Active Template Strategies for the Assembly of Mechanically Interlocked Molecules

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Dedicated to my Family
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Abstract

Chemical templates have allowed the synthesis of increasingly complex mechanically interlocked molecular architectures. Transition metals are useful templating agents. Their coordination requirements result in the well-defined, three-dimensional orientation of reactive fragments. Judicious choice of ligand and metal leads to a mechanically interlocked product upon covalent bond formation between the fragments. In such ‘passive’ templates a stoichiometric quantity of metal, with respect to the reacting components, is required. The metal atom acts as ‘glue’ until covalent, and consequent mechanical, bond formation has occurred. Recently in the Leigh group a fundamentally novel approach to interlocked architectures has been discovered and takes its cue from transition metal catalysis: in addition to inducing the necessary degree of preorganization in the system, the metal also mediates the covalent bond formation. This thesis describes further investigation of the original active template reaction—a ‘click’ reaction—and the subsequent extension of the strategy to new reactions and architectures.

The effect of varying the macrocyclic ligand on the original Cu(I)-catalyzed 1,3-dipolar cycloaddition between alkynes and azides was investigated. Notably, the interlocked nature of the products provided new mechanistic insights into the nature of this widely used reaction. Following this, a Ni(II) active template was developed for the homocoupling of terminal alkynes. An unusual Ni/Cu system for this reaction was discovered and the resulting [2]rotaxanes were produced in excellent yield. The utility of the active template strategy was further demonstrated by the synthesis of a [3]rotaxane from a bifurcated macrocycle with a pyridyl bridging unit. Cu(I) catalyzed the formation of a triazole thread through each cavity, showing that multiple mechanical bonds can be formed from a single active template binding site. Lastly, the potential of carbene transfer reactions in the active template approach was investigated. A stoppered diazoester compound was synthesized and used in studies towards X-H insertion and cycloaddition reactions in the presence of a range of macrocyclic ligands.
Declaration

The scientific work described in this thesis was carried out in the School of Chemistry at the University of Edinburgh between September 2005 and September 2008. Unless otherwise stated, it is the work of the author and has not been submitted in whole or in support of an application for another degree or qualification of this or any other University or institute of learning.

Signed..........................................

Date........................................
Conferences and Meetings Attended

1. **Scottish Organic and Biomolecular Chemistry meeting**, University of Aberdeen, UK, 12/08.


3. **Scottish Chemical Industries Postgraduate Symposium**, University of Strathclyde, UK, 04/08. 20 minute oral presentation entitled ‘Active Template Strategies for the Synthesis of Mechanically Interlocked Architectures’.


8. **Scottish Organic and Biomolecular Chemistry meeting**, University of Strathclyde, 12/05.
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The research described would not have been possible without the fantastic technical support I have received over the last three years, for which I would like to thank: Diego Gonzales, Mark Symes, Paul McGonigal and Max Von Delius, for keeping all things NMR running smoothly; Alan Taylor, for a first class mass spectrometry service; Prof. Alexandra Slawin for solving crystal structures and Stewart Franklin and Louise Hogg for synthesizing some starting materials, saving me countless lab hours by doing so.

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Finally I would like to thank my family for their continued support and encouragement throughout both my PhD and my first degree, and thanks to Scott for keeping me sane (or doing his best!) during the hectic last months of lab work and the writing-up period.
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>Å</td>
<td>Angstrom</td>
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<tr>
<td>δ</td>
<td>Chemical shift</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
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<tr>
<td>App.</td>
<td>Apparent</td>
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<tr>
<td>Bipy</td>
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<td>Boc</td>
<td>t-Butyloxycarbonyl</td>
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<td>CPK</td>
<td>Corey-Pauling-Koltun</td>
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<tr>
<td>DB24C8</td>
<td>Dibenzo-24-crown-8</td>
</tr>
<tr>
<td>Decomp.</td>
<td>Decomposition</td>
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<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N'$-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>EDCI</td>
<td>1-(3-Dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylenediamine tetraacetic acid</td>
</tr>
<tr>
<td>Equiv.</td>
<td>Equivalent</td>
</tr>
<tr>
<td>ESI</td>
<td>Electrospray Ionization</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>FAB</td>
<td>Fast Atom Bombardment</td>
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<tr>
<td>g</td>
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<tr>
<td>Gly</td>
<td>Glycine</td>
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<td>h</td>
<td>Hours</td>
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<tr>
<td>H-bonding</td>
<td>Hydrogen bonding</td>
</tr>
<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectrometry</td>
</tr>
<tr>
<td>IPA</td>
<td>Isopropyl Alcohol</td>
</tr>
<tr>
<td>IUPAC</td>
<td>International Union of Pure and Applied Chemistry</td>
</tr>
<tr>
<td>$J$</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>--------------</td>
<td>------------------------------------------------</td>
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<tr>
<td>LRMS</td>
<td>Low Resolution Mass Spectrometry</td>
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<tr>
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<tr>
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</tr>
<tr>
<td>mmol</td>
<td>Millimoles</td>
</tr>
<tr>
<td>M.p.</td>
<td>Melting point</td>
</tr>
<tr>
<td>MS</td>
<td>Mass Spectrometry</td>
</tr>
<tr>
<td>m/z</td>
<td>Mass-to-charge ratio</td>
</tr>
<tr>
<td>NHC</td>
<td>N-Heterocyclic Carbene</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>NOBA</td>
<td>m-Nitrobenzyl alcohol</td>
</tr>
<tr>
<td>ppm</td>
<td>Part per million</td>
</tr>
<tr>
<td>Pybox</td>
<td>Pyridine 2,6-bisoxazoline</td>
</tr>
<tr>
<td>RCM</td>
<td>Ring Closing Metathesis</td>
</tr>
<tr>
<td>RT</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>Sat.</td>
<td>Saturated</td>
</tr>
<tr>
<td>Terpy</td>
<td>Terpyridine</td>
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<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>THIOG</td>
<td>Thioglycerol</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>TM</td>
<td>Transition Metal</td>
</tr>
<tr>
<td>TMEDA</td>
<td>Tetramethyl Ethylenediamine</td>
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</tbody>
</table>
General Comments on Experimental Data

Unless stated otherwise, all reagents were purchased from Aldrich Chemicals and used without further purification. Anhydrous solvents were obtained by passing the solvent through an activated alumina column on a PureSolv™ solvent purification system (Innovative Technologies Inc., MA). Column chromatography was carried out using Kieselgel C60 (Merck, Germany) as the stationary phase, and TLC was performed on pre-coated silica gel plates (0.25 mm thick, 60F254, Merck, Germany). All ¹H and ¹³C NMR spectra were recorded on a Bruker AV400 instrument at a constant temperature of 300 K. All ¹³C NMR experiments were proton decoupled. Chemical shifts are reported in parts per million from low to high field and referenced to TMS. Coupling constants (J) are reported in hertz (Hz). Standard abbreviations indicating multiplicity are used as follows: m = multiplet, br = broad, d = doublet, q = quartet, ‘quint.’ = quintet, t = triplet, s = singlet. All melting points were determined using Sanyo Gallenkamp apparatus and are reported uncorrected. Low resolution ESI mass spectrometry was performed with a Micromass Platform II mass spectrometer controlled using Masslynx v2.3 software while FAB, EI and high resolution ESI mass spectrometry was carried out by the laboratory services at the University of Edinburgh.
Thesis Layout

This thesis describes the active template strategy towards the formation of mechanically interlocked architectures. Chapter 1 provides an introduction to the work described in this thesis by covering background information and relevant literature. The research carried out during this PhD is described in Chapters 2 to 5. For this reason, numbering of compounds starts at 1 at the beginning of Chapter 2, and any compounds referred to after this are within the ‘results and discussion’ chapters (2 to 5).

