen, to amino alcohols **3.5** and **3.6** is presented in Scheme 3.4 and Scheme 3.6 respectively. The synthetic steps required to access macrocycle precursor **3.3** from **3.4** to **3.6** are shown in Scheme 3.8.

3.2 Initial Route to Amino Alcohol 3.5 Developed by Pauline Glen

A retrosynthetic route to amino alcohol **3.5** is presented in Scheme 3.3. Amino alchohol **3.5** can be accessed from commercially available 4-hydroxy-L-phenylglycine *via* consecutive protection, reduction, alkylation and deprotection. By conducting the reduction step before the alkylation step, the acidity of the proton at the chiral centre is reduced which, in turn, reduces the likelihood of epimerisation under the basic conditions required for alkylation at the phenolic position of **3.10**.

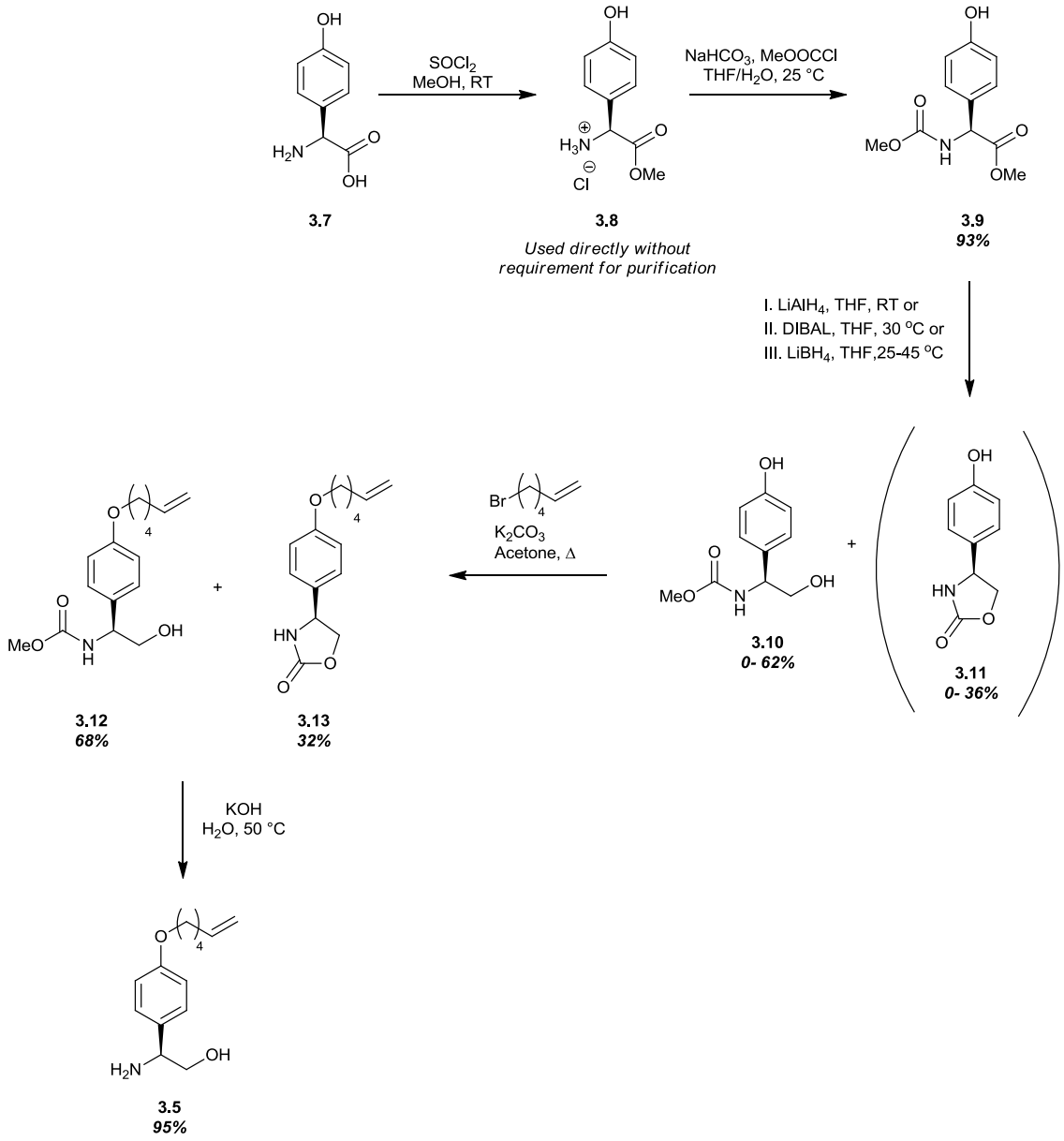


Scheme 3.2 Retrosynthetic analysis of target macrocycle 3.1



Scheme 3.3 Retrosynthetic route to amino alcohol 3.5

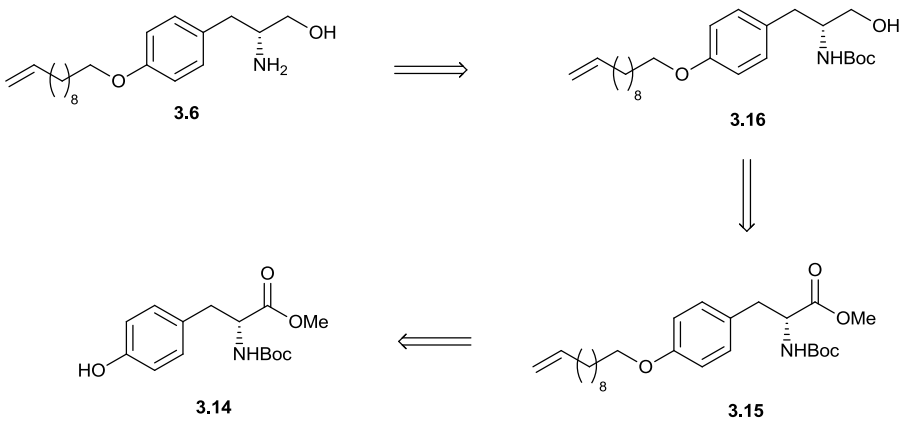
During the initial synthesis (Scheme 3.4), the carbamate protection of 4-hydroxy-L-phenylglycine **3.7** by treatment with methyl chloroformate and sodium bicarbonate was achieved in 98% yield, following a procedure by Huang and co-workers.[137] Next, reduction of **3.9** was conducted using a range of reducing agents, all resulting in low to moderate yields and mixed reaction products (see Table 3.1). Alcohol **3.10** was then treated with potassium carbonate and 6-bromo-1-hexene in acetone and underwent alkylation to afford an ether mixture (**3.12** and **3.13** in 68% and 32% yield respectively). Treatment of both **3.12** and **3.13** with aqueous potassium hydroxide resulted in amino alcohol **3.5** in 95% yield, producing *ca*. 9 grams of **3.5**, albeit this was quickly consumed in further experimentation within the group.



Scheme 3.4 Pre-established small scale synthetic route to amino alcohol 3.5

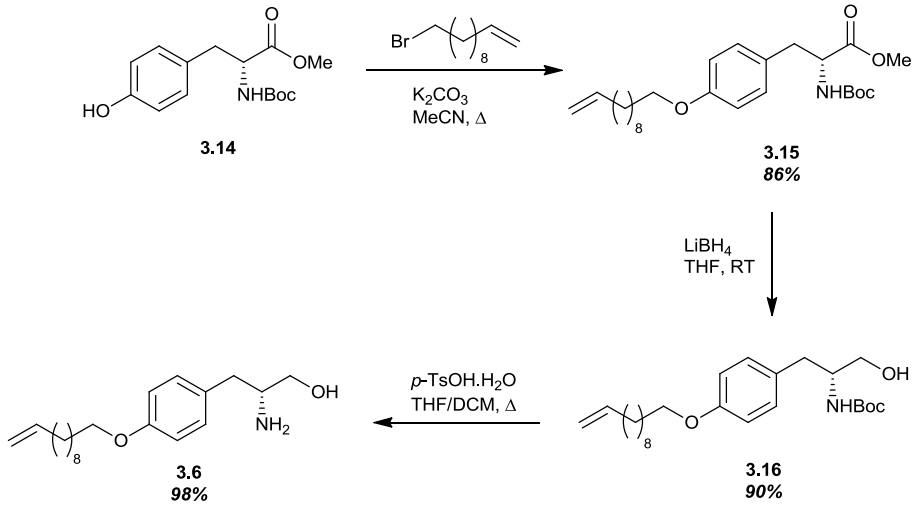
3.3 Initial Route to Amino Alcohol 3.6 Developed by Pauline Glen

A retrosynthetic route to amino alcohol **3.6** is shown in Scheme 3.5. Amino alcohol **3.6** can be accessed from commercially available Boc-D-tyrosine methyl ester **3.14** through successive alkylation, reduction and deprotection steps.



Scheme 3.5 Retrosynthetic route to amino alcohol 3.14

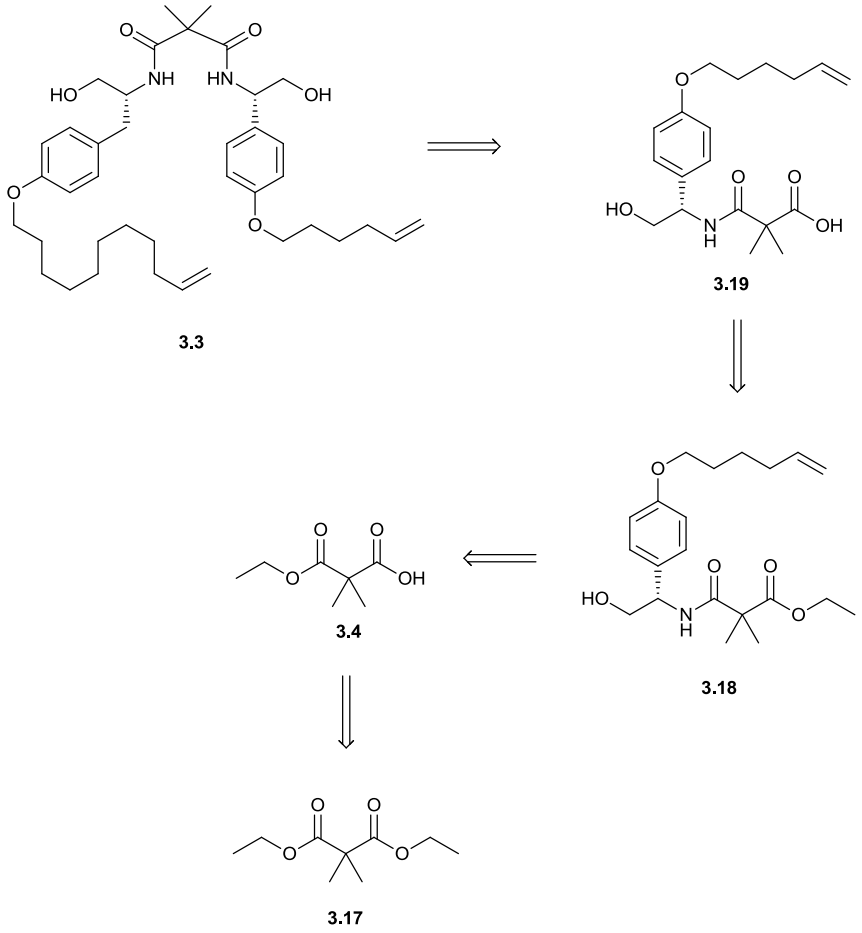
During small scale synthesis (Scheme 3.6), Boc-D-tyrosine methyl ester **3.14** underwent alkylation with 11-bromo-1-undecene in acetonitrile to provide ether **3.15** in an 86% yield. Treatment of the resulting ether **3.15** with lithium borohydride reduced the ester and afforded alcohol **3.16** in 90% yield. Removal of the *N*- Boc protecting group using *p*-TsOH yielded amino alcohol **3.6** in 98% yield, producing *ca*. 10 grams in total. Again this was consumed quickly during further experimentation within the group.



Scheme 3.6 Pre-established small scale synthetic route to amino alcohol 3.6

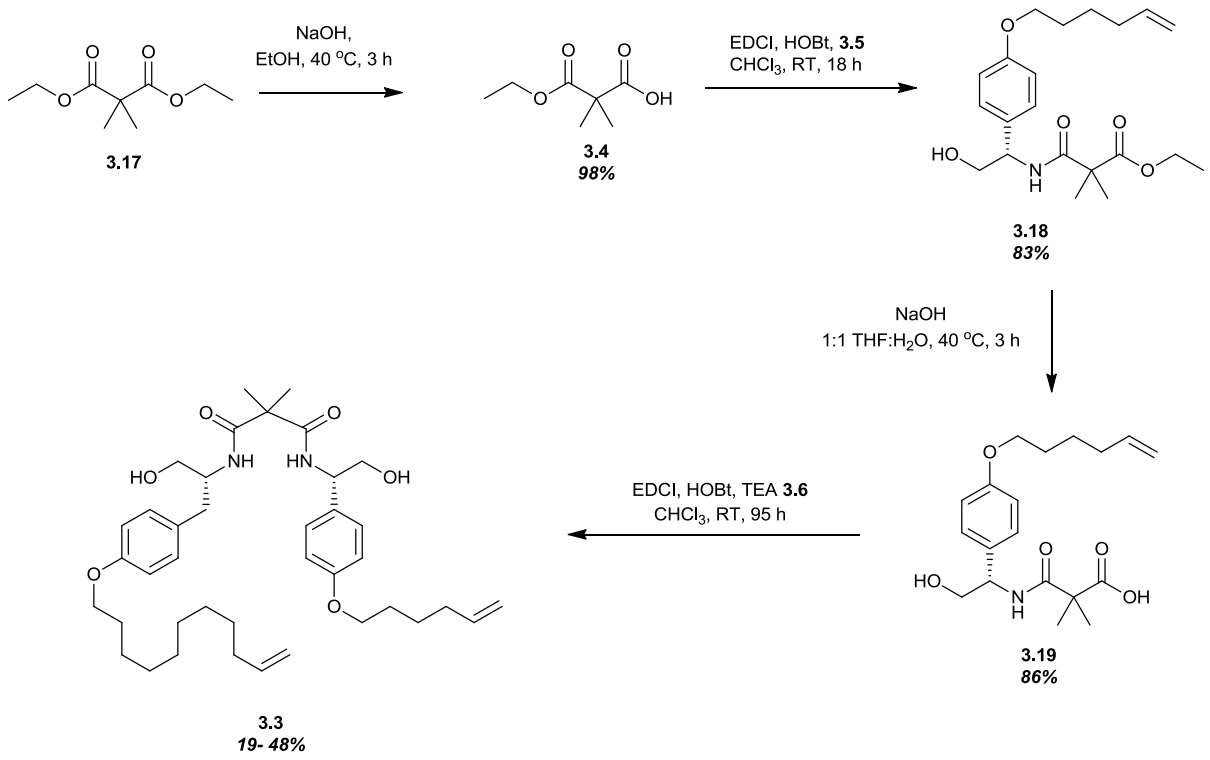
3.4 Initial Route to Macrocycle Precursor 3.3 Developed by Pauline Glen

A retrosynthetic route to macrocycle precursor **3.3** is shown in Scheme 3.7. Precursor **3.3** can be accessed through successive amide coupling reactions using fragments **3.4**, **3.5** and **3.6**. Acid **3.4** is itself accessed by hydrolysis of commercially available dimethyl diethyl malonate **3.17**.



Scheme 3.7 Retrosynthetic route to macrocycle precursor 3.3

During small scale synthesis of macrocycle precursor **3.3** (Scheme 3.8), dimethyl diethyl malonate **3.17** underwent base induced hydrolysis (NaOH) to afford acid **3.4** in 98% yield. Subsequent EDCI mediated coupling of **3.4** and **3.5** gave **3.18** in 83% yield. Next, a second NaOH induced ester hydrolysis furnished acid **3.19** from **3.18** in 86% yield. Finally, another EDCI mediated coupling of **3.19** and **3.6** was attempted. Initially the same reaction conditions used for the coupling of **3.4** and **3.5** were used but this afforded only 19% yield of **3.3**. By addition of excess triethylamine, the yield was then improved to a moderate 48% yield of macrocycle precursor **3.3** (*ca*. 2.5 grams).

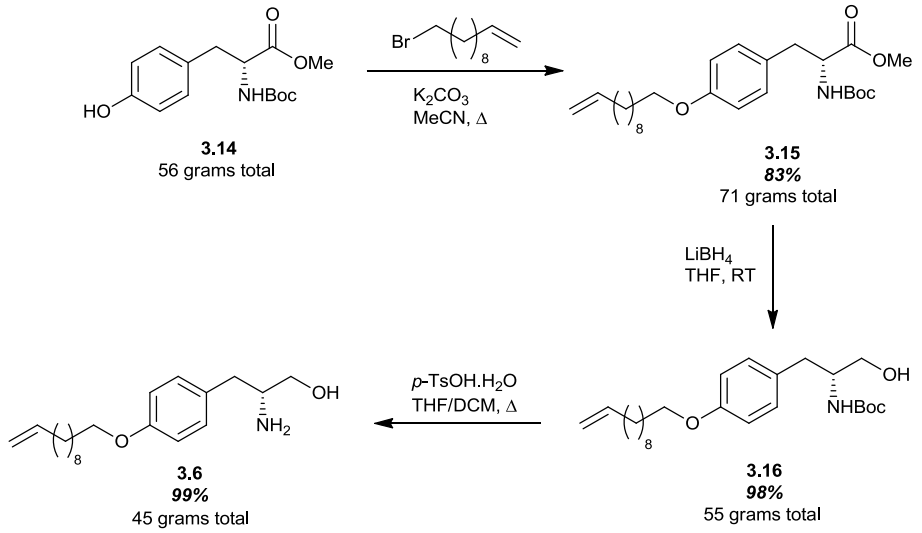


Scheme 3.8 Pre-established small scale synthetic route to macrocycle precursor 3.3

At the time, the initial routes presented in Scheme 3.4, Scheme 3.6 and Scheme 3.8 had only permitted a very small quantity of macrocycle **3.2** to be synthesised and partially characterised. Furthermore, the remaining amount of several key precursors was finite due to other experimentation within the group. This was, in part, due to the number of steps in the synthesis, compared to the mass of starting materials used during the small scale investigative reactions conducted by Pauline, and compounded by the low and moderate yielding steps which occurred throughout the synthetic pathway.