Chapter 2 describes further investigations into the first active-template reaction, the CuACC ‘click’ reaction, the effect of varying the macrocyclic ligand on the outcome of the reaction and some interesting mechanistic implications. Chapter 3 describes an unusual Ni-Cu-mediated alkyne homocoupling active template reaction. Chapter 4 describes the synthesis of doubly threaded [3]rotaxanes using active template methodology, generating multiple mechanical bonds with one metal binding site within a bifurcated macrocycle. Chapter 5 describes attempts to develop an active template reaction using carbene transfer reactions, the rational choice of reactions and reactants and the most promising results.

Chapter 2 presents portions of work from a published article. No attempt has been made to rewrite the work out of context, although only the results relevant to this thesis have been reported and the compounds have been re-numbered.
Chapter 1: Introduction to the Templated Assembly of Mechanically Interlocked Molecules
1.1 Mechanical Bonds and Interlocked Molecules

Mechanically interlocked architectures are kinetically stable ‘entanglements’ of covalently bonded backbones. Unlike classical molecular structures, interlocked molecules consist of two or more separate, covalent, components which are not connected to each other by covalent bonds. These structures are true molecules and not supramolecular species as each component is intrinsically linked to the other by what is termed a ‘mechanical bond’ and cannot be separated without the cleavage of a covalent bond.

The two most commonly studied mechanically interlocked architectures are rotaxanes and catenanes (Figure 1.1). A catenane, from the Latin, catena, meaning ‘chain,’ consists of interlocked rings. A ring trapped on a linear unit (or ‘thread’) by two bulky substituents (‘stoppers’) is known as a rotaxane (from the Latin rota, meaning ‘wheel’ and axle, meaning ‘axis’).

A numerical prefix denotes the number of mechanically bonded components in the molecule. Figure 1.1 shows the simplest example of a catenane, a [2]catenane. However, a catenane can theoretically contain any number of rings linked in a number of ways. The simplest rotaxane is a [2]rotaxane (Figure 1.1, a). However the thread of a rotaxane could accommodate more than one ring or indeed one ring could encircle multiple threads. Catenanes are topological isomers of their non-interlocked components because they cannot be separated from each other without breaking one of the rings. Rotaxanes are not topological isomers of their non-interlocked components because by infinitely stretching the ring (which is only mathematically,
not physically, possible) it could slip over the stoppers and dissociate from the thread.

Catenanes and rotaxanes are widely studied due the interesting physical and chemical properties they possess compared to their non-interlocked analogues and the potential of the components to move, in response to external stimuli, relative to one another. This large amplitude mechanical motion at the molecular level can be harnessed and utilized in the operation of molecular machines.1

1.2 History and Early Synthetic Attempts

Mechanically interlocked molecules were realized synthetically in 1960 by Frisch and Wasserman, who synthesized the first catenane.2 It was some time later before the first rotaxane was synthesized, by Harrison, using a solid-supported thread.3 These syntheses were statistical, that is they relied on chance interlocking before covalent bond formation. As a result of this, yields were very low. Although Frisch and Wasserman had discussed the possibility of using Möbius strips to direct catenane formation,4 the first directed synthesis of a catenane was reported by Schill and co-workers and made use of covalent bonds to direct interlocking of the rings (Scheme 1.1).5 The tetrahedral nature of the sp3 carbon of the acetal group in 1 directs bond formation above and below the plane of the existing ring.

1.3 Template-Directed Synthesis

Schill’s covalent bond-directed catenane synthesis was the first example of the use of a chemical template for the generation of mechanically bonded molecules and it paved the way for the subsequent surge of interest in these molecules. Chemical templates ‘organize an assembly of atoms, with respect to one or more geometric loci, in order to achieve a particular linking of atoms.’ Such templates exploit attractive interactions between covalently bound components. The result is a complex which is predisposed to form mechanical bonds when the components become covalently linked together.

There are classically two main strategies for the template-directed synthesis of rotaxanes: the ‘clipping’ strategy proceeds via a preformed thread coordinated to a ‘u-shape’ which is closed, or ‘clipped’ around the thread (Figure 1.2, a). The macrocycle may also be assembled about the thread from multiple fragments in this strategy. In the ‘stoppering’ approach, the axle is threaded through the macrocycle, followed by attachment of the stoppers (Figure 1.2, b). It should be noted that a third approach to pseudorotaxane assembly, ‘slippage’, also exists, whereby a system is heated so that the ring may slip over the stoppers, where it is kinetically trapped upon cooling. However this is not template-directed and the molecules produced are not, according to the IUPAC definition, rotaxanes.

Figure 1.2. Schematic representations of: a) clipping approach to rotaxanes; b) stoppering approach to rotaxanes; c) single clipping approach to catenanes; d) double clipping approach to catenanes.
Although the seminal work of Schill and co-workers described the exploitation of the geometry of covalent bonds to direct mechanical bond formation, the majority of subsequent syntheses have made use of non-covalent (supramolecular) interactions.

### 1.3.1 Transition Metal Templates

Following Schill’s pioneering work on directed synthesis, in 1984 the group of Jean-Pierre Sauvage developed one of the first non-covalent bond chemical templates. This transition metal-directed synthesis marked the beginning of a new phase for the field of interlocked molecules, by making them synthetically accessible. The use of transition metals (TMs) to hold ligands in a specific orientation, directing bond formation to result in the interlocked product, is very attractive to the synthetic chemist. The interactions are strong, thus less preorganization is required, and the shapes of the complexes are well defined as they are dictated by the preferred geometry of the metal.

The elegant strategy of Sauvage and co-workers made use of the tetrahedral geometry of Cu(I) to hold two phenanthroline-containing fragments orthogonally while covalent bond formation led to a catenane. In the first report, the two rings were closed using a Williamson ether synthesis (Scheme 1.2), but greater success was later achieved using ring closing metathesis (RCM). Both double RCM and closure of one ring around a pre-formed macrocycle gave impressive yields (92-93% and 90% respectively) of the corresponding catenate (that is, the metal-complexed catenane) which was demetallated almost quantitatively, using KCN, to give the corresponding catenand 6.
This copper-ligand core has also been used by Sauvage and others to generate more complex molecules, including rotationally constrained rotaxanes, topologically chiral [2]rotaxanes, [3]catenanes and a ‘hook and ladder’ molecular knot, synthesized via a [2]catenane.