It was clear, therefore, that in order to access an appreciable quantity of macrocycle **3.2** for full characterisation and further experimentation, the synthetic route to precursor **3.3** would have to be scaled up and low yielding steps further developed and optimised to minimise losses.

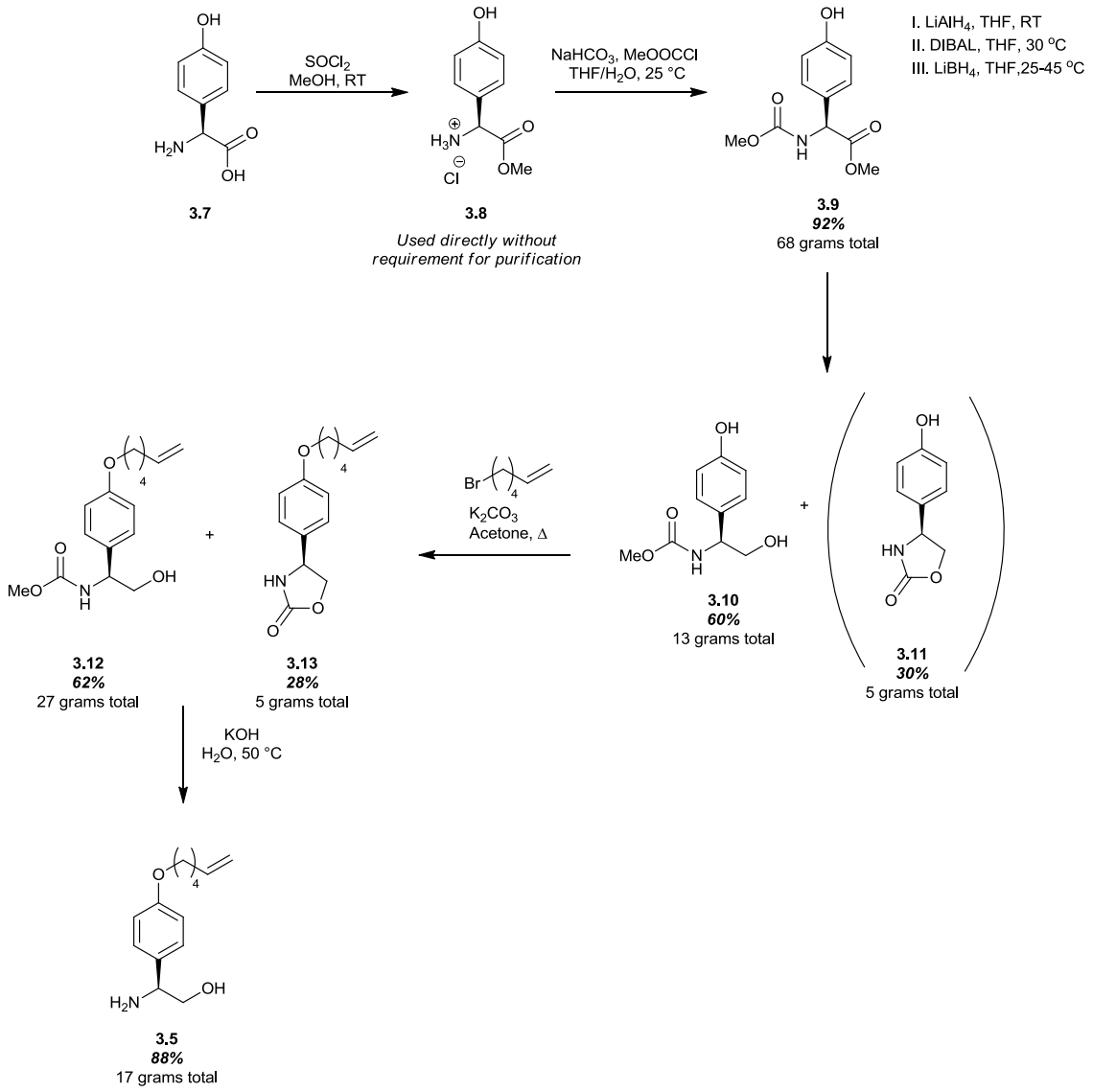
3.5 Scale up Synthesis of Precursor 3.6



Scheme 3.9 Scale up synthesis of amino alcohol 3.6

The scale-up synthesis of precursor **3.6** (Scheme 3.9) again began with Boc-D-tyrosine methyl ester **3.14** which readily underwent alkylation with 11-bromo-1-undecene and potassium carbonate in acetonitrile to afford ether **3.15** in an 83% yield (71 gram scale). This yield was found to be slightly lower than that achieved during the initial small scale development of the reaction route (86%). However, conducting the reaction on this scale afforded an 18 fold increase in the amount of **3.15** which could be taken forward. Next, alcohol **3.16** was synthesised directly from ester **3.15** *via* a lithium borohydride reduction of the ester. An improved yield of 98% (compared to 90% achieved on small scale) was achieved by carefully monitoring the internal temperature of the reaction during addition of the reducing agent, ensuring that the temperature did not exceed 5 ^{o}C. This was thought to decrease the likelihood of any potential side reactions. Furthermore, the reaction time was reduced from 43 h to within 16 h and, pleasingly, the near quantitative yield meant that the product could be purified on scale (55 g) by simply triturating with cold *n*-hexane, rather than using flash chromatography. Removal of the *N*- Boc protecting group on **3.16**, to afford amino alcohol **3.6** was routinely achieved in quantitative yield when conducted on *ca*. 60 g scale by reaction of **3.16** with tosic acid in THF/H_2O. The reaction was complete within 16 hours.

3.6 Scale up Synthesis of Precursor 3.5



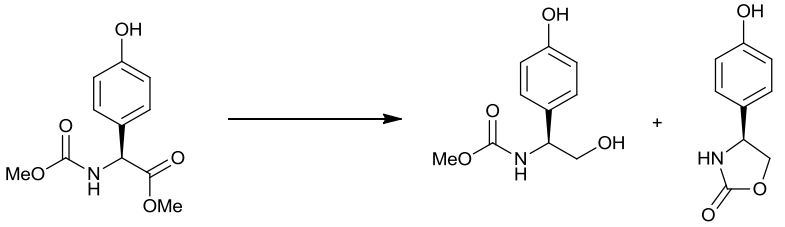
Scheme 3.10 On scale synthesis of amino alcohol 3.5

Preparation of **3.5** (Scheme 3.10) began with commercially available 4-hydroxy-L-phenylglycine **3.7**. Following the same protection procedure used during the small scale synthesis, protection of the amine moiety of **3.7** was achieved in 92% yield (68 g **3.9** was afforded). Although the yield was comparable to that achieved when reaction was conducted on a 10 fold smaller scale, the ^{1}H NMR spectrum of the scaled up crude reaction product revealed some unidentified impurities. Rather than using this impure product directly, it was found that the compound **3.9** could be easily purified by recrystallisation from EtOAc/ *n*-hexane rather than using column chromatography.

With **3.9** in hand, the next stage of the synthesis involved a reduction of the ester moiety of **3.9** to the corresponding primary alcohol of **3.10**. On small scale, this step had

proved particularly problematic. A series of reducing agents had been utilised as shown in Table 3.1. Using $LiAlH_4$ (powder form) afforded only oxazolidinone **3.11** in 35% yield (resulting from reaction of the intermediate alkoxide with the carbamate group to afford the 5-membered ring). When the reducing agent was changed to DIBAL, a low yielding mixture of **3.10** and **3.11** (19% and 36% respectively) was observed. Finally, using lithium borohydride as the reducing agent, a moderate yield of 62% of **3.10** had been achieved, with no observation of **3.11**.

In order for any large scale preparatio of precursor **3.5** to be viable, it was identified that improving this step in the synthesis was critical. It was postulated that both **3.10** and **3.11** could be viable reaction intermediates towards **3.5** as the basic conditions used in the final carbamate deprotection step would ring open any undesired oxazolidinone moiety to afford the target amino alcohol **3.5** (after alkylation of the phenolic oxygen).



3.9 3.10 3.11

Entry	Reducing Agent	Yield Of 3.10	Yield Of 3.11
1[a]	$LiAlH_4$	0	35
2[b]	DIBAL	19	36
3[c]	$LiBH_4$	62	0

[a] Reagents and conditions: $LiAlH_4$, THF, RT, 18 h. [b] Reagents and conditions: DIBAL, THF, 30 °C, 120 h. [c] Reagents and conditions: $LiBH_4$, THF, 25 °C, 66.5 h, 40 °C, 43.5 h.

Table 3.1 Reduction of Ester 3.9 attempted by Pauline Glen

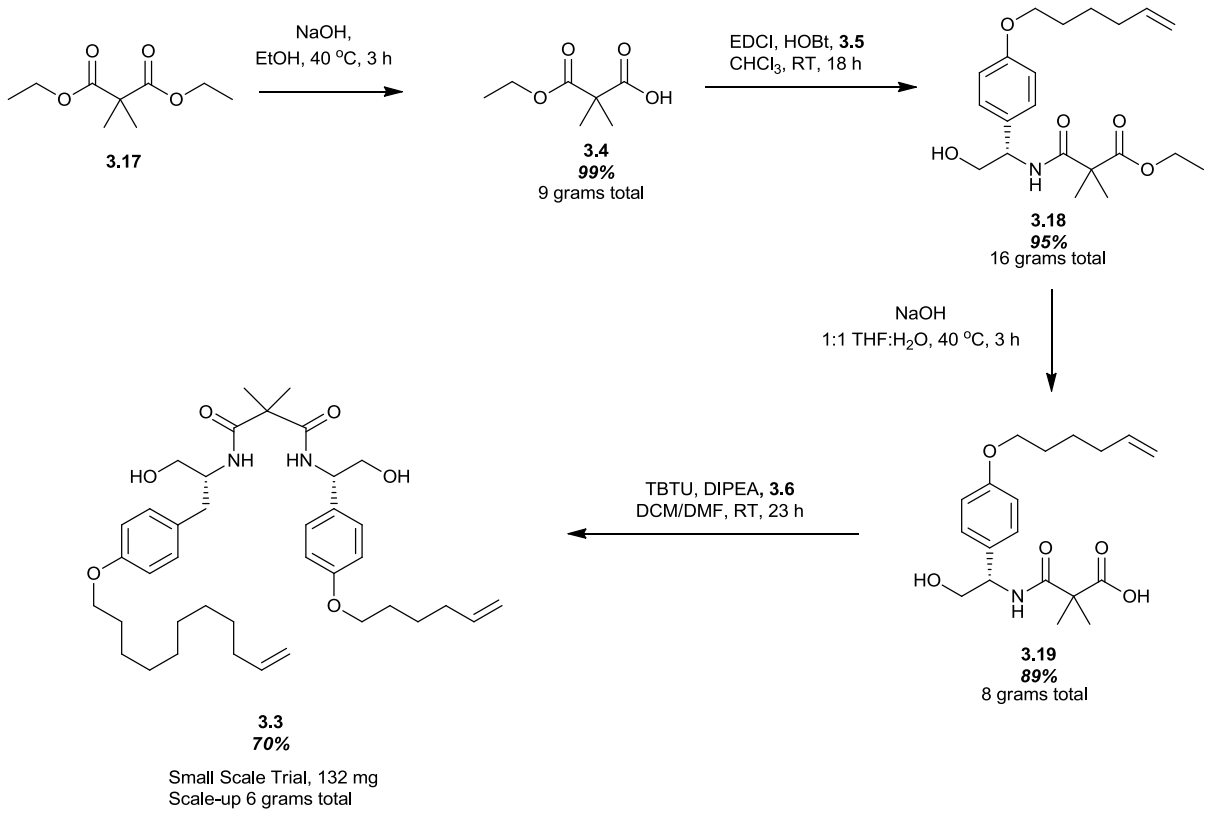
It was postulated that modification of the work-up condition pertaining to the use of $LiAlH_4$ for the reduction of **3.9** may afford an improved yield of **3.10** and/or **3.11**. Formerly, the reaction mixture was simply quenched with a mixture of water andmethanol, filtered through Celite™ and the pH of the resulting filtrate adjusted to pH 1 prior to extraction into an organic solvent. Instead a Fieser[138] method (successive additions of water, aqueous 15% NaOH and then water) was used to liberate products **3.10** and **3.11** from the crude reaction mixture. Following careful work-up and purification by column chromatography, a combined yield of 90% (60% **3.10** and 30% **3.11**) was achieved on large scale. By improving the conversion and yield of this

reaction to afford a pair of useable products (**3.10** and **3.11**), the losses in mass seen previously no longer impacted on large scale production of **3.5**.

Having synthesised a **3.10** / **3.11** mixture, the next stage in the synthesis involved alkylation at the phenolic oxygen with 6-bromohex-1-ene. Following the precedent set during small the small scale synthesis of **3.12** and **3.13**, successful alkylation of **3.10** and **3.11** on 42 gram scale afforded a mixture of **3.12** and **3.13** in 62% and 28% yield respectively. These yields were comparable to those achieved for the small scale reaction where yields of 68% (**3.12**) and 32% (**3.13**) had been achieved.

The final step in the synthesis of precursor **3.5** was the deprotection and ring opening of compounds **3.12** and **3.13** with base (KOH) to afford **3.5**. This reaction was conducted on *ca*. 24 gram scale in 8 h to afford **3.5** in 88% yield. Although this yield was slightly lower than what had been achieved with the smaller scale reaction (95%), this was deemed satisfactory for scale-up purposes.

3.7 Scale up Synthesis of Precursor 3.4 and 3.3



Scheme 3.11 On scale synthesis of macrocycle precursor 3.3

Dimethyl malonic acid monoethylester **3.4** was readily prepared on multi-gram scale in quantitative yield by treating commercially available dimethyl diethyl malonate **3.17** with an aqueous solution of sodium hydroxide (Scheme 3.11).

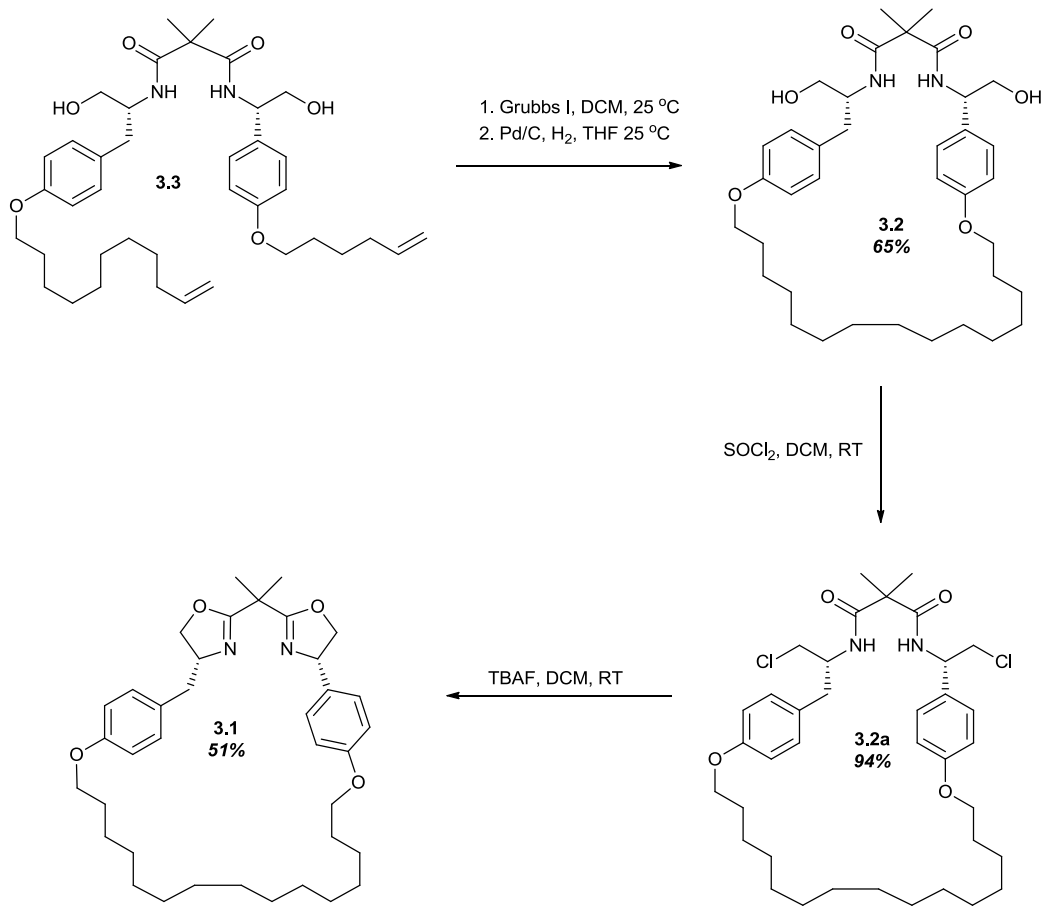
Having synthesised acid **3.4** and amino alcohol **3.5** in reasonable quantity, the first of two amide coupling reactions were conducted. Following precedent set during small scale preparations of **3.18** from **3.4** and **3.5** (83% yield), an EDCI-promoted coupling reaction in chloroform, with the addition of HOBt to inhibit racemisation, afforded an improved yield of 95% when conducted on moderately large scale.

Hydrolysis of ester **3.18** to acid **3.19** was readily achieved on scale-up, in a slightly improved yield (89%), by reaction of **3.18** with 10 equivalents of NaOH in aqueous THF.

The final synthetic step towards macrocycle precursor **3.3** was the coupling of acid **3.19** with amino alcohol **3.6**. During small scale investigative preparations, a second EDCI-promoted coupling had been used to achieve this, albeit with formation of relatively complex product mixtures, resulting in low yields of **3.3** (19-48%), in addition to a 95 hour reaction time. To address this problem, a small scale reaction was carried out in which to probe the suitability of TBTU as an alternative coupling agent to EDCI. Pleasingly, reaction of **3.19** and **3.6** with TBTU and DIPEA in DCM/DMF afforded macrocycle precursor **3.3** in 70% yield. Furthermore, the pure product could be easily isolated by column chromatography as the product mixture contained fewer unidentified side products than when EDCI had been used. With this success, this reaction was later conducted on *ca*. 6 gram scale to afford a slight improvement in yield to 73%.

3.8 Synthesis of Macrocycle 3.1

By improving the low yielding steps encountered during the small scale synthesis of macrocycle precursor **3.3** and conducting reactions on a much larger scale, several grams of macrocycle precursor **3.3** had been successfully synthesised. This allowed macrocycle **3.1** to be accessed from precursor **3.3** in three steps, using the method developed by Pauline during small scale preparations (Scheme 3.12).



Scheme 3.12 Synthetic route to target box macrocycle 3.1 conducted by Pauline Glen

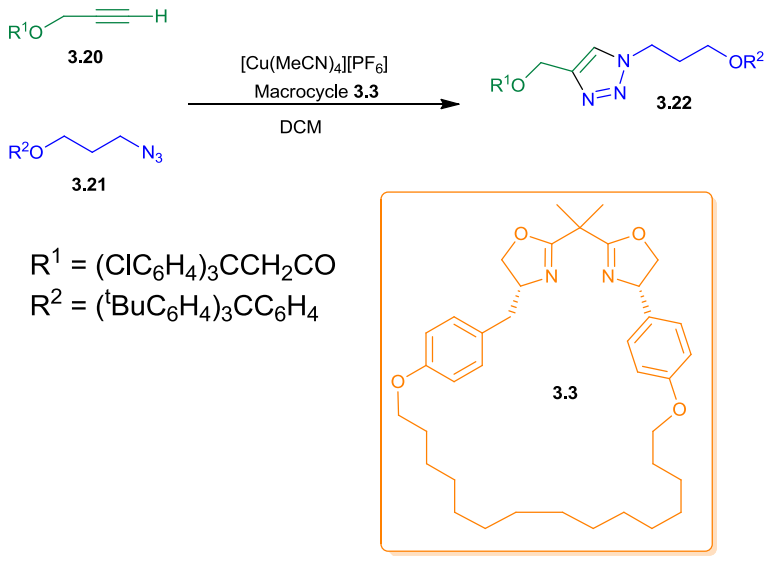
Treatment of diene **3.3** with Grubbs' first generation catalyst at high dilution in DCM, followed by hydrogenation of the resulting alkene moiety with a Pd/C catalyst resulted in macrocycle **3.2** in 65% yield over two steps. Target box macrocycle **3.1** was then synthesised from bis-amide macrocycle **3.2** in two steps. Firstly, **3.2** was reacted with thionyl chloride to give dichloride macrocycle **3.2a** in high yield (94%). Cyclisation to box macrocycle **3.1** was then achieved by reaction of **3.2a** with TBAF[139] in 51% yield.

3.9 Conclusion

The primary objective of the multi-gram synthesis of the C_1 symmetric macrocycle **3.1** was successfully achieved *via* two main processes. Firstly, by improving low yielding steps encountered during the small scale route to macrocycle precursor **3.3**, losses in mass were minimised. Secondly, selected reactions were optimised and conducted on multi-gram scale throughout the synthesis. In addition to permitting several grams of diene **3.3** to be synthesised, reaction times were generally decreased and conversions to desirable products increased. This, in turn, allowed bulk recrystallisation techniques to

be developed for product purification as opposed to laborious large scale purifications by means of column chromatography.

The application of macrocycle **3.3** towards rotaxane forming reactions was later reported by our group[140] (e.g. Scheme 3.13). Unfortunately macrocycle **3.3** was ultimately found to be not suitable for the synthesis of rotaxanes through the active template methods investigated (Cadiot-Chodkiewicz, CuAAC and oxidative Heck, e.g. Scheme 3.13). The results of the model studies and attempts at rotaxane formation nevertheless provide valuable insight into the behavior of bis(oxazoline) as ligands (which had previously not or scarcely investigated) in these copper- and palladium-catalysed reactions. Despite control reactions showing that box macrocycle **3.3** can successfully bind to an active metal template species, in the future a more structurally rigid macrocycle may be necessary to prevent 'de-threading' of the rotaxane species back to the corresponding non-interlocked thread and macrocycle as only trace quantities of rotaxane were observed.



Entry	Temp. (°C)	Conc. (mM) w.r.t. 3.3	Time	Conv. of alkyne 3.20 to thread 3.22 (%)
1	25	400	48 h	100

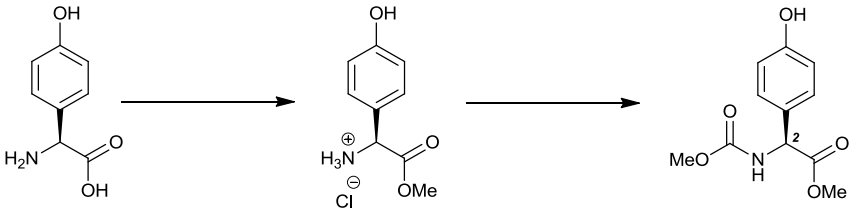
Scheme 3.13 Example of Attempt to Form Rotaxane Using Macrocycle 3.3 using a CuAAC Active Metal Template Reaction.[140] Non-interlocked thread formed, only trace rotaxane observed.

3.10 Experimental

General Information

^{1}H NMR spectra were recorded on Bruker AV 300 and AV 400 spectrometers at 200 and 400 MHz respectively and referenced to residual solvent. ^{13}C NMR spectra were recorded using the same spectrometers at 75 and 100 MHz respectively. Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks (e.g. $CDCl_3$ at δ_H 7.26). *J* values are given in Hz and s, d, dd, t, q, quint and m abbreviations correspond to singlet, doublet, doublet of doublet, triplet, quartet, quintet and multiplet. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat to a diamond/ZnSe plate. Melting points were recorded on a Stuart Scientific SMP10 and are uncorrected. Flash column chromatography was carried out using Matrix silica gel 60 from Fisher Chemicals and TLC was performed using Merck silica gel 60 F254 pre-coated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$ or aqueous acidic ammonium molybdate as appropriate. Unless otherwise stated, reagents and solvents were purchased from commercial sources and used with no further purification. Pet. ether refers to petroleum ether which distils in the range 40 – 60 °C.

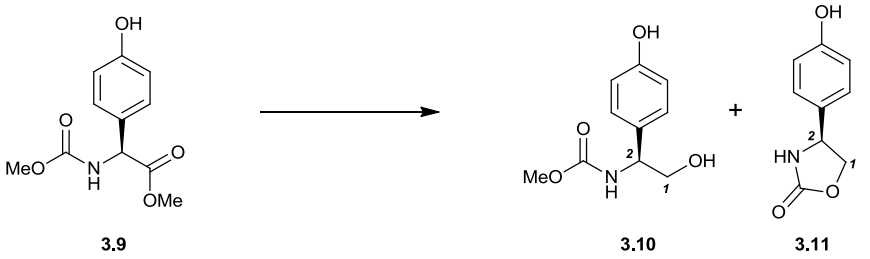
(*S*)-Methyl 2-(4-hydroxyphenyl)-2-((methoxycarbonyl)amino)acetate 3.9



A 2L round bottom flask equipped with a magnetic stirrer was charged with (*S*)-2-amino-2-(4-hydroxyphenyl)acetic acid **3.7** (52.5 g, 0.31 mol) and subsequently suspended in 1.1 L of MeOH. Thionyl chloride (41.0 mL, 0.56 mol) was then added via a dropping funnel under N_2 and the reaction stirred at 25 $^{\circ}$C for 16 hours. The reaction was then concentrated *in vacuo* to afford a colourless salt which was washed thoroughly with Et_2O (200 mL) and dried by vacuum filtration. The crude (*S*)-1-(4-hydroxyphenyl)-2-methoxy-2-oxoethanaminium chloride intermediate product **3.8** (68.0 g, 0.31 mol) was then transferred to a 2L round-bottomed flask equipped with a magnetic stirrer, charged with $NaHCO_3$ (78.8 g, 0.94 mol) and the mixture suspended in 1:1 *v/v* THF/H_2O (1L). Methyl chloroformate (26.6 mL, 0.34 mol) was added *via* a dropping funnel under N_2, taking care to monitor the resulting gas evolution. The reaction was stirred vigorously at 25 °C for 16 hours. The reaction was then quenched by addition of H_2O (500 mL) and extracted thrice with EtOAc (500 mL). The organic extracts were then combined and dried over $MgSO_4$ before being concentrated *in vacuo* to furnish an off-white solid. The crude product was recrystallised from EtOAc/*n*-hexane to afford the title compound as a colourless solid (68.8 g, 92%).

Mp 138-139 °C; R_f 0.29 (1:1 ethyl acetate-petroleum ether) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{21}$ +153.5 (*c* 0.99, MeOH); ν_{max} /cm^{-1} 3371 (NH), 3279 br (OH), 3000 (CH), 2951 (CH), 2845 (CH), 1756 (C=O), 1698 (C=O),1616 (Ar C=C), 1598 (Ar C=C), 1510 (Ar C=C), 1440 (Ar C=C), 1264 (N-CO-O), 1213 (C-OH), 1171 (Ar CH), 1059 (N-COO), 1011 (C-OH), 780 (Ar CH); δH (200 MHz, C_2D_6SO) 8.00 (1 H, d, *J* 7.5, N*H*), 7.29 - 7.04 (2 H, m, Ar-*H*), 6.79 - 6.60 (2 H, m, Ar-*H*), 5.08 (1 H, d, *J* 7.5, *H*-2), 3.60 (3 H, s, OCH_3), 3.55 (3 H, s, OCH_3); δC (50 MHz, C_2D_6SO) 171.8 (*C*), 157.4 (*C*), 156.5 (*C*), 129.1 (*C*H), 126.4 (*C*), 115.3 (*C*H), 57.5 (*C*H), 52.1 (*C*H_3), 51.6 (*C*H_3); Found (ESI): $[M+H]^+$ 240.0869, $C_{11}H_{14}NO_5$ requires 240.0866.

(*S*)-Methyl (2-hydroxy-1-(4-hydroxyphenyl)ethyl)carbamate 3.10 & (*S*)-4-(4-hydroxyphenyl)oxazolidin-2-one 3.11



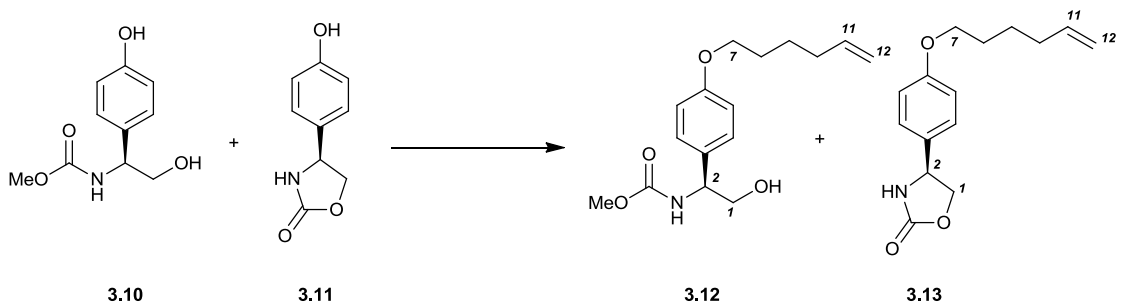
3.9 3.10 3.11

To a 3 L round-bottomed flask equipped with a magnetic stirrer was added (S)-methyl 2-(4-hydroxyphenyl)-2-((methoxycarbonyl)amino)acetate **3.9** (24.0 g, 0.10 mol) then dissolved in THF (1.5 L) and cooled to 0 ^{o}C. The flask was flushed with N_2 and $LiAlH_4$ pellets (7.6 g, 0.20 mol) were added portionwise. The reaction was stirred for 1 hour at 0 °C and then allowed to warm to room temperature over 24 hours. The reaction mixture was then re-cooled to 0 °C and quenched via a modified Fieser method. To the cooled reaction mixture was carefully added 16 mL of ice-cold H_2O and left to stir for 10 minutes. 16 mL $NaOH_{(aq)}$ (15%) was then added and the reaction mixture stirred for a further 10 minutes. H_2O (48 mL) was then added to the reaction mixture and the reaction allowed to stir for a further 30 minutes to ensure maximum product recovery. The internal temperature of the reaction mixture was kept below 10 °C throughout the workup. The resulting fine precipitate was then removed by vacuum filtration and the filtrate dried with $MgSO_4$ before being concentrated *in vacuo* to afford an off-white solid. Purification by flash column chromatography (100% pet. ether, 1:1 pet. ether:EtOAc, 100% EtOAc) afforded the title compounds (12.7 g, 60% product **3.10**, 5.4 g, 30% product **3.11**) as colourless solids.

3.10: Mp 112-115 °C; R_f 0.20 (2:1 ethyl acetate-petroleum ether) viewed: UV (254 nm) or CAM dip; $[\alpha]_D^{18}$ +70.6 (c 1.02, MeOH); ν_{max} /cm^{-1} 3339 (OH/NH), 2944 (CH), 1685 (C=O), 1600 (NH), 1534 (Ar C=C), 1517 (Ar C=C), 1452 (Ar C=C), 1360 (OH), 1218 (Ar CO), 1173 (N-CO-O), 1058 (N-CO-O), 1013 (C-O); δH (300 MHz, C_2D_6SO) 7.40 (1 H, d, *J* 8.1, N*H*), 7.13 - 7.03 (2 H, m, Ar-*H*), 6.78 - 6.53 (2 H, m, Ar-*H*), 4.75 (1 H, t, *J* 5.5, O*H*), 4.46 (1 H, dt, *J* 8.1, 6.2, *H*-2), 3.50 (3 H, s, OCH_3), 3.44 (2 H, t, *J* 6.2, *H*-1); δC (75 MHz, C_2D_6SO) 156.8 (*C*), 156.7 (*C*), 132.1 (*C*), 128.3 (*C*H), 115.2 (*C*H), 65.3 (*C*H_2), 57.0 (*C*H), 51.6 (*C*H_3); Found (ESI): [M+H]+ 212.0919, $C_{10}H_{14}NO_4$ requires 212.0917.

3.11: Mp 203-205 °C [lit.[141] mp 201-204 °C]; R_f 0.32 (4:1 ethyl acetate-petrol ether) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{20}$ (*c* 1.48, MeOH) [lit.[141] $[\alpha]_D^{20}$ +41.4 (*c* 1.7, EtOH)]; ν_{max} /cm^{-1} 3304 (NH), 3226 br (OH), 2925 (CH), 2833 (CH), 1724 (C=O), 1614 (Ar C=C), 1601 (NH), 1513 (Ar C=C), 1487 (Ar C=C), 1374 (OH), 1238 (N-COO), 1212 (C-O), 1029 (N-CO-O), 825 (Ar CH); δH (300 MHz, C_2D_6SO) 8.04 (1 H, s, N*H*), 7.19 - 7.09 (2 H, m, Ar-*H*), 6.82 - 6.72 (2 H, m, Ar-*H*), 4.81 (1 H, dd, *J* 8.6, 7.0, *H*-1a), 4.60 (1 H, dd, *J* 8.6, 8.6, *H*-2), 3.95 (1 H, dd, *J* 8.6, 7.0, *H*-1b); δC (75 MHz, C_2D_6SO) 158.9 (*C*), 157.2 (*C*), 131.0 (*C*), 127.4 (*C*H), 115.4 (*C*H), 71.6 (CH_2), 54.8 (*C*H); Found (ESI): $[M+H]^+$ 180.0654, $C_9H_{10}NO_3$ requires 180.0655.

(*S*)-Methyl 1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethyl carbamate 3.12 & (*S*)-4-(4-(hex-5-en-1-yloxy)phenyl)oxazolidin-2-one 3.13

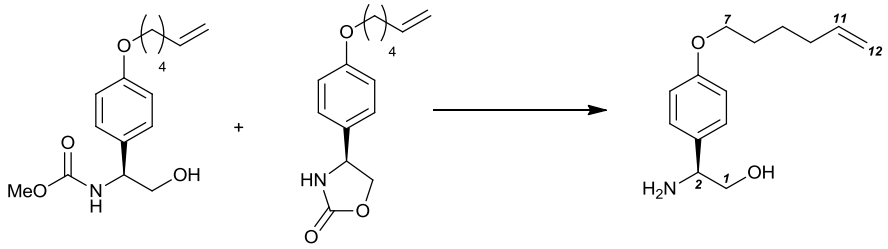


To a 2L round-bottomed flask equipped with a reflux condenser and magnetic stirrer was added (*S*)-methyl 2-hydroxy-1-(4-hydroxyphenyl)ethylcarbamate **3.10** (29.4 g, 139.2 mmol), (*S*)-4-(4-hydroxyphenyl)oxazolidin-2-one **3.11** (12.6 g, 70.3 mmol), potassium carbonate (31.85 g, 230.5 mmol) and acetone (500 mL). The resulting mixture was heated at reflux for 24 h. After cooling, the reaction was quenched with water (300 mL) and the aqueous layer extracted thrice with ethyl acetate (500 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (1:1 *v/v* ethyl acetate-petroleum ether to 10:1 *v/v* ethyl acetate-petroleum ether) to afford the title compounds as colourless solids: **3.12** (26.5 g, 62%) and **3.13 (**5.1 g, 28%).