Gibson and co-workers used the same motif in the first transition metal-directed synthesis of a rotaxane in 1991 (Scheme 1.3). Following formation of the Cu(I) complex, attachment of bulky stoppers, by Williamson ether synthesis, and subsequent demetallation using cyanide, gave the desired [2]rotaxane in 42% yield.
Following Gibson’s rotaxane synthesis, the Sauvage group described [2]-, [3]-\(^{17,18}\) and [5]rotaxanes\(^{18}\) using the Cu(I)-phenanthroline template. The group of Sauvage have also synthesized a trefoil knot using this Cu(I) template.\(^{19,20}\)

A 6-coordinate metal template was reported by the Sauvage group in 1991.\(^{21}\) This allowed the use of tridentate, terpy ligands, which were coordinated to Ru(II), generating a *pseudo-octahedral* complex (9) (Scheme 1.4). Ring-closure by Williamson ether synthesis afforded [2]catenate 10 in a rather modest 11% yield. The high affinity of Ru(II) for terpy ligands meant that the ruthenium could not be removed from the catenate.

The use of Fe(II) as a more labile substitute was discussed in the same paper and later attempted,\(^{22}\) however, unexpected formation of a large macrocycle, rather than the desired catenate, during the RCM ring-closing reaction meant that this route was unsuccessful.

Over a decade after the first Ru-(II) catenate, Sauvage and co-workers reported a Ru(II)-template catenane synthesis from a macrocycle containing two phenanthroline binding sites and a bipy-containing thread.\(^{23}\) This catenate was applied as the first TM-based, light-driven molecular machine.\(^{24}\) The same three-chelation point template was also applied to a threading rotaxane strategy where this
time the thread contained the bis-phenanthroline motif and the macrocycle contained the bipy binding site.\textsuperscript{25}

A Rh(III) template\textsuperscript{23} has also been developed by the Sauvage group for [2]catenane synthesis. This made use of the same components and clipping strategy as for the previously reported Ru(II)\textsuperscript{26} template. However, in the Rh(III) system, the bipyridyl thread forms an \textit{exo} complex with the rhodium due to its 4,4-substitution pattern, in contrast to the \textit{endo} nature of the Ru(II) complex (Scheme 1.5). The threaded complex, 11, was isolated in 14\% yield before being subjected to RCM conditions. The Rh(III) catenate 12 was obtained in 34\% yield.

\textbf{Scheme 1.5} Sauvage’s Rh(III) template for catenate assembly.\textsuperscript{23}

Fe(II) has been used as a templating ion for the synthesis of a trefoil knot, by Sauvage, using four terpy ligands (Figure 1.3).\textsuperscript{27} Knot 13 was obtained in 20\%, from the non-interlocked complex, from an RCM reaction followed by quantitative hydrogenation.
In 2001 Leigh and co-workers reported octahedral analogues of the original Sauvage tetrahedral Cu(I) catenate (Scheme 1.6). Two bis(2,6-diiminopyridine)-derived ligands formed a complex, 14, with a range of transition metals. Ring closing metathesis of the preformed complex gave the corresponding [2]catenate, 17, in yields of between 5% (Hg$^{2+}$) and 81% (Zn$^{2+}$), from which the metal could be removed to give the catenand. The catenate could also be assembled from bis-amine 16 and 2,6-pyridinecarbaldehyde (15) in the presence of Zn(ClO$_4$)$_2$.6H$_2$O in 53% yield, and showed promising results for the other transition metals by this route.

![Scheme 1.6. Leigh's octahedral transitional metal template for [2]catenate synthesis.](image)

**Figure 1.3.** An Fe(II)-template trefoil knot.
In 2004 this template was extended to rotaxanes.\textsuperscript{29} This elegant five-component self-assembly occurs by imine bond formation under thermodynamic control (Scheme 1.7). Despite the fact that imine N donors often form stronger coordination bonds than the corresponding amines\textsuperscript{30} the rotaxane-metal complex (22) is thermodynamically favoured over the dithread-metal complex, as demonstrated by the excellent isolated yields of metallated rotaxanes obtained (Scheme 1.7). This is proposed to be due to a lack of favourable π-stacking interactions in the dithread complex, which are present in the rotaxane.

Scheme 1.7. Leigh's five-component self-assembly of a [2]rotaxane under thermodynamic control, using a 6-coordinate metal template.\textsuperscript{29}

Sauvage and co-workers have used Zn(II) to template [2]catenane assembly,\textsuperscript{31} using a 5-coordinate analogue of their original Cu(I) template. The templating effects of Zn(II) ions were also utilized in what is arguably one of the most elegant multi-component, metal-templated self-assemblies to date: the synthesis of molecular borromean rings. This mathematically interesting structure, in which three rings are
linked such that scission of any one ring results in dissociation of the other two, was synthesized from DNA by Mao et al in 1997. The strategy adopted by Stoddart and co-workers used six Zn(II) ions to template the self-assembly of borromeate $24$ from imine bond formation between six 2,6-pyridinecarbaldehyde ligands (15) and six bipyridyl ligands (23) under thermodynamic control (Scheme 1.8). After 36 h at reflux in MeOH the thermodynamically favoured borromeate $24$ was obtained in 78% yield following recrystallization. Single crystals were also grown and the crystal structure (shown in Scheme 1.7) proved unequivocally the formation of molecular borromean rings.

![Scheme 1.8. Stoddart's eighteen-component, Zn(II)-templated self-assembly of molecular borromean rings.](image)

It is not only three-dimensional TM complexes that lend themselves well to template-directed synthesis. Leigh and co-workers have made use of a square planar Pd(II) template to synthesize rotaxanes and catenanes, generating three-dimensional molecules from two-dimensional templates (Scheme 1.9). Complex $25$.Pd(MeCN) forms a complex with a pyridine-containing thread to give complex $26$.Pd; it is thought that formation of this three-dimensional complex is driven by intercomponent $\pi-\pi$ stacking, which encourages the donor N atom of the thread to bind the metal ion orthogonally to the tridentate ligand. The result is formation of [2]rotaxane $28$ following RCM/hydrogenation of $26$.Pd and subsequent demetallation. The same palladium complex can be used to assemble a catenane via
27.Pd, giving the catenate 31.Pd in 78% yield following RCM/hydrogenation of 27.Pd. Removal of the metal gave catenand 31. From complex 29.Pd(MeCN) [the ring-closed analogue of 25.Pd(MeCN)] complex 30.Pd was formed (a complex in which the open pyridine diether ligand does not penetrate the ring but binds in an *exo* fashion was also formed, but is not shown). RCM/hydrogenation of 30.Pd and subsequent demetallation, gave 25% of catenand 31.

![Scheme 1.9. Leigh's Pd(II)-directed synthesis of a) a rotaxane and b), c) a catenane. A third product, a large macrocycle, results when both the monodentate and tridentate ligands are acyclic, but is not shown. Reagents and conditions: i) 1. Grubbs 1 (0.1 equiv.), CH₂Cl₂, 2. H₂, Pd/C, THF, 3. KCN, MeOH, CH₂Cl₂.](image-url)
Leigh and co-workers have also recently reported the use of a linear, Au(I) template for the synthesis of a homocircuit [2]catenane in 41% yield (Scheme 1.10) and a [2]rotaxane in 24% yield. The reduction in yield when the template is applied to rotaxane synthesis arises from ligand scrambling, leading to production of some [2]catenane as a side product.


1.3.2 Non-Transition Metal Templates

In addition to metal-ligand interactions, non-metal-containing templates are also widely used in the assembly of interlocked architectures. While TM-templated synthesis is more relevant to the work described in this thesis, a brief overview of non-TM templates is given for completeness.

Hydrophobic Effects

Cyclodextrins (CDs) are useful structures for the macrocyclic component of mechanically interlocked molecules. Their hydrophilic exterior and rigid hydrophobic cavity makes threading long chains through them a convenient route to rotaxanes via the stoppering method. The first synthesis of a rotaxane that did not rely on statistics was directed by the hydrophobic effect by Ogino and co-workers in 1981. A stoppering strategy was employed, by coupling bis(ethylenediamine)cobalt(III) complexes to either end of 1,10-diaminodecane, threaded through α-CD. Such rotaxanes are of course ionic and therefore water soluble; only one example of a completely non-ionic cyclodextrin rotaxane, soluble
in organic solvents, has been reported.\textsuperscript{38} Cyclodextrin rotaxanes have been designed for a range of applications such as photochemically switchable molecular shuttles (Figure 1.4),\textsuperscript{39,40} encapsulation of dyes for protection or modification of properties\textsuperscript{41,42} and, more recently, photoswitchable enzymatic cleavage of a peptide-linked CD rotaxane has been described.\textsuperscript{43} Cyclodextrins are also capable of forming supramolecular assemblies with various polymers, leading to polyrotaxanes or ‘molecular necklaces’.\textsuperscript{44} When the thread is highly conjugated such polyrotaxanes are often referred to as \textit{insulated molecular wires}.\textsuperscript{45} Cyclodextrin catenanes have also been synthesised; the first example was reported by Stoddart in 1993.\textsuperscript{46}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{A CD-rotaxane photoswitchable shuttle.\textsuperscript{39}}
\end{figure}

\textit{\pi-\pi} Interactions

The group of Professor J. F. Stoddart led the way in the use of \textit{\pi-\pi} interactions in the assembly of mechanically interlocked architectures.\textsuperscript{47} The potential of such host-guest chemistry to aid synthesis of interlocked assemblies became apparent to the group during the design of a receptor unit for paraquat (which contains \pi electron deficient bipyridinium rings). The PF\textsubscript{6} salt of paraquat (37) became sandwiched
between the parallel aromatic rings of a π-electron rich receptor unit (36), resulting in *pseudo-rotaxane* like inclusion complex 38 (Scheme 1.11).\(^{48}\)

![Scheme 1.11. Formation of an inclusion complex of paraquat and a π-electron rich receptor.\(^{48}\)](image)

These interactions were exploited to assemble a [2]catenane\(^{49}\) and subsequently more complex architectures such as [n]catenanes \(n>2\)\(^{50,51}\) and a trefoil knot.\(^{52}\) The same recognition motif was used by the Stoddart group to synthesize the first molecular shuttle\(^{53}\) and the first stimuli-responsive molecular shuttle (39) (Figure 1.5).\(^{54}\)

![Figure 1.5. Stoddart’s redox responsive molecular shuttle, synthesized and operated using π-π interactions.\(^{54}\)](image)
Hydrogen Bonding

Hydrogen bond templates usually employ multiple recognition sites and a high level of preorganization. The first use of hydrogen bonds to template formation of an interlocked molecule was described by Hunter in 1992 (Scheme 1.12). A four-component double macrocyclization reaction between dianilide 40 and isophthaloyl dichloride (41) led to 34% of [2]catenane 42, along with 51% of the non-interlocked dimer he had been intending to synthesize from this reaction.


Hunter’s discovery was shortly followed by a report of a very similar molecule by Vögtle and co-workers.56 Since then, the amide motif has been put to good use in hydrogen bond-directed synthesis of interlocked architectures. Leigh and co-workers also made a chance discovery regarding hydrogen bond templates: they obtained catenane 44 in 20% yield (remarkable for an eight-component condensation), instead of the expected [2+2] macrocyclic product, from the reaction of isophthaloyl chloride (41) and p-xylylenediamine (43) (Scheme 1.13). They demonstrated the synthetic scope of the reaction by assembling a range of structurally diverse [2]catenanes from commercially available diamines and chlorides58 and later extended the template to rotaxane formation by clipping of the macrocycle about a stoppered benzylic amide thread, 45, to give rotaxane 46 in 28% yield59 (Scheme 1.13). The use of a glyglycine thread gave [2]rotaxane in yields of up to 62%60 and the use of a more rigid,
fumaramide binding motif afforded the ‘world record’ yield of 97% for synthesis of a [2]rotaxane.\textsuperscript{61}

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{Scheme1}
\caption{Leigh's hydrogen bond-assisted assembly of a) a catenane\textsuperscript{57} and b) a rotaxane.\textsuperscript{59}}
\end{figure}

Such amide rotaxanes have been the basis for many sophisticated molecular shuttles which operate in response to various stimuli such as a oxidation/reduction,\textsuperscript{62,63} photochemistry,\textsuperscript{64,65} and reversible covalent bond formation\textsuperscript{66} and have been shown to be capable of doing work.\textsuperscript{67,68} As well as using the peptidic glyglycine motif in a rotaxane thread, the Leigh group have also synthesized the first rotaxane with a cyclic peptide as the ring component.\textsuperscript{69}

The hydrogen bonding between crown-ethers and ammonium ions is another useful interaction in aiding rotaxane formation, as originally shown by both Busch\textsuperscript{70} and Stoddart.\textsuperscript{71} Busch and co-workers demonstrated that a mono-stoppered thread containing an internal secondary amine and a terminal primary amine could form a

Scheme 1.14. Busch’s interfacial synthesis of a rotaxane, aided by hydrogen bonding, by threading and stoppering of a bifunctional axle.70

Busch refers to this method as ‘snapping’ and inclusion complexes can also be synthesised this way, existing as equilibrium mixtures of threaded and non-threaded states.72 Shortly after this Stoddart and co-workers carried out the assembly of [2] and [3]rotaxanes via the stoppering approach, using the same macrocycle and a thread containing two secondary amine templates.71,73

Anion Templates

Anions have been used as directing agents for a wide range of inorganic and organic assemblies,74,75 however anion templates remain relatively underused in the synthesis of interlocked molecules. In 1999 Vögtle reported the first anion-templated synthesis of a rotaxane by the nucleophilic substitution reaction of a tetralactam-coordinated phenolate anion stopper with a primary bromide stopper.76 The group of Paul Beer have made use of chloride anions as templates for the synthesis of rotaxanes77 and catenanes78 (Figure 1.6).
This template relies on the close association of a chloride-pyridinium ion pair; RCM to close the blue ring gives rotaxane 49 in 47% yield and catenane 50 in 45% yield. In both cases the Cl\(^-\) can be removed by addition of AgPF\(_6\). Beer and co-workers recently reported a double clipping strategy templated by a sulfate anion to give an impressive 80% yield of [2]rotaxane after RCM.\(^7\) Leigh and co-workers have reported a novel ion-pair template for rotaxane formation in which substitution of an acetonitrile ligand with chloride on the fourth coordination site of a Pd-macrocycle complex leads to threading onto a pyridinium-containing thread, aided by ion pairing.\(^8\) The group then exploited this strategy to construct an anion switchable molecular shuttle.\(^8\)

### 1.3.3 The Active Template Strategy

As has been shown, a wealth of chemical templates to aid the formation of interlocked molecules has been developed over the last few decades, providing access to increasingly sophisticated systems. Transition metal templates for the synthesis of mechanically interlocked architectures generally all have one feature in common: they require stoichiometric quantities of the metal with respect to each ligating component. The role of the metal is essentially a ‘glue’ to hold together the reacting fragments which will form the mechanically bonded product.
Besides holding the reacting fragments together in the right orientation for interlocking, the template is otherwise passive during the reaction.