3.12: Mp 73-74 °C; R_f 0.48 (4:1 ethyl acetate-petroleum ether) viewed: UV (254 nm) or CAM dip; $[\alpha]_D^{20}$ +64.0 (*c* 1.00, CHCl3); ν_{max} /cm^{-1} 3337 br (OH, NH), 2945 (CH), 2867 (CH), 1692 (C=O), 1641 (C=C), 1613 (Ar C=C), 1586 (Ar C=C), 1533 (NH), 1513 (Ar C=C), 1478 (Ar C=C), 1460 (OH), 1265 (N-CO-O), 1241 br (C-O-C), 1178 (Ar CH), 1114 (CO-C), 1089 (C-O), 1056 (N-CO-O), 1030 (C-OH), 997 (=CH), 915 (=CH), 825 (Ar CH), 779 (OH); δH (200 MHz, $CDCl_3$) 7.25 - 7.16 (2 H, m, Ar-*H*), 6.96 - 6.72 (2 H, m, Ar-*H*), 5.83 (1 H, ddt, *J* 17.0, 10.4, 6.6, *H*-11), 5.37 (1 H, d, *J* 7.1, N*H*), 5.11 - 4.92 (2 H, m, *H*-12), 4.77 (1 H, dd, *J* 7.1, 5.4, *H*-2), 3.95 (2 H, t, *J* 6.2, *H*-7), 3.84 (2 H, t, *J* 5.4, *H*-1), 3.68 (3 H, s, O*CH*$_3$), 2.31-2.04 (3 H, m, alkyl-*H*, O*H*), 1.90 - 1.69 (2 H, m, alkyl-*H*), 1.68 - 1.46 (2 H, m, alkyl-*H*); δC (50 MHz, $CDCl_3$) 158.8 (*C*), 157.1 (*C*), 138.5 (*C*H), 130.9 (C), 127.7 (*C*H), 114.8 (*C*H), (plus 1 overlapping *C*H_2 peak), 67.8 (*C*H_2), 66.6 (*C*H_2), 56.6 (*C*H), 52.4 (*C*H_3), 33.4 (*C*H_2), 28.6 (*C*H_2), 25.3 (*C*H_2); Found (ESI): $[M+H]^+$ 294.1703, $C_{16}H_{24}NO_4$ requires 294.1700.

3.13: Mp 96-97 °C; R_f 0.68 (2:1 ethyl acetate-petroleum ether) viewed: UV (254 nm) or CAM dip; $[\alpha]_D^{22}$ +28.6 (*c* 0.14, $CHCl_3$); ν_{max} /cm^{-1} 3233 (NH), 3139 (Ar CH), 2936 (CH), 2921 (CH), 1740 (C=O), 1640 (Ar C=C), 1614 (NH), 1586 (Ar C=C), 1512 (Ar C=C), 1393 (=CH), 1239 (C-O), 1061 (C-O), 1025 (N-CO-O), 925 (=CH), 828 (Ar CH); δH (200 MHz, $CDCl_3$) 7.33 - 7.21 (2 H, m, Ar-*H*), 6.98 - 6.85 (2 H, m, Ar-*H*), 5.84 (1 H, ddt, *J* 17.0, 10.0, 6.6, *H*-11), 5.50 (1 H, s, N*H*), 5.14 - 4.84 (3 H, m, *H*-1a, *H*-12), 4.67 (1 H, dd, *J* 8.3, 8.3, *H*-1b), 4.17 (1 H, dd, *J* 8.3, 7.1, *H*-2), 3.97 (2 H, t, *J* 6.4, *H*-7), 2.16 - 2.04 (2 H, m, alkyl-*H*), 1.90 - 1.72 (2 H, m, alkyl-*H*), 1.61 - 1.48 (2 H, m, alkyl-*H*); δC (50 MHz, $CDCl_3$) 159.5 (*C*), 138.4 (*C*), 131.0 (*C*), 127.4 (*C*H), (plus 1 overlapping *C*H peak), 115.0 (*C*H), 114.8 (*C*H_2), 72.7 (*C*H_2), 67.9 (*C*H_2), 55.9 (*C*H), 33.4 (*C*H_2), 28.6 (*C*H_2), 25.2 (*C*H_2); Found (ESI): $[M+H]^+$ 262.1441, $C_{15}H_{20}NO_3$ requires 262.1438.

(*S*)-2-Amino-2-(4-(hex-5-enyloxy)phenyl)ethanol 3.5

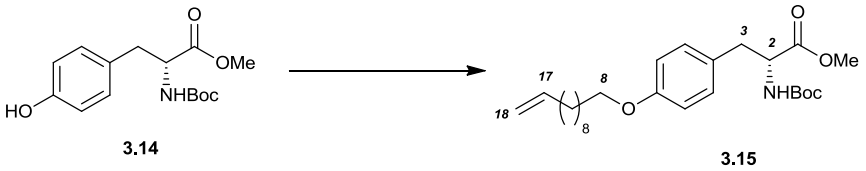


3.12 **3.13** **3.5**

To a 1 L round bottom flask equipped with a reflux condenser and magnetic stirrer was added (*S*)-methyl 1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethylcarbamate **3.12** (16.20 g, 52.7 mmol) and (*S*)-4-(4-(hex-5-enyloxy)phenyl)oxazolidin-2-one **3.13** (7.80 g, 29.8 mmol). A solution of potassium hydroxide (30% aq., 500 mL) was added to the reaction mixture to afford a white suspension which was stirred vigorously at 50 °C for 8 h. After cooling, the reaction was quenched with water (500 mL) and extracted with thrice with ethyl acetate (500 mL). The combined organic layers were washed with brine and dried over MgSO4 before being concentrated *in vacuo* to afford the title compound **3.5** (17.02 g, 88%) as an off white solid.

Mp 72-73 °C; R_f 0.03 (20:1 DCM-methanol) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{20}$ +28.3 (*c* 1.27, $CHCl_3$); ν_{max} /cm^{-1} 3500 br (OH), 3323 (NH), 3067 (Ar CH), 2936 (CH), 2865 (CH), 1713 (Ar C-H), 1642 br (C=C, NH2), 1611 (Ar C=C), 1559 (Ar C=C), 1512 (Ar C=C), 1469 (Ar C=C), 1389 (C-N), 1245 (C-O-C), 1176 (C-N), 1155 (C-N), 1065 (Ar CH), 1028 (C-OH), 993 (=CH), 907 (=CH), 827 (Ar CH, NH2), 809 (NH2); δH (200 MHz, $CDCl_3$) 7.26 - 7.19 (2 H, m, Ar-*H*), 6.97 - 6.70 (2 H, m, Ar-*H*), 6.00 - 5.68 (1 H, m, *H*-11), 5.14 - 4.84 (2 H, m, *H*-12), 4.09 - 3.84 (3 H, m, *H*-7, *H*-2), 3.69 (1 H, dd, *J* 10.8, 4.6, *H*-1a), 3.52 (1 H, dd, *J* 10.8, 8.3, *H*-1b), 2.40 (3 H, s, N*H*2, O*H*), 2.22 - 2.00 (2 H, m, alkyl-*H*), 1.91 - 1.69 (2 H, m, alkyl-*H*), 1.68 - 1.39 (2 H, m, alkyl-*H*); δC (50 MHz, $CDCl_3$) 158.4 (*C*), 138.5 (*C*H), 134.4 (*C*), 127.5 (*C*H), 114.7 (*C*H), 114.5 (CH_2), 67.9 (CH_2), 67.7 (CH_2), 56.7 (*C*H), 33.4 (CH_2), 28.6 (CH_2), 25.2 (*C*H2); Found (ESI): $[M+Na]^+$ 258.1467, $C_{14}H_{21}NNaO_2$ requires 258.1465.

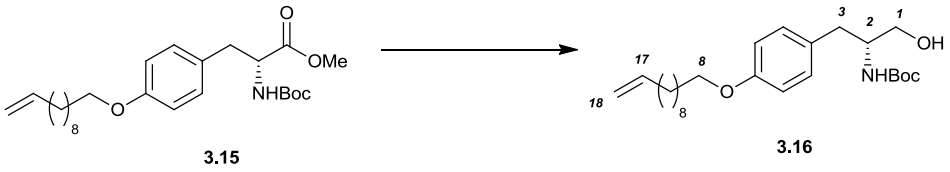
(*R*)-Methyl 2-(*tert*-butoxycarbonylamino)-3-(4-(undec-10-yloxy)phenyl)propanoate 3.15



To a 1 L two-necked round bottomed flask equipped with a dropping funnel, reflux condenser and magnetic stirrer was added (*R*)-methyl 2-((*tert*-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanoate **3.14** (56 g, 190 mmol) and K_2CO_3 (32 g, 230 mmol) in acetonitrile (250 ml). A solution of 11-bromoundec-1-ene (53 g, 230 mmol) in acetonitrile (100 ml) was added dropwise to the reaction mixture. Upon final addition, the dropping funnel was removed, the flask side arm securely stoppered and the resulting mixture refluxed for 18 h. After cooling, the reaction was quenched with water (500 ml) and the aqueous layer extracted thrice ethyl acetate (250 mL). The combined organic layers were washed with brine (250 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by column chromatography (petroleum ether to 4:1 petroleum ether-ethyl acetate) then recrystallised from toluene-petroleum ether to yield the title compound **3.15** (71 g, 83%) as a white solid.

Mp 59-62 °C; R_f 0.30 (9:1 petroleum ether-ethyl acetate) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{20}$ -33.9 (*c* 1.12, CHCl3); ν_{max} /cm^{-1} 3367 (NH), 2980 (Ar CH), 2920 (CH), 2851 (CH), 1737 (C=O), 1691 (C=O), 1641 (C=C), 1614 (Ar C=C), 1583 (NH), 1524 (Ar C=C), 1512 (Ar C=C), 1467 (CH), 1367 (CH), 1242 (C-O-C), 1161 (C-O-C/N-CO-O) 994 (=CH), 909 (=CH), 826 (Ar CH); δH (300 MHz, $CDCl_3$) 7.08 - 6.99 (2 H, m, Ar-*H*), 6.89 - 6.77 (2 H, m, Ar-*H*), 5.82 (1 H, ddt, *J* 16.9, 10.3, 6.6, *H*-17), 5.06 - 4.90 (3 H, m, *H*-18, N*H*), 4.61 - 4.46 (1 H, m, *H*-2), 3.93 (2 H, t, *J* 6.6, *H*-8), 3.72 (3 H, s, OCH_3), 3.11 - 2.92 (2 H, m, *H*-3), 2.11 - 1.98 (2 H, m, alkyl-*H*), 1.84 - 1.68 (2 H, m, alkyl-*H*), 1.51 - 1.25 (21 H, m, alkyl-*H*, C(CH_3)$_3$); δC (75 MHz, $CDCl_3$) 172.4 (*C*), 158.2 (*C*), 154.9 (*C*), 139.2 (*C*H), 130.2 (*C*H), 127.7 (*C*), 114.5 (*C*H), 114.1 (*C*H_2), 79.9 (*C*), 68.0 (*C*H_2), 54.5 (*C*H), 52.2 (*C*H_3), 37.5 (*C*H_2), 33.8 (*C*H_2), 29.5 (*C*H_2), 29.42 (*C*H_2), 29.37 (*C*H_2), 29.3 (*C*H_2), 29.1 (*C*H_2), 28.9 (*C*H_2), 28.3 (*C*H_3), 26.0 (*C*H_2); Found (ESI): $[M+H]^+$ 448.3053, $C_{26}H_{42}NO_5$ requires 448.3057.

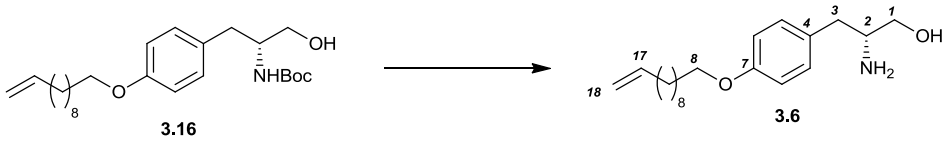
(*R*)-*tert*-Butyl 1-hydroxy-3-(4-(undec-10-enyloxy)phenyl) propan-2-ylcarbamate 3.16



A 2 L two-necked round bottom flask equipped with a magnetic stirrer and thermometer was charged with (*R*)-methyl 2-((*tert*-butoxycarbonyl)amino)-3-(4-(undec-10-en-1-yloxy)phenyl)propanoate **3.15** (60 g, 130 mmol) in THF (1.2 L) and the reaction mixture cooled to 0 °C. $LiBH_4$ (5.9 g, 270 mmol) was added portionwise to the reaction mixture ensuring the reaction temperature did not exceed 5 ^oC between each $LiBH_4$ addition. The resulting mixture was allowed to slowly warm to RT over 16 h. The reaction was carefully quenched with 1M HCl until effervescing ceased and the aqueous layer extracted thrice with ethyl acetate (300 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was repeatedly triturated with ice-cold hexane (2 x 500 ml) and sonicated briefly. The resulting precipitate was filtered, washed with hexane and dried *in vacuo* to yield the title compound **3.16** (55 g, 98%) as a white solid.

Mp 67-69 °C; R_f 0.15 (4:1 petroleum ether-ethyl acetate) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{22}$ +12.3 (*c* 2.11, CHCl3); ν_{max} /cm^{-1} 3358 br (NH, OH), 2974 (Ar CH), 2920 (CH), 2852 (CH), 1689 (C=O), 1642 (Ar C=C), 1614 (Ar C=C), 1582 (NH), 1528 (Ar C=C), 1510 (Ar C=C), 1268 (N-CO-O), 1241 (C-O-C), 1171 (N-CO-O), 1061 (C-OH), 1035 (C-OH), 1004 (=CH), 906 (=CH); δH (300 MHz, $CDCl_3$) 7.16 - 7.08 (2 H, m, Ar-*H*), 6.89 - 6.80 (2 H, m, Ar-*H*), 5.82 (1 H, ddt, *J* 13.2, 10.3, 6.6, *H*-17), 5.07 - 4.90 (2 H, m, *H*-18), 4.73 (1 H, d, *J* 7.7, N*H*), 3.93 (2 H, t, *J* 6.6, *H*-8), 3.88 - 3.72 (1 H, m, *H*-2), 3.72 - 3.48 (2 H, m, *H*-1), 2.78 (2 H, d, *J* 7.3, *H*-3), 2.41 (1 H, br. s, O*H*), 2.11 - 1.98 (3 H, m, alkyl-*H*), 1.85 - 1.71 (3 H, m, alkyl-*H*), 1.52 - 1.24 (19 H, m, alkyl-*H*, C(C*H*3)3); δC (75 MHz, $CDCl_3$) 157.9 (*C*), 156.2 (*C*), 139.2 (*C*H), 130.1 (*C*H), 129.4 (*C*), 114.6 (*C*H), 114.1 (*C*H2), 79.7 (*C*), 68.0 (*C*H2), 64.4 (*C*H2), 53.9 (*C*H), 36.2 (*C*H2), 33.8 (*C*H2), 29.5 (*C*H2), 29.42 (*C*H2), 29.39 (*C*H2), 29.3 (*C*H2), 29.1 (*C*H2), 28.9 (*C*H2), 28.3 (*C*H3), 26.0 (*C*H2); Found (ESI): $[M+H]^+$ 420.3101, $C_{25}H_{42}NO_4$ requires 420.3108.

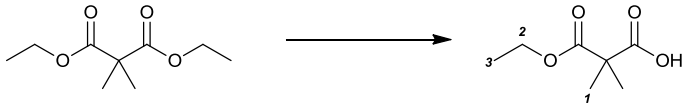
(*R*)-2-Amino-3-(4-(undec-10-enyloxy)phenyl)propan-1-ol 3.6



To a 3 L round bottomed flask equipped with a reflux condenser and magnetic stirrer was added (*R*)-*tert*-butyl 1-hydroxy-3-(4-(undec-10-en-1-yloxy)phenyl)propan-2-ylcarbamate **3.16** (59 g, 140 mmol) in 1:1 THF-H_2O (1.5 L). *p*-toluenesulfonic acid monohydrate (54 g, 280 mmol) was added portionwise to the reaction mixture which was then refluxed for 18 h. After cooling, the reaction was quenched with 2M NaOH (500 ml) and the aqueous layer extracted with ethyl acetate (250 ml) and then DCM (250 ml). The combined organic layers were washed with brine (250 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the title compound **3.6** (45 g, 99%) as a white solid.