Inspired by the principles of transition metal catalysis, a new strategy has recently been developed in which the metal not only induces the necessary degree of preorganization for interlocking, but also mediates the covalent bond formation that captures the interlocked structure. This is a major shift away from classical ‘passive templates’ as here the metal performs a dual function; acting as both a template and a catalyst for covalent bond formation. This strategy, developed by the Leigh group, has been named the ‘active template’ approach (Figure 1.7).

There are several potentially attractive features of this synthetic approach to mechanically interlocked architectures, including: i) The inherent efficiency in combining multiple functions in a single step/set of reagents; ii) in some cases only substoichiometric quantities of the active template may be required; iii) the potential for application of the strategy to many different types of well-known transition metal-catalyzed reactions; iv) the lack of requirement for permanent recognition elements in each component of the interlocked product both increases the structural diversity possible in mechanically interlocked molecules and provides for the ‘traceless’ assembly of catenanes and rotaxanes; v) reactions that only proceed through threading may prove advantageous for the synthesis of certain classes of mechanically linked macromolecular architectures; and, finally, vi) the unusual mechanistic requirements of active-template reactions could provide insight into the mechanism of certain metal-catalyzed reactions (in order to generate a mechanically interlocked architecture, the metal must remain bound to both the macrocyclic ligand and the stoppers during key stages of the reaction).
Figure 1.7. The ‘active template’ strategy to rotaxane architectures. The formation of a covalent bond between the green and orange ‘stoppered’ units to generate the thread is promoted by the metal ion (shown in grey) and directed through the cavity of the macrocycle (shown in blue) by the metal’s coordination requirements. a) Stoichiometric active-metal template synthesis of a [2]rotaxane: i) template assembly and covalent bond forming catalysis, ii) subsequent demetallation. b) Catalytic active-metal template synthesis of a [2]rotaxane, requiring only a substoichiometric quantity of metal.

The concept was first demonstrated within the Leigh group\textsuperscript{81} by using the Cu(I)-catalyzed 1,3-cycloaddition of organic azides with terminal alkynes, a so-called ‘click’ reaction. This thesis describes further investigation of the original ‘click’ active template reaction and the subsequent extension of this methodology to new TM-catalyzed reactions and more complex architectures.
Chapter 2: A Cu(I)-Catalyzed Azide-Alkyne 1,3-Cycloaddition Active Template Reaction


Acknowledgements:
The following people are gratefully acknowledged for their contribution to this chapter: Aurelien Viterisi and Kevin Hänni synthesized rotaxanes from macrocycles 1a, 1b and 1m and carried out kinetic studies. Stewart Franklin synthesized alkyne stopper 2 and azide stopper 3. Dr. Vincent Aucagne synthesized diol 9. X-ray quality crystals of 20m were obtained by Aurelien Viterisi and the structure was solved by Prof. Alexandra Slawin.
2.1 Introduction

Recently, there has been a tremendous surge of interest in so-called “click” methodologies for functional molecule synthesis, the most popular of which is the Huisgen-Meldal-Fokin\(^{85}\) Cu(I)-catalyzed 1,3-cycloaddition of organic azides with terminal alkynes (the CuAAC reaction). The most common catalyst systems for this reaction employ water or alcohol solvents and use a Cu(II) salt in the presence of a reducing agent (often sodium ascorbate) to generate the required Cu(I) catalyst \textit{in situ}.\(^{86, 87}\) Metallic copper\(^{86, 87}\) or copper clusters\(^{88}\) have also been employed as precatalysts and, in some cases, Cu(I) salts can be used directly. However, in apolar solvents Cu(I) salts usually require the presence of nitrogen\(^{86, 87, 89-91}\) or phosphorus\(^{91}\) ligands, or acetonitrile as a co-solvent, to stabilize the Cu(I) oxidation state and undesired alkyne-alkyne homocoupling products are often observed under such reaction conditions.\(^{86, 87}\) The basic mechanism of the CuAAC reaction is believed to be that shown in Scheme 2.1. A [2+3] cycloaddition — the mechanism of the thermal (i.e. uncatalyzed) Hüisgen reaction\(^{87,92}\) — can be ruled out\(^{93}\) for the Cu(I)-catalyzed reaction on the basis of DFT calculations which show that reaction \textit{via} a (formally Cu(III)) metallacycle is a more favorable pathway by up to 11.7 kcal mol\(^{-1}\) (Scheme 2.1).\(^{86,94,95}\)

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme21.png}
\caption{Proposed mechanism of the Huisgen-Meldal-Fokin Cu(I)-catalyzed cycloaddition of organic azides with terminal alkynes (the CuAAC reaction).}
\end{scheme}
The same calculations suggest that the rate determining step is the formation of the Cu-metallacycle from a reactive intermediate involving copper-coordinated alkyne and, presumably, azide (organoazido-metal complexes are likely intermediates in many transition metal-mediated reactions of azides and Cu(I)-N₃R complexes have been characterized by X-ray crystallography⁹⁶). However, the exact nature of this reactive intermediate is unclear (Figure 2.1, A-C).

In the absence of competing ligands,⁹⁷ copper(I) acetylides exist as complex multi-metal atom aggregates⁹⁸ and kinetic studies⁸⁹,⁹⁹ by Fokin and Finn on the generic ligand-free⁹⁷ Cu(I)-catalyzed alkyne-azide reaction show that in DMSO-water mixtures the reaction mechanism is second order with respect to copper. The same studies found first order kinetics with respect to the azide and alkyne (actually slightly higher than first order with respect to alkyne).⁹⁹ However, relatively little is known about the ligand-promoted Cu(I)-catalyzed cycloaddition in organic solvents.
Recent experiments by Straub, in which mononuclear Cu(I)-acetylides ligated to a sterically demanding N-heterocyclic carbene react efficiently with bulky organoazides at room temperature, support the notion that a single copper atom mechanism (A(i), Figure 2.1) is viable for the reaction, at least when the copper is bound to bulky ligands. Recent DFT calculations suggest that π-activation of the copper-acetylide unit by coordination of a second copper atom (e.g. A(ii) or, more likely, under ligand-free conditions or with small monodentate ligands, bridged intermediates such as B(i) or B(ii), Figure 2.1) greatly enhances the reactivity of the Cu-σ-acetylide, accelerating formation of the metallacycle. Alternatively, a pathway in which the reacting azide and alkyne are coordinated to different copper(I) atoms (intermediate C(i) or (ii)) would also be consistent with the second order kinetics observed in DMSO/water. It may well be that several or all of these types of intermediate can provide viable pathways for the CuAAC reaction, with the different characteristics of the intermediates being relatively favoured or inhibited by factors such as the solvent, bulk and coordination number of an added ligand, the strength of ligand-copper binding and the amount of free Cu(I) present in solution. Given the tendency of Cu(I)-acetylides to aggregate, however, doubly-bridged intermediates such as B or C(ii) should be abundant species under most conditions. Accordingly, if coordination of the azide to the same copper atom significantly increases the reactivity of the π-acetylide, type B(ii) intermediates are probably involved in the dominant pathways in most reported CuAAC reactions.