Mp 75-78 °C; R_f 0.03 (9:1 petroleum ether-ethyl acetate) viewed: UV (254 nm) or CAM dip; $[\alpha]_D^{20}$ +7.7 (*c* 1.04, $CHCl_3$); ν_{max} /cm^{-1} 3355 (NH), 3298 (NH), 3077 (Ar CH), 2923 br (OH), 2851 (CH), 1613 (Ar C=C), 1582 (Ar C=C), 1509 (Ar C=C), 1467 (Ar C=C), 1243 (C-O-C), 1059 (C-OH), 909 (=CH); δH (400 MHz, $CDCl_3$) 7.13 - 7.03 (2 H, m, Ar-*H*), 6.90 - 6.79 (2 H, m, Ar-*H*), 5.82 (1 H, ddt, *J* 17.0, 10.3, 6.7, *H*-17), 5.06 - 4.88 (2H, m, *H*-18), 3.93 (2 H, t, *J* 6.5, *H*-8), 3.63 (1 H, dd, *J* 10.6, 3.2, *H*-1a), 3.37 (1 H, dd, *J* 10.6, 6.5, *H*-1b), 3.13 - 3.02 (1 H, m, *H*-2), 2.73 (1 H, dd, *J* 13.5, 5.3, *H*-3a), 2.47 (1 H, dd, *J* 13.5, 8.5, *H*-3b), 2.24 - 1.99 (5 H, m, alkyl-*H*, N*H*$_2$, O*H*), 1.85 - 1.70 (2 H, m, alkyl-*H*), 1.51 - 1.23 (12 H, m, alkyl-*H*); δC (101 MHz, $CDCl_3$) 157.8 (*C*-7), 139.2 (*C*-17), 130.3 (Ar-*C*H), 130.1 (*C*-4), 114.6 (Ar-*C*H), 114.1 (*C*-18), 68.0 (*C*-8), 66.1 (*C*-1), 54.3 (*C*-2), 39.8 (alkyl-*C*H_2), 33.8 (*C*-3), 29.5 (alkyl-*C*H_2), 29.45 (alkyl-*C*H_2), 29.4 (alkyl-*C*H_2), 29.3 (alkyl-*C*H_2), 29.1 (alkyl-*C*H_2), 27.6 (alkyl-*C*H_2), 26.0 (alkyl-*C*H_2); Found (ESI): [M + H]+ 320.2588, $C_{20}H_{34}NO_2$ requires 320.2584.

3-Ethoxy-2,2-dimethyl-3-oxopropanoic acid 3.4[142]

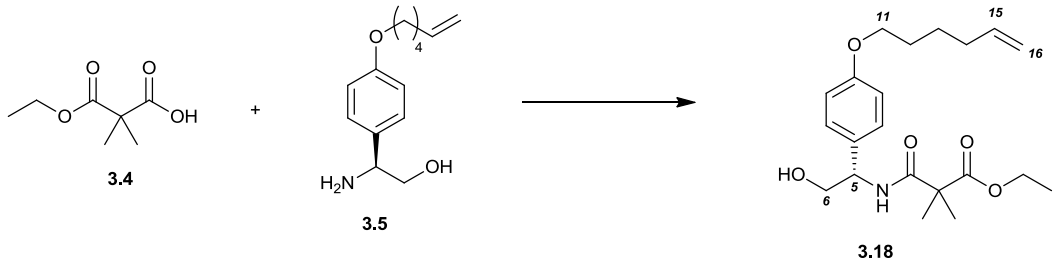


3.17 3.4

To a 250 mL round bottomed flask equipped with a reflux condenser and magnetic stirrer was added was added a solution of diethyl dimethylmalonate **3.17** (10.09 g, 53.6 mmol) in ethanol (65 mL). To the stirring reaction mixture was added a solution of sodium hydroxide (2.36 g, 59.0 mmol) in water (30 mL) and the reaction warmed to 40 °C. The resulting mixture was stirred at 40 °C for 6 h. After cooling, the reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in water (150 mL) and extracted with *n*-hexane (150 mL). The resulting aqueous layer was triturated with 3M HCl until *ca*. pH 1 was achieved and the aqueous layer subsequently extracted twice with ethyl acetate (150 mL). The combined ethyl acetate layers were dried over MgSO4 and concentrated *in vacuo* to afford the title compound **3.4** (8.50 g, 99%) as a colourless liquid.

R_f 0.21 (2:1 ethyl acetate-petroleum ether) viewed: UV (254 nm) or PMA dip; νmax /cm^{-1} 3200 br (OH), 2987 (C-H), 1705 br (C=O), 1471 (C-H), 1389 (OH), 1368 (C-OH), 1263 br (C-O), 1142 br (C-O-C), 1025 (CH), 859 (OC-OH); δH (400 MHz, $CDCl_3$) 4.18 (2 H, q, *J* 7.1, *H*-2), 1.42 (6 H, s, *H*-1), 1.25 (3 H, t, *J* 7.1, *H*-3); δC (101 MHz, $CDCl_3$) 178.9 (*C*), 174.1 (*C*), 61.8 (*C*H_2), 50.6 (*C*), 23.2 (*C*H_3), 14.2 (*C*H_3); Found (ESI): $[M+H]^+$ 161.0805, $C_7H_{13}O_4$ requires 161.0808.

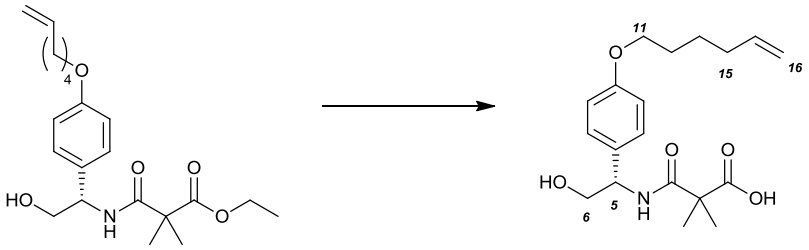
(*S*)-Ethyl 3-(1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethylamino)-2,2-dimethyl-3-oxo propanoate 3.18



To a 1 L round bottomed flask equipped with a dropping funnel and a magnetic stirrer was added (*S*)-2-amino-(4-(hex-5-enyloxy)phenyl)ethanol **3.5** (12.0 g, 50 mmol), HOBt (6.7 g, 50 mmol) and chloroform (400 ml). The reaction mixture was cooled to 0 °C prior to dropwise addition of EDCI (9.5 g, 50 mmol) in chloroform (50 ml). The reaction mixture was stirred at 0 °C for 1.5 h. A solution of 3-ethoxy-2,2-dimethyl-3-oxopropanoic acid **3.4** (8.5 g, 45 mmol) in chloroform (80 ml) was added dropwise. The resulting mixture was allowed to slowly warm to RT overnight. The reaction was then quenched with 3M HCl (100 ml) and the aqueous layer extracted thrice with chloroform (100 mL). The combined organic layers were washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude reaction product was purified by column chromatography (1:1 petroleum ether-ethyl acetate) to yield the title compound **3.18** (16.0 g, 95%) as a colourless solid.

Mp 73-75 °C; R_f 0.35 (1:1 petroleum ether-ethyl acetate) viewed: UV (254 nm) or CAM dip; $[\alpha]_D^{19}$ +37.0 (*c* 1.08, CHCl3); ν_{max} /cm^{-1} 3309 (NH), 3258 br (OH), 3074 (Ar CH), 2985 (CH), 2939 (CH), 2862 (CH), 1730 (C=O), 1644 (C=O), 1611 (Ar C=C), 1584 (Ar C=C), 1548 (NH), 1511 (Ar C=C), 1477 (Ar C=C), 1265 (C-N), 1246 (C-O-C), 1174 (C-O-C), 1151 (C-O), 1028 (C-OH), 997 (C=C), 917 (C=C), 827 (Ar CH); δH (200 MHz, $CDCl_3$) 7.24 - 7.09 (3 H, m, Ar-*H*, N*H*), 6.89 - 6.78 (2 H, m, Ar-*H*), 5.81 (1 H, ddt, *J* 17.0, 10.4, 6.6, *H*-15), 5.10 - 4.86 (3 H, m, *H*-5, *H*-16), 4.15 (2 H, q, *J* 7.1, O*C*H_2CH_3), 3.91 (2 H, t, *J* 6.4, *H*-11), 3.82 - 3.69 (2 H, m, *H*-6), 3.47 (1 H, s, O*H*), 2.20 - 1.96 (2 H, m, alkyl-*H*), 1.88 - 1.68 (2 H, m, alkyl-*H*), 1.64 - 1.48 (2 H, m, alkyl-*H*), 1.45 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 1.23 (3 H, t, *J* 7.1, OCH$_2$CH_3); δC (50 MHz, $CDCl_3$) 174.6 (*C*), 172.2 (*C*), 158.4 (*C*), 138.3 (*C*H), 130.8 (*C*), 127.5 (*C*H), 114.6 (*C*H_2), 114.5 (*C*H), 67.5 (*C*H_2), 65.9 (*C*H_2), 61.5 (*C*H_2), 55.1 (*C*H), 49.7 (*C*), 33.2 (*C*H_2), 28.5 (*C*H_2), 25.1 (*C*H_2), 23.4 (*C*H_3), 13.8 (*C*H_3); Found (ESI): $[M+H]^+$ 378.2275, $C_{21}H_{32}NO_5$ requires 378.2275.

(*S*)-3-(1-(4-(Hex-5-enyloxy)phenyl)-2-hydroxyethylamino)-2,2-dimethyl-3-oxo propanoic acid 3.19

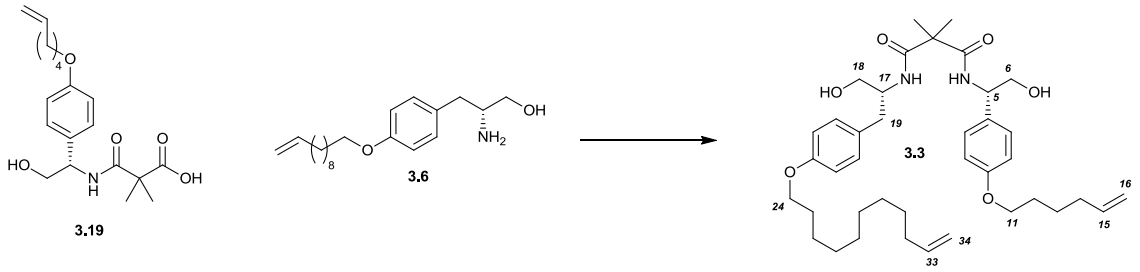


3.18 3.19

To a 2 L round bottom flask equipped with a reflux condenser and magnetic stirrer was charged with (*S*)-ethyl 3-(1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethylamino)-2,2-dimethyl-3-oxopropanoate **3.18** (10.0 g, 26 mmol) and 500 mL of THF/H_2O (1:1 *v/v*). A solution of NaOH (11.0 g, 260 mmol) in 1:1 THF-H_2O (300 ml) was added to the reaction mixture and stirred at 45 °C for 4 h. The reaction was subsequently cooled to 0 °C and carefully acidified with 6M HCl until *ca*. pH 1 was achieved. The mixture was extracted with twice with ethyl acetate (250 mL) and once with DCM (250 mL) and the combined organic layers washed with water (250 mL), brine (250 mL) and dried over $MgSO_4$. The resulting solution was concentrated *in vacuo* to afford the title compound **3.19** (8.2 g, 89%) as a colourless solid.

Mp 118-121 °C; R_f 0.05 (9:1 ethyl acetate-petroleum ether) viewed: UV (254 nm) or CAM dip; $[\alpha]_D^{21}$ +73.0 (*c* 1.26, $CHCl_3$); ν_{max} /cm^{-1} 3308 br (OH/NH), 2980 (Ar CH), 2935 (CH), 2865 (CH), 1715 (Ar CH), 1679 (C=O), 1655 (C=O), 1613 (Ar C=C), 1559 (NH), 1512 (Ar C=C), 1466 (Ar C=C), 1389 (C-N), 1247 (C-O-C/C-N), 1175 (C-N), 1156 (C-O), 1028 (C-OH), 992 (=CH), 900 (=CH), 827 (Ar CH), 810 (NH); δH (200 MHz, $CDCl_3$) 7.92 (1 H, d, *J* 5.8, N*H*), 7.20 (2 H, d, *J* 8.3, Ar-*H*), 6.82 (2 H, d, *J* 8.3, Ar-*H*), 5.83 (1 H, ddt, *J* 16.8, 10.1, 6.6, *H*-15), 5.22 - 4.92 (3 H, m, *H*-5, *H*-16), 4.04 - 3.70 (4 H, m, *H*-6, *H*-11), 2.24 - 2.04 (2 H, m, alkyl-*H*), 1.90 - 1.67 (2 H, m, alkyl-*H*), 1.65 - 1.35 (8 H, m, alkyl-*H*); δC (50 MHz, $CDCl_3$) 177.2 (*C*), 173.8 (*C*), 158.6 (*C*), 138.5 (*C*H), 130.6 (*C*), 127.6 (*C*H), 114.7 (CH_2), 114.7 (*C*H), 67.7 (CH_2), 64.8 (CH_2), 55.4 (*C*H), 49.5 (*C*), 33.4 (CH_2), 28.6 (CH_2), 25.3 (CH_2), 23.5 (CH_3), 23.4 (CH_3); Found (ESI): $[M+H]^+$ 350.1965, $C_{19}H_{28}NO_5$ requires 350.1962.

N^1-((*S*)-1-(4-(Hex-5-enyloxy)phenyl)-2-hydroxyethyl)-N^3-((*R*)-1-hydroxy-3-(4-(undec-10-enyloxy)phenyl)propan-2-yl)-2,2-dimethylmalonamide 3.3



A 25 mL round bottomed flask was charged with (*S*)-3-(1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethylamino)-2,2-dimethyl-3-oxopropanoic acid **3.19** (100 mg, 0.29 mmol), *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate (TBTU) (129 mg, 0.4 mmol), *N*,*N*-diisopropylethylamine (DIPEA) (175 µl, 1 mmol) and 4:1 DCM-DMF (8 ml). (*R*)-2-amino-3-(4-(undec-10-enyloxy)phenyl)propan-1-ol **3.6** (110 mg, 0.34 mmol) was added to the stirring reaction mixture. The resulting mixture was stirred at RT for 23 h. The reaction was quenched by addition of water (50 ml) and the aqueous layer extracted thrice with DCM (10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by column chromatography (petroleum ether to 95:5 ethyl acetate-methanol) to yield the title compound **3.3** (132 mg, 70%) as a colourless solid.

Mp 77-78 °C; *R*f 0.47 (4:1 ethyl acetate-petrol ether) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{20}$ +37.9 (*c* 0.95, $CHCl_3$); ν_{max} /cm^{-1} 3335 br (OH/NH), 2926 (CH), 2855 (CH), 1640 (C=O), 1613 (Ar C=C), 1583 (NH), 1510 (Ar C=C), 1471 (Ar C=C), 1243 (C-O-C), 1176 (C-O), 1034 (C-OH), 994 (=CH), 909 (=CH), 829 (Ar CH); δH (400 MHz, $CDCl_3$) 7.22 - 7.04 (5 H, m, Ar-H, N*H*), 6.89 - 6.78 (4 H, m, Ar-H), 6.65 (1 H, d, *J* 7.9, N*H*, N*H*'), 5.89 - 5.77 (2 H, m, *H*-15, *H*-33), 5.08 - 4.90 (5 H, m, *H*-5, *H*-16, *H*-34), 4.16 - 4.05 (1 H, m, *H*-17), 3.96 - 3.88 (4 H, m, *H*-11, *H*-24), 3.85 - 3.72 (2 H, m, *H*-6), 3.63 (1 H, dd, *J* 11.2, 3.8, *H*-18a), 3.55 (1 H, dd, *J* 11.2, 5.6, *H*-18b), 2.94 (2 H, br. s., O*H*, O*H*'), 2.82 (1 H, dd, *J* 13.8, 6.7, *H*-19a), 2.73 (1 H, dd, *J* 13.8, 7.6, *H*-19b), 2.18 - 2.00 (4 H, m, alkyl-*H*), 1.84 - 1.72 (4 H, m, alkyl-*H*), 1.61 - 1.51 (2 H, m, alkyl-*H*), 1.49 - 1.28(18 H, m, alkyl-*H*); δC (101 MHz, $CDCl_3$) 174.1 (*C*=O), 173.8 (*C*=O), 158.7(Ar-*C*), 157.9 (Ar-*C*), 139.2 (*C*-15), 138.5 (*C*-33), 130.5 (Ar-*C*), 130.1 (Ar-*C*H), 129.2 (Ar-*C*), 127.6 (Ar-*C*H), 114.8 (*C*-16/*C*-34), 114.7 (Ar-*C*H), 114.6 (*C*-16/*C*-34), 114.1 (Ar-*C*H), 68.0 (*C*-11), 67.8 (*C*-24), 66.2 (*C*-6), 64.0 (*C*-18), 55.4 (*C*-5), 53.3 (*C*-17), 49.8 (*C*$(CH_3)_2$), 35.9 (*C*-19), 33.8 (alkyl-*C*H_2), 33.4 (alkyl-*C*H_2), 29.5 (alkyl-*C*H_2), 29.41

(alkyl-*C*H_2), 29.38 (alkyl-*C*H_2), 29.3 (alkyl-*C*H_2), 29.1 (alkyl-*C*H_2), 28.9 (alkyl-*C*H_2), 28.7 (alkyl-*C*H_2), 26.0 (alkyl-*C*H_2), 25.3 (alkyl-*C*H_2), 23.8 (*C*H_3), 23.6 (*C*H_3'); Found (ESI): [M+H]+ 651.4362, $C_{39}H_{59}N_2O_6$ requires 651.4368.

CHAPTER 4– AU(III)-OXO COMPLEXES AS CATALYSTS FOR INTRAMOLECULAR HYDROAMINATION

4.1 Introduction

With the initial failure of the two strategies discussed in chapters 2 and 3 towards mechanically planar rotaxanes and with insufficient time to attempt a re-designed macrocycle to overcome the shortcomings of the first two, we decided to explore the possibility of using bipy macrocycles such as **2.42** to form rotaxanes via gold-catalysis. The reason for this is two-fold: the Lee Group has particular expertise in gold catalysis and active-metal template synthesis of rotaxanes via gold catalysis has never before been achieved.

The last ten years has seen the field of homogenous gold catalysis become an incredibly active area of research.[143-151] Its attractiveness to chemists is partly due to its outstanding selectivity and the ability of gold catalysts to act as π-Lewis acids, which means that they can activate C-C π bonds such as alkynes, allenes, dienes and alkenes.[152-161] Furthermore, by carefully selecting appropriate ligands and counterions, gold catalysts can be optimised to afford tight control over the reactivity and selectivity of reactions in which they are employed.[152]

Whilst Au(I) complexes continue to be thoroughly investigated with regard to reactivity and reaction selectivity, Au(III) complexes remain relatively unexplored by comparison. A recent commentary has highlighted a need for continued development of Au(III)-based enantioselective catalysis.[162] In particular, the development of novel organometallic Au(III) complexes with both tuneable ligands and counterions needs to be conducted. While many organometallic groups specialise in synthesising new *N*-ligated Au(III) complexes, investigations into their applications have been targeted towards biological activity rather than catalysis.[163-165]

This chapter presents investigations into the application of novel 6,6'-dimethyl-2,2'-bipyridine- and 2,9-dimethyl-1,10-phenanthroline- based Au(III) complexes as catalysts for the alkyne hydroamination reaction.

4.2 Results & Discussion

Our work in this area was initiated whilst reviewing existing literature on macrocycles containing bipyridine and phenanthroline motifs, widely used in the active metal template synthesis of rotaxanes. By examining the variety of 'active' metals already known and their respective affinities for the selected ligands in each case, we postulated whether it could be possible to use our expertise in gold catalysis to develop an entirely new Au(III) active metal template reaction pathway. In such a pathway, it is anticipitated that a Au(III) complex could act as a template for rotaxane formation. In the limited research time remaining, it was decided it would be prudent to firstly research and investigate the synthesis of a series of structurally simplified bipy/phenanthroline Au(III) complexes in which to model any future Au(III) active metal template reaction.

A focussed literature search led to the discovery that whilst unsubstituted bipy Au(III) complexes such **4.1 (**Figure 4.1**)** are relatively well known and have been assessed as catalysts, their 6,6'-disubstituted bipy (or 2,9-disubstituted phenanthroline) analogues **4.2** (Figure 4.1) were unknown. With respect to their potential use as catalysts, tolerance to a variety of substitution at the indicated positions would be extremely advantageous. In order for desirable chiral induction to be achieved, substitution would typically be positioned at the 6,6'- positions. In addition, in any future applications that macrocyclic versions of complex **4.2** may have, ring forming substituents must be incorporated at the 6,6'- positions, as indicated, for successful active template reactions to be achieved. Following a thorough literature search, we commenced an investigation to discover whether substituted complexes like **4.2** could be successfully synthesised and to probe their activity as catalysts in a model reaction.

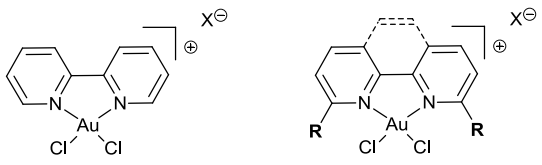
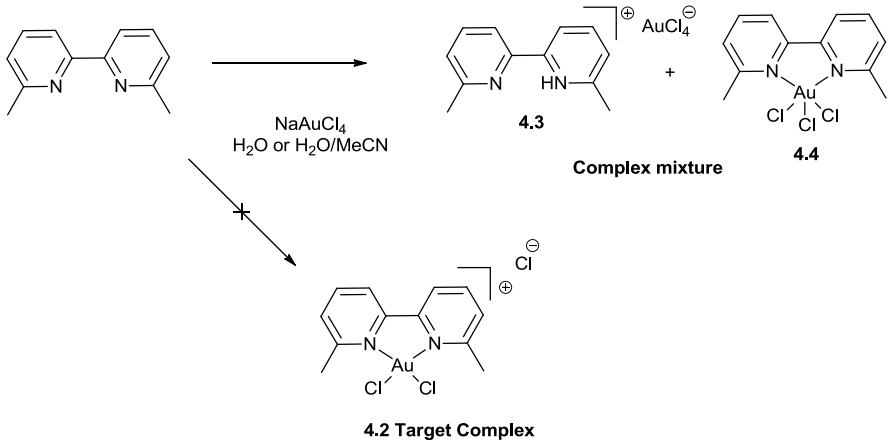


Figure 4.1 Au(III)- bipy complex 4.1 and target R-substituted complex 4.2

An initial set of reactions were set up to attempt to synthesise **4.2** (bipy, R=Me) where X^- was expected to be a chloride co-ordinating counterion. The general procedure[166] outlined for the synthesis of **4.1** in the unsubstituted bipyridine equivalent was used and

modified to probe the generality of the reaction outcome. Table 4.1 summarises the general observations from these reactions.

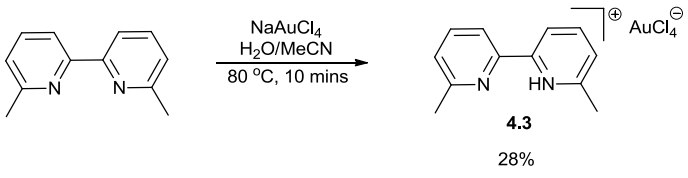
The conditions shown in entry 1 afforded only unreacted 6,6'-dimethyl bipyridine (determined by comparison of the reaction mixture with a 6,6'-dimethyl bipyridine reference standard and by the absence of shift in the aromatic protons in the ^{1}H NMR reportedly observed for bipy-Au(III) complexes). This was postulated to be due to a combination of (a) poor solubility of 6,6'-dimethyl bipyridine in water when compared to unsubstituted bipyridine and (b) the likelihood of a longer reaction time being required for the gold species to bind with a more sterically demanding ligand such as that in use. With this in mind, two further experiments were conducted where the reaction time was increased to 3 hours (entry 2) and MeCN was added to the reaction mixture to fully solvate the ligand (entry 3). Unfortunately, in both cases, TLC could not be used to monitor reaction progress due to the ionic and polar nature of the reaction components, therefore a reaction time of 3 hours was used as an estimate based on literature precedent for reactions of this type.[166] Once again, conditions used in entries 2 and 3 resulted in proton signals consistent with unreacted 6,6'-dimethyl bipyridine. In a final attempt to access target complex **4.2**, the reaction temperature was increased to reflux (*ca*. 80 ^{o}C) and left for 10 minutes (entry 4) and 3 hours (entry 5) to compensate for the extra steric demand the substituted ligand provided. In contrast to entries 1-3, a bright yellow-orange suspension resulted after approximately 5 minutes in both reactions, indicating the likelihood of a reaction. Following work-up of each to a crude reaction mixture, ^{1}H NMR was used to give qualitative analysis of the reaction mixture, which at this stage were only tentatively assigned due to the complexity of mixture. Further experimentation later afforded characterised products with matching proton signals to those observed for entries 4 & 5, which permitted retrospective product assignment to a mixture of structures **4.3** and **4.4.** Product ratios could not be calculated due to the complexity of the mixtures. Comparing the crude ^{1}H NMR spectra for entries 4 and 5, the apparent levels of unreacted ligand were higher in entry 4 (conducted in water) than in entry 5 (conducted in a water/MeCN (1:1 *v*/*v*) mixture) suggesting that reaction of 6,6'-dimethyl bipyridine is improved by having the ligand fully solvated before its addition to the reaction vessel.



Entry	Temp/ ^{o}C	Time/ mins	Solvent	Result
1	25	10	H_2O	No reaction
2	25	180	H_2O	No reaction
3	25	180	H_2O/MeCN (1:1 v/v)	No reaction
4	80	10	H_2O	Complex mixture of SM, **4.3** & **4.4**
5	80	180	H_2O/MeCN (1:1 v/v)	Complex mixture of SM **4.3** & **4.4**

Table 4.1 Summarised reaction conditions for the attempted synthesis of 4.2

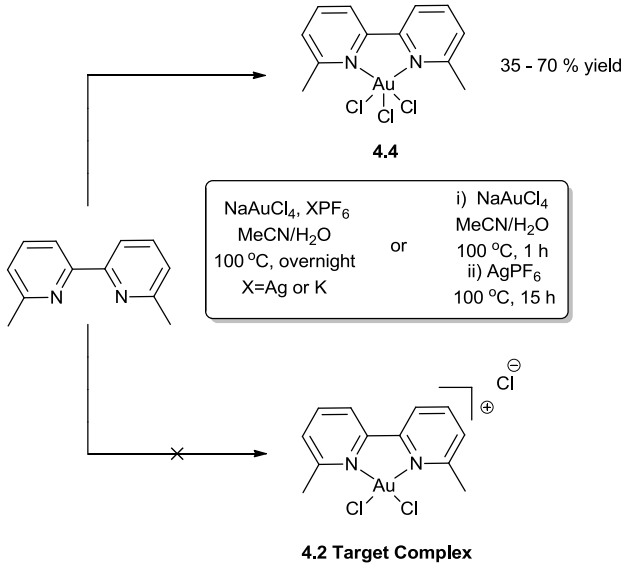
With tentative ^{1}H NMR assignments in hand as to the identity of the products shown in Table 4.1, the reaction was repeated for 10 mins at reflux. This time equimolar amounts of ligand and $NaAuCl_4$ were used in order to reduce the quantity of unreacted ligand and facilitate possible recrystallisation of a product. After work-up and purification by recrystallisation from MeCN/Et_2O, product **4.3 (**Scheme 4.1**)** was isolated in 28% yield. Due to time constraints, it was decided at this stage that compound **4.3** would have little or no further use and so it was stored and other possible routes to compounds of the type represented by structure **4.2** were explored.



Scheme 4.1 Isolation of unexpected gold complex 4.3

Whilst conducting an investigation into a plausible mechanism and encouraged by the literature that it had been discovered the that the use of Ag^{+} and K^{+} additives were being routinely used by other groups to facilitate formation of Au(III)-bipy and Au(III)-phenanthroline architectures; albeit with either no ring substitution or tolerated substitution at the 4,4'- positions. It was hypothesised that the *in situ* formation of AgCl

or KCl, depending on the additive, may provide the driving force required for the formation of the target Au(III)-bipy complex **4.2.** Furthermore, it was envisaged that, by sequestering chloride ions from the tetrachloroaurate counterion seen in **4.3**, any resulting $AuCl_3$ intermediate may preferentially bind to the ligand in a fashion reported by Zhang *et. al.*[166] and represented by structure **4.2**. Scheme 4.2 shows the two methods extracted from the literature pertaining to synthesis of Au(III)-bipy and Au(III)-phenanthroline architectures and applied to the more sterically demanding 6,6'-dimethyl bipyridine ligand.



Scheme 4.2 Use of K^+ and Ag^+ additives in the attempted synthesis of 4.2

Potassium hexafluorophosphate was readily available in the laboratory and as such was the first reaction additive to be trialled. An equimolar amount of KPF_6 was added to the reaction mixture before heating it to reflux for 16 hours. Following work-up and purification by recrystallisation, compound **4.4 (**Scheme 4.2**)** was isolated in 35% yield. X-ray diffraction of the product revealed a neutral Au(III) complex (Figure 4.2), structurally similar to target **4.2** however, it was thought that the saturated gold centre may hinder its use as a (pre)catalyst. With this in mind, we turned our attention to the use of a silver hexafluorophosphate additive. Direct substitution of KPF_6 for $AgPF_6$ led to the same reaction outcome (following identical workup conditions) to that when KPF_6 had been employed, albeit with a marked decrease in unwanted side reactions (forming compound **4.3**) and unreacted ligand (monitored by ^1H NMR of the crude reaction mixture). This was reflected in an improved isolated yield of **4.4** (58%) and as a result only one recrystallisation was required to afford X-ray quality crystals.

Upon repeating this reaction, it was discovered that if instead of combining the reagents in a "one-pot" fashion and before being left at reflux overnight, the $AgPF_6$ was rapidly added *ca*. 1 hour after initiation of the 16 hour reaction, the final isolated reaction yield could be further augmented to 70%.

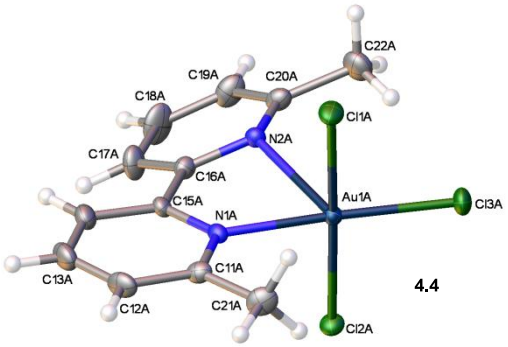
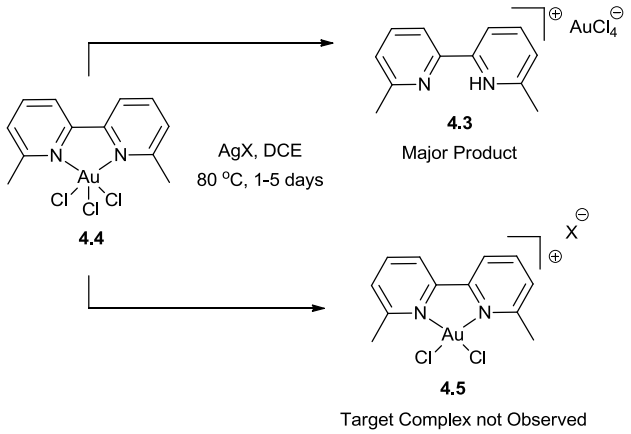


Figure 4.2 Confirmation of Au(bipy^{2Me})Cl_3 by X-ray diffraction

In the remaining project time and with a reliable route to Au(III) compound **4.4** now in hand, it was decided to approach the synthesis of **4.2** directly from complex **4.4**. This strategy involved reacting compound **4.4** with a range of commercially available silver salts (Table 4.2). A broad selection of silver salts (AgOAc, $AgOCOCF_3$, $AgBF_4$, $AgSbF_6$, $AgPF_6$, AgOTf, $AgNO_3$, $AgClO_4$) were purchased to allow potential access to a range of Au(III)-complexes of the type represented by **4.5 (**Table 4.2**)**, each with a different counterion. Dichloroethane was selected as the reaction solvent to encourage precipitation of AgCl from the reaction mixtures. This was thought to have a role in achieving the higher conversions required for purification of the products by recrystallisation. The reactions were also conducted at reflux based on literature precedent[167] and the elevated yields observed previously working with the dimethyl bipyridine ligand. Each reaction was conducted in tandem for 24 hours after which time a grey precipitate was observed in reactions using $AgClO_4$ and $AgPF_6$. Reactions were left for a further 5 days to try to enhance conversion to an isolable product. Following work-up and crude ^{1}H, ^{19}F and ^{31}P NMR as appropriate, a mixture of reaction components was observed in each case and these are summarised in Table 4.2. Unfortunately, none of the reactions afforded the intended Au(III)-complex **4.5** and only the reaction conducted with $AgClO_4$ afforded a satisfactory conversion to a product which could be isolated, purified (by recrystallisation) and characterised. This showed that here the major product as **4.3** (75% yield). ^{1}H NMR resonances corresponding to major product **4.3** were tentatively identified by NMR stacking with crude NMR data recorded for the other reactions using AgOAc, $AgBF_4$, $AgSbF_6$, $AgPF_6$ and AgOTf.

The presence of an unassigned minor product and/or starting material **4.4**, as indicated in Table 4.2, resulted in a product mixture which was too complex to separate successfully and permit further structural elucidation.



X = $^{-}$OAc, $^{-}$TFA, $^{-}BF_4$, $^{-}SbF_6$, $^{-}PF_6$, $^{-}$OTf, $^{-}NO_3$, $^{-}ClO_4$

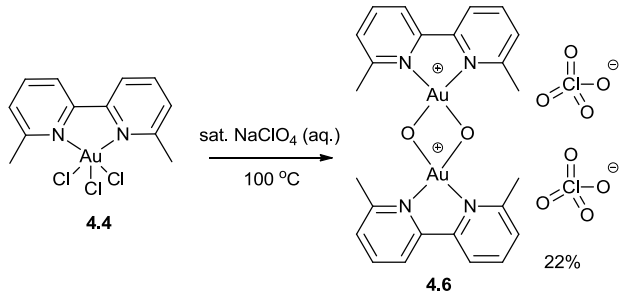
Counterion X^-	Product Ratios (**4.3**:P_{minor}:SM)[a]
OAc	1:9:3
$OCOCF_3$	Complex mixture
BF_4	1:0.4:0
SbF_6	1:3:2
PF_6	1:0.5:0
OTf	1:0.71
NO_3	Complex mixture

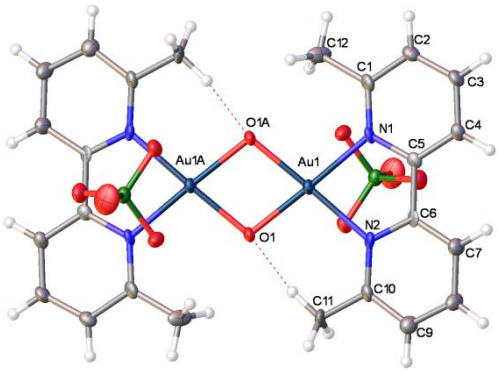
[a] P_{minor} = unidentified product, determined by ^{1}H NMR, SM = starting material **4.4**

Table 4.2 Reaction of 4.4 with a variety of Ag^+ salts

Once again, these results demonstrated that the R substituents at 6,6' positions hindered the synthesis of a $[(N\text{-}N)Au(III)Cl_2]^+X^-$ complex **4.2**.