Despite the uncertainty over the precise nature of the reactive intermediate, since tertiary amines and pyridines facilitate the reaction in organic solvents it was reasoned that a macrocycle (1a) bearing an endotopic ligating nitrogen atom might be able to direct the CuAAC reaction of a ‘stoppered’ alkyne, 2, and a ‘stoppered’ azide, 3, through the macrocycle cavity to give a [2]rotaxane, 4a, in an active-metal template synthesis (Scheme 2.2). Indeed this is the case, and [2]rotaxane 4a was produced in 57% yield, under the conditions outlined for Scheme 2.2, along with 41% of non-interlocked thread 5.
Here, the results of an extended investigation of the original system are presented, showing that the active template rotaxane-forming alkyne-azide cycloaddition reaction works well for both mono- and bidentate pyridine-containing macrocyclic ligands. Furthermore, under certain conditions [3]rotaxanes, with two macrocycles on a single thread, are somewhat unexpectedly produced by the active-metal template reaction. The latter result suggests that the mechanism of the Cu(I)-catalyzed azide-alkyne cycloaddition in dichloromethane involves a reactive intermediate complex featuring two metal ions.
2.2 Results and Discussion

Synthesis of Macrocyclic Ligands

Macrocycle 1b was designed as a bidentate analogue of 1a (Figure 2.2), and synthesized in order to compare efficacy in the active template CuAAC reaction.

![Image of 1a and 1b](image)

**Figure 2.2** A monodentate (1a) and analogous bidentate (1b) macrocyclic ligand for the CuAAC active template assembly of rotaxanes.

The first generation synthesis of 1b involved a Williamson ring-closure between a dihalide and an diol as the final step (Scheme 2.3). Compounds 6 and 7 are commercially available but expensive (7 in particular) but could be readily synthesized on a reasonable scale. The final reaction between 8 and 9 however, proved problematic; it was unreliable and it was not possible to cleanly separate 1b from oligomeric side-products.
Scheme 2.3 Reagents and conditions: i) 1. 2-Aminopicoline, HBr (48 % aqueous), RT 2. Br₂, – 20 °C, 2 h, 3. NaNO₂, – 20 °C-RT, 4. NaOH, – 20 °C→RT, 69%; ii) NiCl₂.6H₂O, PPh₃, Zn, DMF, 50 °C, 80%; c) NBS, dibenzoyl peroxide, benzene, Δ, 40%; iv) NaH, NaI, THF, Δ.

The synthesis was improved by a redesign so that the final Williamson ring-closure was between a diphenol and 1,10-dibromodecane (Scheme 2.4), a much more facile reaction that requires a milder base. The final product, 1b, could be easily purified by column chromatography and changing conditions for the last step from refluxing THF to DMF at 80 °C also improved the ease of reaction. This route also made use of building block 8, which was already in hand from the first route.
Scheme 2.4 Reagents and conditions: i) K$_2$CO$_3$, allyl bromide, butanone, $\Delta$, 80%; ii) dibromide 8, NaI, THF, $\Delta$, 50%; iii) Pd(PPh$_3$)$_4$, aniline, THF, 30 °C, 88%; iv) K$_2$CO$_3$, 1,10-dibromodecane, NaI, DMF, 80 °C, 30%.

However, to produce this macrocycle continually and on a larger scale, it was necessary to undertake a redesign that would omit the necessity for the synthesis of dibromide 8. As well as being low-yielding to begin with, this radical reaction proved capricious when repeated and it was undesirable to have low-yielding reaction early in the synthesis. A reversal of the nucleophile and electrophile for the synthesis of 11 removed the need to produce dibromide 8, and improved the overall yield (Scheme 2.5). Diol 15 could be obtained from Ni(II)-catalyzed coupling of 14 and alcohol 10 can be readily brominated by treatment with HBr to give 16.
Scheme 2.5 Reactions and conditions: i) a. n-BuLi, THF, –78 ºC, b. DMF, –78 ºC, c. MeOH, RT, 92%; ii) NaBH₄, MeOH, 0 ºC → RT, 68%; iii) NiCl₂.6H₂O, PPh₃, Zn, DMF, 50 ºC, 82%; iv) HBr (48% aqueous), 40 ºC under reduced pressure, 79%; v) NaH, NaI, DMF, 0 ºC → RT, 84%.

Macrocycle 1a had previously been used in a Pd(II)-directed passive template synthesis of a [2]catenane.³⁵ The reported synthesis of 1a (Scheme 2.6) was analogous to that initially tried for bipyridyl macrocycle 1b (Scheme 2.3). In this case commercially available 2,6-bis(bromomethyl)pyridine was reacted with diol 9 under Williamson conditions (Scheme 2.6).

Scheme 2.6. Reagents and conditions: i) 1,10-Dibromodecane, K₂CO₃, NaI, butanone, Δ, 70%; ii) NaBH₄, CHCl₃/MeOH, Δ, 73%; iii) 2,6-bis(bromomethyl)pyridine, NaH, THF, Δ, 60%.

However, like the initial synthesis of 1b, this final step proved to be capricious and unfeasible for production of 1a on a large scale.
The synthesis was adapted to use the same protocol developed for \(1b\), to make it more convergent (Scheme 2.7).

Scheme 2.7 Reagents and conditions: i) NaH, 2,6-dimethanol pyridine, NaI, DMF, 0 °C→RT, 79%; ii) Pd(PPh\(_3\))\(_4\), aniline, THF, 30 °C, 78%; iii) K\(_2\)CO\(_3\), 1,10-dibromodecane, butanone, Δ, 29%.

An Active-Metal Template CuAAC Rotaxane Synthesis

Stirring of an equimolar mixture of the pyridine macrocycle \(1a\), alkyne \(2\), azide \(3\) and \([\text{Cu(CH\(_3\)CN)}\(_4\])\text{(PF}_6\text{)}\) in CH\(_2\)Cl\(_2\) for 24 hours afforded—after demetallation with KCN—a mixture of [2]rotaxane \(4a\) (57%) and the non-interlocked triazole thread \(5\) (41%), together with some of the unconsumed starting macrocycle (Scheme 2.8 and Table 2.1, Entry 1).\(^8\)
Scheme 2.8 Synthesis of a [2]rotaxane by the CuAAC active template, using macrocycle 1a, under both stoichiometric and catalytic conditions. Reagents and conditions: (i) 1a (0.01 M), [Cu(CH$_3$CN)$_4$](PF$_6$), poorly coordinating solvent (generally CH$_2$Cl$_2$, see text) and, in the catalytic version of the active-metal template reaction, 3 equiv. pyridine. (ii) KCN, CH$_2$Cl$_2$/CH$_3$OH. For the effect of reaction conditions and reagent stoichiometry on the yields of 4a and 5, see Table 2.1.
By varying the reaction conditions and reactant stoichiometry (Table 2.1), yields of up to 94% of [2]rotaxane with respect to the amount of macrocycle used were achieved (5.0 equiv. \(2\) and \(3\); Table 2.1, Entry 2) for this stoichiometric active-metal template reaction. The use of sub-stoichiometric amounts of copper was investigated to determine whether the metal would turn over as both a template and a cycloaddition catalyst (i.e. a catalytic active-metal template synthesis). Addition of pyridine enabled the catalyst to turn over, producing a sub-stoichiometric reaction, but the reaction was extremely slow at 25 °C (Table 2.1, entry 3). Elevating the temperature (70 °C, \(\text{ClCH}_2\text{CH}_2\text{Cl}\)) gave an improved yield (82%) of rotaxane \(\text{4a}\) in a reasonable time period (36 h) using only 4 mol% \(\text{Cu(I)}\) with respect to both \(2\) and \(3\) (Table 2.1, entry 4).