During further attempts to synthesise complex **4.2** from **4.4**, it was accidentally discovered that treatment of **4.4** with a saturated aqueous solution of $NaClO_4$ resulted in a novel gold(III)-oxo complex **4.6** (Scheme 4.3).





Scheme 4.3 Synthesis and X-ray structure of Au(III)-oxo complex 4.6

Gold(III)-oxo complexes of this type have been synthesised and studied by Cinellu and co-workers in relation to their anti-cancer properties and as precursors to gold-alkene complexes.[163, 168-172] However, a survey of the literature revealed that gold(III)-oxo complexes had never been explored as homogenous catalysts or pre-catalyst species in gold catalysed reactions. Importantly, these species bore some structural similarity to compounds required to fulfil our criteria whereby substituents were present at the 6,6' positions, they were cationic in nature and possessed a weakly co-ordinating counterion. As a result, a series of gold(III)-oxo complexes, **4.7**, **4.8**, **4.9** and **4.10** were synthesised and together with **4.4**, **4.6** and ligandless complexes $AuCl_3$ and $NaAuCl_3$, they were applied to a model alkyne hydroamination reaction to probe their activity as potential (pre)catalysts.

The cyclisation of pent-4-yn-1-amine was chosen as a suitable model reaction to evaluate the (pre)catalysts due to the relative ease in which the starting material could be synthesised in the remaining time available. It was also envisaged that yields could be determined from ^{1}H NMR spectra using an internal standard whose ^{1}H NMR resonances would not overlap with those associated with products. Furthermore, the volatile nature of the target product and the associated difficulties encountered when attempting to isolate products of this type are alluded to in the literature.[173] The structures of the evaluated Au(III) complexes are shown in Figure 4.3. The yields from the model hydroamination reaction were determined by ^{1}H NMR analysis using mesitylene as an internal standard. The NMR yields and observations and summarised in Table 4.3.

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Au(III)-oxo compound **4.7** exhibited the most promising catalytic activity when administered to the model hydroamination reaction, affording a unoptimised yield of

70% (2 h, entry 1). In an effort to allow milder reaction conditions to be used, the reaction temperature was lowered to room temperature (*ca*. 25 ^{o}C). It was found that the reaction proceeded well at room temperature also to afford the 5-*exo*-dig product **4.12**, albeit when extending the reaction time to 16 hours. Modifying the counterion from PF_6^- to ClO_4^- (**4.6**) resulted in a moderate product yield of 60% (entry 3). Next, we were eager to investigate the effect on the reaction outcome of switching the 6,6'-dimethyl-2,2'-bipyridine ligand for a 2,9-dimethyl-1,10-phenanthroline ligand. Complex **4.8** was found to still have pre-catalytic activity, however the reaction yield was lower (62%, entry 4). To evaluate the effect of the pendant 6,6'-methyl substituents on the catalysis reaction, complex **4.9** was evaluated. Perhaps surprisingly, complex **4.9** afforded a lower (55%, entry 5) yield when compared to the substituted variant, **4.7**, which may imply that some degree of steric protection around the gold centre is advantageous.

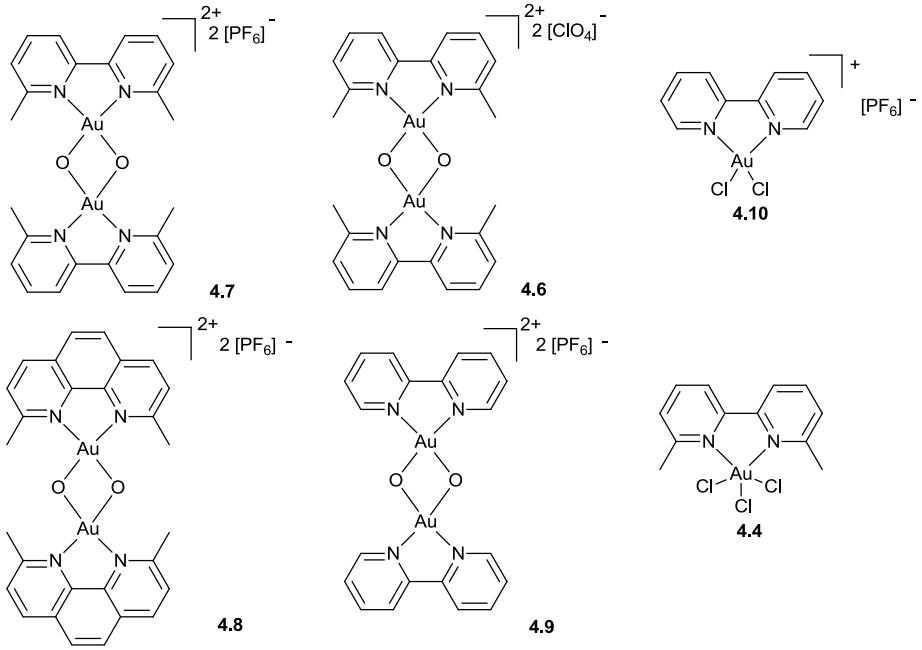
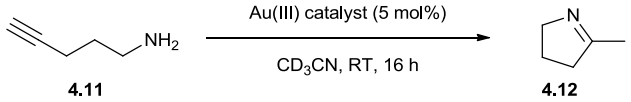


Figure 4.3 Au(III) complexes evaluated as (pre)catalysts in the hydroamination reaction



4.11 4.12

Entry	Catalyst	Yield (%)[a]	Unreacted Starting Material[b]
1[c]	**4.7**	70	-
2	**4.7**	70	-
3	**4.6**	60	-
4	**4.8**	62	-
5	**4.9**	55	-
6	**4.10**	50	Trace + side products
7	**4.4**	50	25%
8	$AuCl_3$	50	25%
9	$NaAuCl_4$	54	10%
10	$AuCl_3$ + 6,6'-diMe-bipy	27	- Unidentified side products
11	AuCl + 6,6'-diMe-bipy	21	- Unidentified side products

[a] Yield determined by ^{1}H NMR analysis using mesitylene as an internal standard; [b] The 6-*endo*-dig product was not observed; [c] 70 ^{o}C, 2 h.

Table 4.3 Evaluation of catalysts in model alkyne hydroamination reaction

Having already demonstrated the relative difficulty of synthesising complexes of type **4.2** compared to **4.1**, complex **4.10** was evaluated as a candidate catalyst in the hydroamination reaction. Interestingly, complex **4.10** performed worse than the equivalent oxo compound **4.9**, affording a 50% yield. Furthermore, starting material and several unidentified side products were visible in the ^{1}H NMR spectrum (entry 6). For completeness, neutral compound **4.4** was also evaluated (entry 7) together with $AuCl_3$ (entry 8). In both cases, an identical yield of 50% was achieved, with 25% starting material remaining in the crude reaction mixture. These results indicated the significance of using a cationic gold species in order to obtain ligand-tunable Au(III) bipy complexes which exhibit catalytic activity. For comparison purposes, the salt $NaAuCl_4$ was also tested and this too was found to give incomplete conversion when compared to Au(III)-oxo complexes at room temperature (entry 9). Finally, a pair of control experiments were set up using $AuCl_3$ and 6,6'-diMe-bipy (entry 10) and AuCl and 6,6'-diMe-bipy (entry 11) which both furnished unidentified side products and poor yields of **4.12**.

4.3 Conclusion

In the limited time available at the end of this project, a modest range of Au(III)-oxo complexes, **4.6**-**4.9**, were evaluated for the first time and shown to have catalytic activity in a model alkyne hydroamination reaction. Complex **4.7** (bearing a pair of 6,6'-dimethyl-2,2'-bipyridine ligands) was found to exhibit better activity than its phenanthroline analogue **4.8** and the unsubstituted complex **4.9**. The Au(III)-oxo complexes also displayed better catalytic activity than the neutral complex **4.4**, $AuCl_3$ and the simple salt $NaAuCl_4$.

In contrast to the Au(III) dichloride species **4.1** and **4.2**, and of structural importance is the ability of the Au(III)-oxo complexes to tolerate substitution at the 6,6' positions (for the bipy ligand) and 2,9 positions (for the phenanthroline ligand). Therefore, in the future it is anticipated that these Au(III)-oxo complexes have the potential to be modified and have application in the field of asymmetric gold(III) catalysis. Furthermore, if macrocylic bipy ligands are achieved, Au(III) oxo complexes may potentially be useful for active template synthesis of rotaxanes. In 2012, our work in this area was accepted and published in Catalysis Science and Technology.[152]

4.4 Experimental

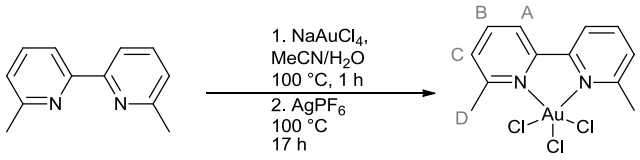
4.4.1 General Information

^{1}H NMR spectra were recorded on Bruker AV 300 and AV 400 spectrometers at 200 and 400 MHz respectively and referenced to residual solvent. ^{13}C NMR spectra were recorded using the same spectrometers at 75 and 100 MHz respectively. Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CDCl_3$ at δ_H 7.26 and CD_3CN at 1.94). *J* values are given in Hz and s, d, dd, t, q, quint and m abbreviations correspond to singlet, doublet, doublet of doublet, triplet, quartet, quintet and multiplet. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat to a diamond/ZnSe plate. Melting points were recorded on a Stuart Scientific SMP10 and are uncorrected. Flash column chromatography was carried out using Matrix silica gel 60 from Fisher Chemicals and TLC was performed using Merck silica gel 60 F254 pre-coated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$ or aqueous acidic ammonium molybdate as appropriate. Unless otherwise stated, reagents and solvents were purchased from commercial sources and used with no further purification. Pet. ether refers to petroleum ether which distils in the range 40 – 60 °C. Sodium tetrachloroaurate was kindly loaned by Johnson Matthey and used without further purification. Gold(III)-catalysed reactions were carried out in Fisherbrand™ one dram screw cap micro vials without the requirement for an inert atmosphere. All other reactions were carried out under an atmosphere of N_2.

4.4.2 Catalyst Synthesis

Catalysts **4.7**[174-175], **4.8**[176], **4.9**[175] and **4.10**[175] were synthesised in accordance with literature procedures.

[Au(bipy^{2Me})Cl$_3$] 4.4



4.4

Method A

To a stirring solution of sodium tetrachloroaurate (1.00 g, 2.76 mmol) in 25 mL of distilled water was added dropwise a solution of 6,6'-dimethyl-2,2'-bipyridine (509 mg, 2.76 mmol) in acetonitrile (40 mL). The resulting orange mixture was heated at reflux (100 °C) for 1 hour. The reaction was then cooled briefly to facilitate the rapid addition of silver hexafluorophosphate (699 mg, 2.76 mmol) and then subsequently returned to reflux for a further 15 hours. The resulting off-white precipitate was removed by passage over a short plug of Celite^{TM} and the filtrate concentrated *in vacuo*. The residue was then reconstituted in DCM, washed thrice with 100 mL distilled water and twice with brine (50 mL), before drying the organics over Na_2SO_4. Concentration *in vacuo* afforded a crude yellow-orange solid which was washed with cold MeOH (5 mL) to afford the target compound **4.4** as an orange solid (942 mg, 70%). Crystals were obtained by slow evaporation of a saturated acetonitrile solution of the product.

Method B

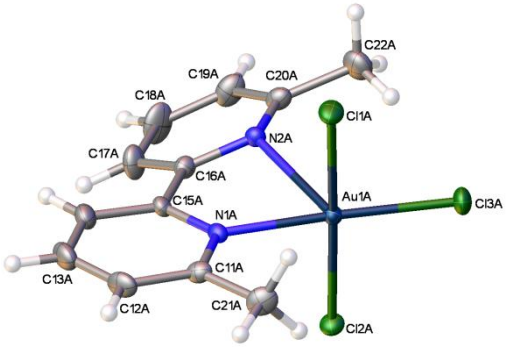
To a stirring solution of sodium tetrachloroaurate (1.00 g, 2.76 mmol) in 25 mL of distilled water and acetonitrile (40 mL) was added 6,6'-dimethyl-2,2'-bipyridine (509 mg, 2.76 mmol) and silver hexafluorophosphate (699 mg, 2.76 mmol). The resulting suspension was heated at 100 °C for 16 hours. The resulting off-white precipitate was removed by passage over a short plug of Celite^{TM} and the filtrate concentrated *in vacuo*. The residue was then reconstituted in DCM, washed thrice with 100 mL distilled water and twice with brine (50 mL), before drying the organics over Na_2SO_4. Concentration

in vacuo afforded a crude yellow-orange solid which was recrystallised from acetonitrile/diethyl ether to give the title compound **4.4** (780 mg, 58%).

Method C

To a stirring solution of sodium tetrachloroaurate (1.00 g, 2.76 mmol) in 25 mL of distilled water and acetonitrile (40 mL) was added 6,6'-dimethyl-2,2'-bipyridine (509 mg, 2.76 mmol) and potassium hexafluorophosphate (508 mg, 2.76 mmol). The resulting suspension was heated at 100 °C for 16 hours. The reaction mixture was then concentrated *in vacuo* before being reconstituted in acetonitrile (50 mL). The resulting suspension was then passed over a short plug of Celite^{TM} and the residue washed with acetonitrile (50 mL) until the eluent was colourless. The resulting solution was then re-concentrated and the residue reconstituted in DCM, washed thrice with 100 mL distilled water and twice with brine (50 mL), before drying the organics over Na_2SO_4. Concentration *in vacuo* afforded a crude yellow-orange solid which was recrystallised from acetonitrile/diethyl ether to give the title compound **4.4** (474 mg, 35%).

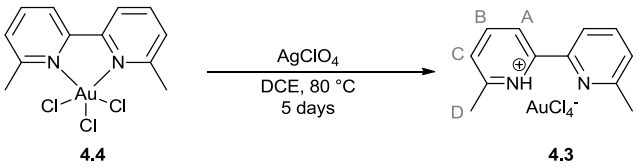
Mp 188 ^{o}C (decomposes); ν_{max} /cm^{-1} 3096 (C-H), 1588 (Ar C=C), 1571 (Ar C=C), 1456 (Ar C=C); δ_H (300 MHz, CD_3CN) 8.04 - 8.15 (4 H, m, H_A, H_B), 7.65 (2 H, dd, *J*=7.7, 1.8 Hz, H_C), 3.05 (6 H, s, H_D); δ_C (75 MHz, CD_3CN) 160.4 (C), 152.5 (C), 142.0 (C-H), 128.7 (C-H), 124.7 (C-H), 26.2 (CH_3); Found (EI+): $[M-H]^+$ 484.9651, C_{12} $H_{11}N_2AuCl_3$ requires 484.9648.



Empirical formula	$C_{24}H_{24}N_4Cl_6Au_2$
Formula weight	487.56
Temperature/K	100.15
Crystal system	Monoclinic
Space group	$P2_1/n$
a/Å	18.1080(10)
b/Å	9.5124(5)
c/Å	18.3546(12)
α/°	90.00
β/°	113.590(8)
γ/°	90.00
Volume/Å^3	2897.4(3)
Z	4
ρ_{calc}mg/mm^3	2.235
m/mm^{-1}	10.691
F(000)	1824
Crystal size/mm^3	0.08 × 0.03 × 0.02
2Θ range for data collection	6.2 to 54.96°
Index ranges	$-23 \leq h \leq 23$, $-11 \leq k \leq 12$, $-13 \leq l \leq 23$
Reflections collected	13122
Independent reflections	6581[R(int) = 0.0217]
Data/restraints/parameters	6581/0/329
Goodness-of-fit on F^2	1.044
Final R indexes [I>=2σ (I)]	R_1 = 0.0175, wR_2 = 0.0437
Final R indexes [all data]	R_1 = 0.0199, wR_2 = 0.0447
Largest diff. peak/hole / e Å^{-3}	0.898/-0.777
Flack Parameter	N/A

6,6'-Dimethyl-[2,2'-bipyridin]-1-ium tetrachloroaurate$^{(III)}$ 4.3

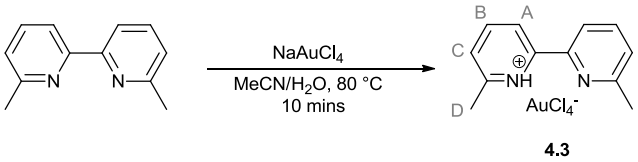
Method A:



4.4 **4.3**

To a stirring solution of [Au(bipy^{2Me})Cl_3] **4.4** (100 mg, 0.21 mmol) in 4 mL of DCE was added $AgClO_4$ (47 mg, 0.23 mmol) and the resulting orange mixture heated to 80 °C for 5 days, during which a grey precipitate formed. The reaction was then cooled to room temperature and the precipitate removed by vacuum filtration. The filter cake was washed thoroughly with DCE (5 mL) and the yellow filtrate concentrated *in vacuo* to afford a yellow-orange solid. The residue was then recrystallised by vapour diffusion (MeCN/Et_2O) to afford the target complex **4.3** as a bright yellow solid (81 mg, 75%).

Method B:



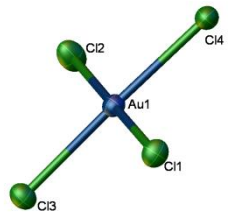
4.3

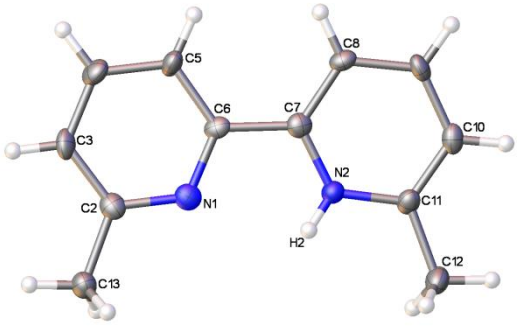
To a stirring solution of $NaAuCl_4$ (100 mg, 0.276 mmol) in H_2O (1 mL) was added 6,6'-dimethyl-2,2'-bipyridine (51 mg, 0.276 mmol) in acetonitrile (1 mL) at the resulting mixture heated to 80 °C for 10 minutes during which time a bright yellow precipitated formed. The precipitate was removed by vacuum filtration and washed consecutively with H_2O (5 mL), EtOH (5 mL) and Et_2O (5 mL). The crude yellow product was then recrystallised from acetonitrile/Et_2O to afford the title compound **4.3** as a bright yellow solid (41 mg, 28%).

Mp 114-116 °C (decomposes); ν_{max} /cm^{-1} 3096 (N-H), 2924 (C-H), 1615 (Ar C=C) , 1595 (Ar C=C), 1520 (Ar C=C), 1446 (Ar C=C); δ_H (300 MHz, CD_3CN) 7.94 - 8.29 (4 H, m, H_A, H_B), 7.65 (2 H, dd, *J*=7.7, 1.8 Hz, H_C), 3.05 (6 H, s, H_D); δ_C (75 MHz,

CD_3CN) 158.8 (C), 147.1 (C), 144.6 (C-H), 129.1 (C-H), 121.9 (C-H), 22.7 (CH_3). Found (ESI): $[M]^+$ 185.1070, $C_{12}H_{13}N_2^+$ requires 185.1073. Found (ESI): $[M]^-$ 336.8424, $AuCl_4^-$ requires 336.8425.

Polymorph using Method A:

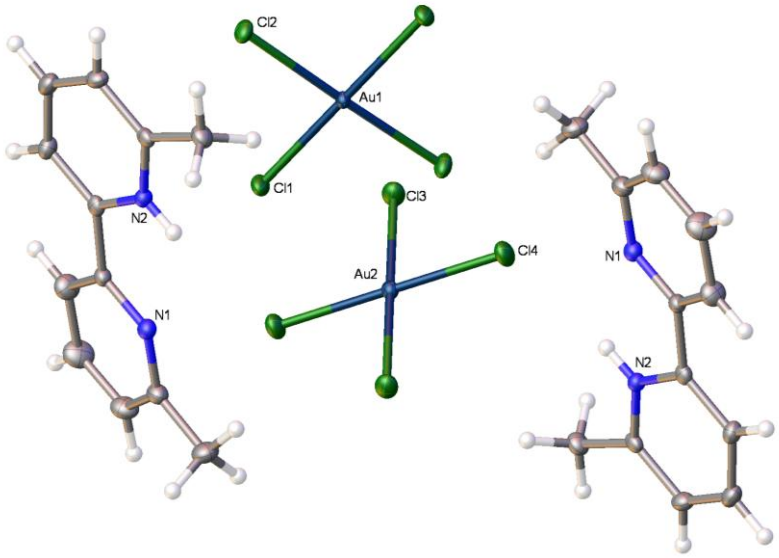




Empirical formula	$C_{12}H_{13}N_2 \cdot AuCl_4$
Formula weight	524.01
Temperature/K	100.15
Crystal system	Monoclinic
Space group	$P2_1/n$
a/Å	10.8712(6)
b/Å	11.7030(7)
c/Å	12.3206(7)
α/°	90.00
β/°	95.806(3)
γ/°	90.00
Volume/$Å^3$	1559.46(15)
Z	4
$\rho_{calc}mg/mm^3$	2.232
m/mm^{-1}	10.11
F(000)	984
Crystal size/mm^3	0.38 × 0.24 × 0.08
2Θ range for data collection	5.2 to 53.4°

Index ranges	$-13 \leq h \leq 13, 0 \leq k \leq 14, 0 \leq l \leq 15$
Reflections collected	63730
Independent reflections	3289[R(int) = 0.059]
Data/restraints/parameters	3289/1/178
Goodness-of-fit on F^2	1.30
Final R indexes [I>=2σ (I)]	$R_1 = 0.041$, $wR_2 = 0.106$
Final R indexes [all data]	$R_1 = 0.0526$, $wR_2 = 0.1056$
Largest diff. peak/hole / e $Å^{-3}$	2.99/-1.02
Flack Parameter	N/A

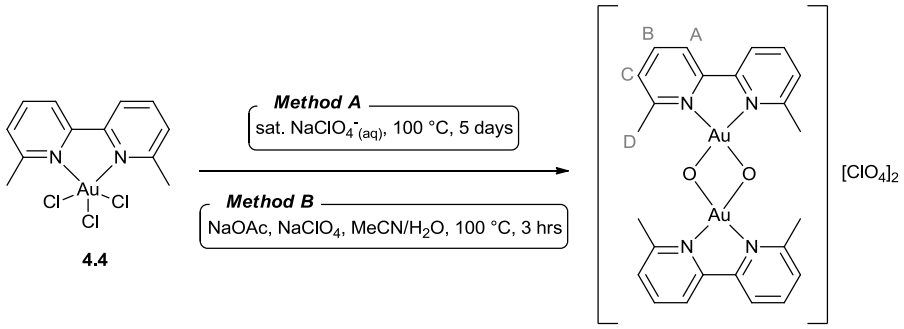
Polymorph using Method B:



Empirical formula	$C_{12}H_{13}N_2 \cdot AuCl_4$
Formula weight	524.01
Temperature/K	100.15
Crystal system	Monoclinic
Space group	C2/c
a/Å	22.1175(10)
b/Å	14.7910(7)
c/Å	9.5257(4)
α/°	90.00
β/°	99.676(2)
γ/°	90.00
Volume/$Å^3$	3071.9(2)
Z	8
$\rho_{calc}mg/mm^3$	2.266

m/mm^{-1}	10.260
F(000)	1968
Crystal size/mm^3	0.24 × 0.12 × 0.08
2Θ range for data collection	5.5 to 65.68°
Index ranges	$-33 \leq h \leq 33$, $-22 \leq k \leq 22$, $-14 \leq l \leq 14$
Reflections collected	40918
Independent reflections	5667[R(int) = 0.0574]
Completeness to Θ = 25.00°	99.9%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.4941 and 0.1921
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5667/0/179
Goodness-of-fit on F^2	1.016
Final R indexes [I>=2σ (I)]	R_1 = 0.0275, wR_2 = 0.0615
Final R indexes [all data]	R_1 = 0.0356, wR_2 = 0.0649
Largest diff. peak/hole / e $Å^{-3}$	2.160/-3.005

[Au(bipy^{2Me})(μ-O)]$_2$[ClO$_4$]$_2$ 4.6



4.4 4.6

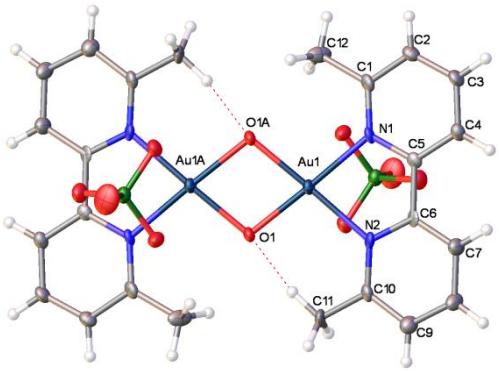
Method A

A saturated aqueous solution of $NaClO_4$ (30 mL) was added to [Au(bipy^{2Me})Cl$_3$] **4.4** (200 mg, 0.41 mmol) and the resulting suspension heated at 100 °C for 5 days. The reaction was then cooled to room temperature and the precipitate removed by vacuum filtration. The filter cake was washed thoroughly with distilled water (50 mL), ice-cold MeCN (3 mL) followed by Et_2O (10 mL). The crude residue was then recrystallised by vapour diffusion (MeCN/Et_2O) to afford the target complex **4.6** as a yellow solid (90 mg, 22%).

Method B

To a stirring suspension of [Au(bipy^{2Me})Cl$_3$] **4.4** (170 mg, 0.35 mmol) in CH_3CN (1 mL) were added an aqueous solution of NaOAc (95 mg, 0.70 mmol, 60 mL) and $NaClO_4$ (128 mg, 1.05 mmol). The resulting suspension was refluxed for 3 hours which corresponded with a lightening of the suspension colour. The reaction was then cooled to room temperature, the precipitate collected by vacuum filtration and the filter cake washed with H_2O (25 mL) then Et_2O (25 mL). Recrystallisation of the crude product from MeCN/Et_2O gave the target compound **4.6** as a pale yellow solid (145 mg, 42%).

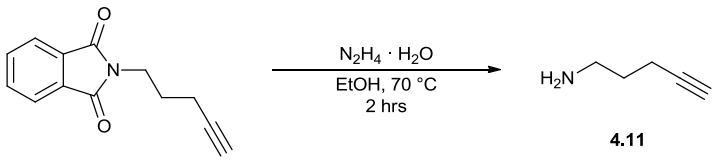
Mp. 203-206 °C (decomposes); ν_{max} /cm^{-1} 3085 (C-H), 1603 (Ar C=C), 1570 (Ar C=C), 1471 (Ar C=C); δ_H (300 MHz, CD_3CN) 8.37 - 8.24 (4 H, m, H_A, H_B), 7.70 (2 H, dd, *J* =1.8, 7.3 Hz, H_C), 2.96 (6 H, s, H_D); δ_C (75 MHz, C_2D_6SO) 162.2 (C), 155.0 (C), 143.3 (C-H), 131.9 (C-H), 123.1(C-H), 20.4 (CH_3); Found (ESI): [M-ClO$_4$]$^+$ 893.0687, $C_{24}H_{24}Au_2N_4O_6Cl$ requires 893.0710.



Empirical formula	$C_{12}H_{12}AuClN_2O_5$
Formula weight	496.65
Temperature/K	200.15
Crystal system	Triclinic
Space group	P-1
a/Å	7.6032(6)
b/Å	7.6032(6)
c/Å	9.9600(9)
α/°	82.321(5)
β/°	85.907(5)
γ/°	88.085(5)
Volume/Å^3	690.65(10)
Z	2
ρ_{calc}mg/mm^3	2.388
m/mm^{-1}	10.867
F(000)	468.0
Crystal size/mm^3	0.34 × 0.12 × 0.04
2Θ range for data collection	4.14 to 61.16°
Index ranges	$-10 \leq h \leq 10$, $-12 \leq k \leq 13$, $-14 \leq l \leq 13$
Reflections collected	14381
Independent reflections	4058[R(int) = 0.0572]
Data/restraints/parameters	4058/421/192
Goodness-of-fit on F^2	1.063
Final R indexes [I>=2σ (I)]	R_1 = 0.0724, wR_2 = 0.1982
Final R indexes [all data]	R_1 = 0.0821, wR_2 = 0.2089
Largest diff. peak/hole / e Å^{-3}	13.15/-4.46
Flack Parameter	N/A

4.4.3 Model Alkyne Hydroamination Reaction

Pent-4-yn-1-amine[177] 4.11

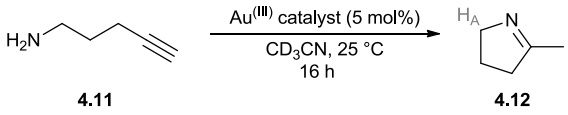


4.11

To a stirring suspension of *N*-(pent-4-yn-1-yl)phthalimide (4.00 g, 0.02 mmol) in EtOH (40 mL) was added hydrazine monohydrate (1.90 g, 0.04 mmol) and the reaction heated at 70 °C for 2 hours, during which time the initial suspension was replaced by a thick white precipitate. The precipitate was fully solvated by addition of distilled water (70 mL) and subsequently cooled to 0 °C. The pH of the solution was then carefully adjusted to pH 3.5 by dropwise addition of 2 M HCl (monitored with a calibrated Hanna Instruments™ pH meter) and the resulting white suspension removed by vacuum filtration. The filtrate was concentrated *in vacuo* to remove the ethanol, before the solution was re-cooled to 0 °C and basified with 10 M NaOH (aq). The aqueous mixture was then extracted twice with DCM (150 ml) and the combined organic extracts washed with brine, before drying over Na_2SO_4. Evaporation of the solvent afforded the title amine **4.11** as a pale yellow oil (0.81 g, 52%) which was used without further purification.

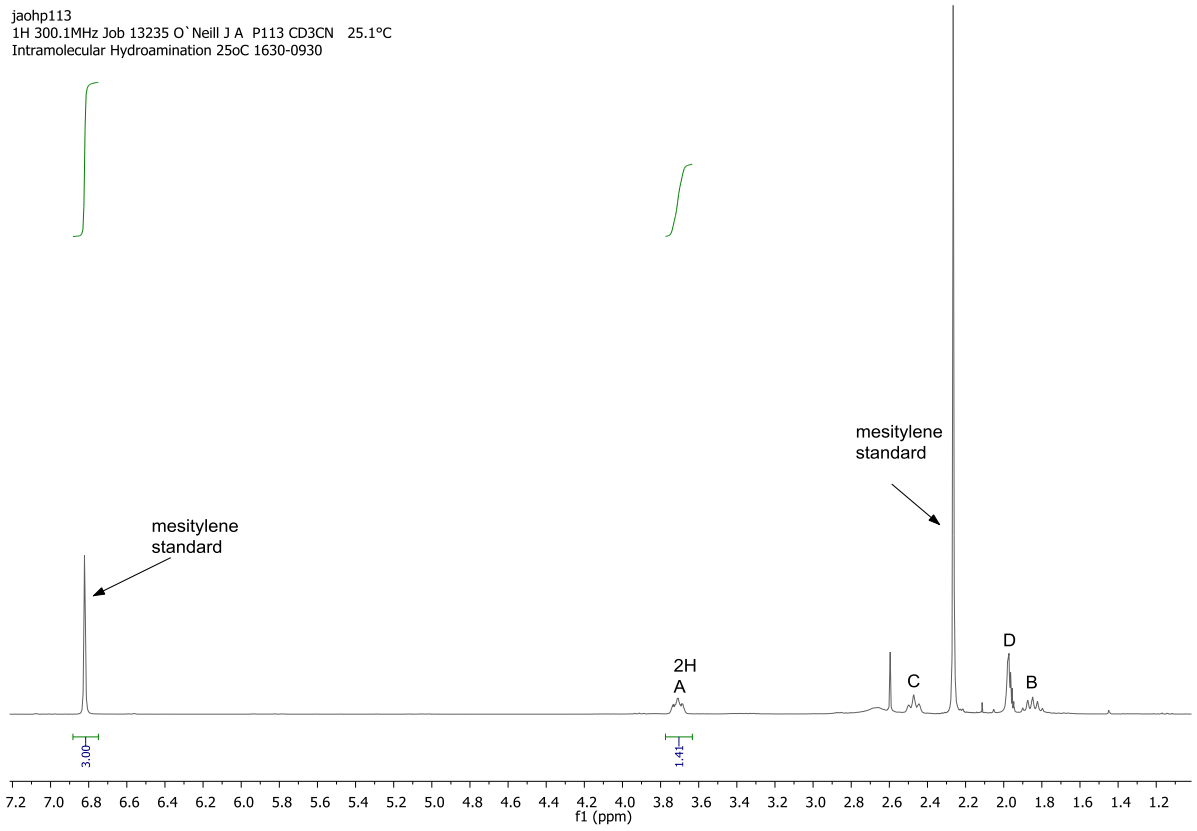
ν_{max} /cm^{-1} 3369 (N-H), 3294 (≡C-H), 3214 (N-H), 2938 (C-H), 2863 (C-H), 2115 (C≡C); δ_H (300 MHz, $CDCl_3$) 2.76 (2H, t, *J*=7.0 Hz, NC$\underline{H}_2$), 2.22 (2H, td, *J*=2.8, 7.0 Hz, C$\underline{H}_2$C≡), 1.92 (1H, t, *J*=2.8 Hz, ≡C-$\underline{H}$), 1.62 (2H, quint., *J*=7.0 Hz, $CH_2C\underline{H}_2CH_2$), 1.41 - 1.18 (2H, br. s, -NH_2); δ_C (75 MHz, $CDCl_3$) 83.9 (C), 68.5 (C-H), 41.0 (CH_2), 32.0 (CH_2), 15.8 (CH_2); Found (CI+): $[M+H]^+$ 84.0807, $C_5H_{10}N$ requires 84.0808.

4.4.4 Au$^{(III)}$ Catalysed Hydroamination Reaction General Procedure



4.11 **4.12**

To a Fisherbrand™ one dram micro-vial equipped with a micro stirrer bar, was added pent-4-yn-1-amine **4.11** (1 equiv) and dissolved in CD_3CN (0.5 M). The appropriate gold catalyst (5 mg, 5 mol%) was added to the vial and the lid screwed on. The reaction was stirred for 16 h at 25 °C before mesitylene (1 equiv.) was added. The reaction mixture was then further diluted with CD_3CN (0.5 mL) and an aliquot taken for crude ^1H NMR analysis. The yield of **4.12**[178] was measured by integration of the multiplet peak corresponding to H_A with respect to the mesitylene aromatic peak (*N.B.* **4.12** is not stable on silica or alumina). δ_H (300 MHz, CD_3CN) 3.78- 3.62 (2H, m, H_A), 2.44 (2H, app. t, J = 11.11 Hz, CH_2), 1.96 (3H, s, CH_3), 1.91- 1.77 (2H, m, CH_2).



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