**Table 2.1 The Effect of Reaction Conditions and Reagent Stoichiometry on the Active-Metal Template CuAAC Synthesis of [2]Rotaxane \(\text{4a}\) (Scheme 2.8).**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. (2) and (3)</th>
<th>Equiv. [(\text{Cu(CH}_3\text{CN)}_4\text{(PF}_6\text{)})]</th>
<th>solvent</th>
<th>(T) (°C)</th>
<th>conversion to triazole (2+3\rightarrow\text{4a+5})</th>
<th>yield of rotaxane (1a\rightarrow\text{4a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^a)</td>
<td>1</td>
<td>1</td>
<td>(\text{CH}_2\text{Cl}_2)</td>
<td>25(^d)</td>
<td>&gt;95%</td>
<td>57%</td>
</tr>
<tr>
<td>2(^a)</td>
<td>5</td>
<td>1</td>
<td>(\text{CH}_2\text{Cl}_2)</td>
<td>25(^d)</td>
<td>92%</td>
<td>94%</td>
</tr>
<tr>
<td>3(^b)</td>
<td>5</td>
<td>0.2</td>
<td>(\text{CH}_2\text{Cl}_2)</td>
<td>25(^d)</td>
<td>44%</td>
<td>59%</td>
</tr>
<tr>
<td>4(^b)</td>
<td>5</td>
<td>0.2</td>
<td>(\text{ClCH}_2\text{CH}_2\text{Cl})</td>
<td>25→70(^e)</td>
<td>94%</td>
<td>82%</td>
</tr>
<tr>
<td>5(^c)</td>
<td>1</td>
<td>0</td>
<td>(\text{ClCH}_2\text{CH}_2\text{Cl})</td>
<td>25→70(^f)</td>
<td>&lt;5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

\(^a\)All reactions were carried out at 0.01 M concentration with respect to \(1a\), using the procedure shown in Scheme 2.8; \(^b\)3.0 equiv. pyridine; \(^c\)Control experiment with no [\(\text{Cu(CH}_3\text{CN)}_4\text{(PF}_6\text{)}\)] present to demonstrate that the thermal reaction does not occur at these temperatures; \(^d\)24 h; \(^e\)12 h then 24 h; \(^f\)12 h then 72 h.
Less than 5% of conversion of the starting materials to triazole products occurred in the absence of a Cu(I) source (Table 2.1, Entry 5), showing that the thermal reaction does not contribute to the products at these temperatures.

**Kinetic Studies**

Some simple kinetic measurements were made to determine whether, under these reaction conditions, the Cu(I)-catalyzed alkyne-azide cycloaddition is actually accelerated by pyridine-based ligands. The rate of formation of triazole products (i.e. thread, plus rotaxane where relevant) was compared for reaction in the absence of pyridine-based ligands and reactions containing pyridine, 2,6-dimethylpyridine (lutidine), 2,6-di(alkyloxymethyl)pyridine macrocycle 1a, and 18, a close but acyclic analogue of 1a (Figure 2.3). The results (Figure 2.3) show that both lutidine and 18 significantly accelerate the CuAAC reaction rate (essentially complete conversion to triazole after 3 h) compared to the Cu(I)-catalyzed reaction when no pyridine-based ligand is added (complete conversion after 6 h). The presence of pyridine also initially accelerates the reaction, but the conversion tails off after 2 h (Figure 2.3), suggesting that using unsubstituted pyridine as a ligand facilitates the oxidation of Cu(I) to non-catalytic Cu(II) under the reaction conditions. The role of the pyridine ligands in the rate acceleration is probably to break up extended Cu(I)-acetylide aggregates to form smaller reactive intermediates of the types shown in Figure 2.1.

Interestingly, the Cu(I)-catalyzed formation of triazole products (both rotaxane and thread) in the presence of macrocycle 1a (with 1 equiv. of Cu)—which also presumably breaks up the Cu-acetylide aggregates—is actually slower (24 h cf. 6 h) than the ligand-free Cu(I)-catalyzed reaction.
Figure 2.3 Conversion to triazole (i.e. thread + rotaxane if applicable) vs. time for different pyridine-based ligands for the CuAAC reaction.\textsuperscript{a,b} \textsuperscript{a}Conditions: i) ligand (1 equiv.), alkyne 2 (1 equiv.), azide 3 (1 equiv.), [Cu(CH\textsubscript{3}CN)\textsubscript{4}](PF\textsubscript{6}) (1 equiv.; 1 or 2 equiv. with 1a), CD\textsubscript{2}Cl\textsubscript{2}, RT, 0.01 M. \textsuperscript{b}The conversion of 2 and 3 into the triazole products (thread 5, + rotaxane 4a where relevant) was monitored by \textsuperscript{1}H NMR.

Whilst this might seem surprising given that excellent yields of rotaxane are obtained under both stoichiometric and catalytic active-metal template conditions (Table 2.1), the rationale for this is quite straightforward: firstly, the alkyne-azide cycloaddition with the macrocyclic ligand must take place through the macrocycle cavity, a sterically restricted environment compared to the Cu(I)-catalyzed reaction in the absence of added ligand, affecting the solvation of the reactive species as well as hindering any motion required to achieve bond formation or changes of geometry at the copper centre. Secondly, the macrocyclic ligand might disfavour certain types of reactive intermediate (e.g. B, Figure 2.1.) on steric grounds and so the reaction may proceed through another type of slower reacting, but still viable, intermediate (e.g. A...
or C rather than B). The reason that the formation of triazole thread (when the copper is not coordinated to the macrocycle) does not dominate, despite being the faster reaction, is that the macrocycle is an excellent ligand for the Cu(I) and sequesters it, preventing this reaction (probably via B(ii)) from occurring. Accordingly, addition of a second equivalent of Cu(I) to the reaction containing 1a should accelerate the rate of triazole formation to close to that of the ligand-free rate. Indeed, this was found to be the case (Figure 2.3). However, whilst it might be expected that this increase would be totally due to thread formation, analysis shows that the rate of rotaxane formation is also increased by adding an extra equivalent of Cu(I) to this reaction (Figure 2.4). In fact, the final yield of [2]rotaxane only falls from 57% to 22% even though the triazole-forming reaction is complete in 6 h instead of 24 h. The acceleration of the rotaxane-forming reaction by excess Cu(I) strongly suggests that π-activation of the copper-acetylide unit (see Scheme 2.1) is an important process in the CuAAC reaction mechanism of 1a.

**Figure 2.4.** Formation of triazole products (rotaxane 4a ■, thread 5 ●) vs. time for the CuAAC reaction in the presence of macrocycle 1a. a, b aConditions: i) 1a (1 equiv.), 2 (1 equiv.), 3 (1 equiv.), [Cu(CH$_3$CN)$_4$](PF$_6$) (1 or 2 equiv.), CD$_2$Cl$_2$, RT, 0.01 M. b The conversion of 2 and 3 into thread 5 and rotaxane 4a was monitored by $^1$H NMR.
To further investigate both the scope and the mechanism of the CuAAC active template rotaxane-forming reaction, the structure of the ligating macrocycle was varied. The macrocycles investigated are shown in Figure 2.5. It should be noted that all macrocycles except 1a and 1b were synthesized by colleagues and while the results have been included in Figure 2.5 for completeness, this thesis will focus on the outcome of the reaction with macrocycles 1a and 1b (as well as 1m) and the information gained from these. In order to compare the relative yields of rotaxane and thread within the ligand series, the macrocyclic ligands were screened using a standard, rather than optimized, set of stoichiometric active-metal template reaction conditions in which the original macrocycle (1a) generates appreciable quantities of both rotaxane and thread. The bipyridyl macrocycle, 1b, directs the CuAAC reaction through its cavity to form rotaxane almost as efficiently as its monodentate analogue (45% 1b → 4b cf. 57% 1a → 4a). However, it severely inhibits the rate of the Cu(I)-catalyzed reaction and it took 3 days for the active-metal template reaction 1b → 4b to go to completion, compared to 24 h for 1a → 4a and 6 h for the Cu(I)-catalyzed control reaction in the absence of added ligand (Figure 2.5). It is noteworthy that the 2,9-diphenylphenanthroline macrocycle (1o), used extensively to assemble rotaxanes and catenanes by the Sauvage group, produces no triazole product. This is particularly interesting given that phenanthroline ligands have previously been reported to promote the CuAAC reaction. The lack of reactivity is presumably a result of the steric bulk about the Cu(I) centre in the complex preventing the complex from undergoing the various structural variations required for reaction to take place (e.g. tolerating the change in geometry from Cu(I) to the formal Cu(III) species, Scheme 2.1), together with the macrocycle being very effective in sequestering the Cu(I) in this unreactive form. A related Cu(I)-macrocycle complex has recently been reported to promote the formation of [2]rotaxanes via a Glaser alkyne homocoupling. However, in that case, intermediates of type B (Figure 2.1) are possible with a bidentate ligand for copper because no azide need be coordinated to the metal atom.
Figure 2.5. Influence of macrocycle structure on the active-metal template CuAAC rotaxane-forming reaction in Scheme 2.8 under a standardized set of reaction conditions.\textsuperscript{a, b, c}

\textsuperscript{a}Conditions: (i) 1a-o, 2, 3, [Cu(CH\textsubscript{3}CN)\textsubscript{4}](PF\textsubscript{6}), CH\textsubscript{2}Cl\textsubscript{2}, RT, 24 h (72 h for 4b and 4o); 0.01 M concentration with respect to each of 1a-o, alkyne 2, azide 3 and [Cu(CH\textsubscript{3}CN)\textsubscript{4}](PF\textsubscript{6}). The reactions were not run under an inert atmosphere, nor using distilled or dried solvents. (ii) KCN, CH\textsubscript{2}Cl\textsubscript{2}/MeOH. \textsuperscript{b}The conversion of each macrocycle to [2]rotaxane is given as a percentage yield in red and the overall conversion of 2 and 3 into triazole products (rotaxane 4a-o and thread 5) is shown for each macrocycle in parentheses. ‘Trace’ means that the rotaxane was observed by ESI-MS but could not be detected by \textsuperscript{1}H NMR. \textsuperscript{c}72 h reaction time.
$^1$H NMR Spectra of [2]Rotaxanes

The $^1$H NMR spectra of the rotaxanes 4a and 4b (Figure 2.6) show characteristic upfield shifts of several signals with respect to the non-interlocked thread, 5. Such shielding is typical of interlocked structures in which the aromatic rings of one component are positioned face-on to another component and is observed for all the non-stopper resonances of the axle (H_fj) indicating that the macrocycle accesses the full length of the thread. This is as expected; there should be no strong intercomponent non-covalent interactions between the thread and the macrocycle in these metal-free rotaxanes.

![Figure 2.6. $^1$H NMR spectra (400 MHz, CDCl₃, 300 K) of a) triazole thread 5, b) [2]rotaxane 4a, c) [2]rotaxane 4b. The assignments correspond to the lettering shown in Scheme 2.8 and Figure 2.5.](image)
The Active-Metal Template CuAAC Reaction at High Macrocycle:Cu(I) ratios: The Unexpected Formation of [3]Rotaxanes

Based on evidence presented thus far, it appears that the [Cu(CH₃CN)₄]PF₆ salt and macrocycle are in equilibrium with the corresponding copper(I)-macrocycle complex which, in most cases, the metal atom directs the cycloaddition of the azide and alkyne through the macrocycle cavity. Although the off-ligand reaction is inherently faster than the active-metal template one, the coordinating ability of the macrocycle means that the rotaxane-forming reaction can become competitive with, or even dominate, the thread-forming reaction. In general, a stronger binding macrocyclic ligand (e.g. 1b cf. 1a) should move this equilibrium in favour of rotaxane formation. However, some changes in coordination geometry about the metal are required for the CuAAC mechanism to operate (Scheme 2.1) and so the most strongly binding macrocycle (1o), which apparently does not tolerate such changes, actually inhibits the triazole-forming reaction. In view of this, other conditions were investigated in an attempt to increase rotaxane formation at the expense of the thread. The active-metal template CuAAC protocol was carried out under the standard set of conditions (1 equiv. 2, 1 equiv. 3, 1 equiv. [Cu(CH₃CN)₄]PF₆, CH₂Cl₂, RT) used previously but in the presence of 10 equivalents of macrocycle (Scheme 2.9). Initial experiments with monodentate macrocycle 1m, showed that the reaction was much slower with 10 equivalents of the macrocycle than it had been with 1 equivalent, the higher macrocycle:Cu(I) reaction taking more than one week to go to completion. Upon reaching this endpoint, the mixture of triazole products was found to consist of 30% thread 5, 37% [2]rotaxane 4m and, surprisingly, 33% [3]rotaxane, 20m (yields quoted with respect to the alkyne and azide reactants). A reaction using macrocycle 1a under the same experimental conditions (1 equiv. 2, 1 equiv. 3, 1 equiv. [Cu(CH₃CN)₄]PF₆ and 10 equiv. 1a, CH₂Cl₂, RT) was again slower than the same reaction with 1 equivalent of macrocycle (3 days to reach completion cf. 24 h) generating a product mixture of 5% thread 5, 90% [2]rotaxane 4a and 5% [3]rotaxane 20a (yields quoted with respect to the alkyne and azide reactants). A similar trend was seen with bidentate macrocycle 1b; with 10 equivalents of 1b the reaction took 10 days to complete (cf. 7 days with 1 equivalent) producing 3% thread

The remarkable features of these high macrocycle:Cu(I) ratio active-metal template reactions are:

(i) The exceptional combined rotaxane yields: 95% ([2]rotaxane 4a + [3]rotaxane 20a) cf. 57% 4a with 1 equiv. 1a; 70% ([2]rotaxane 4m + [3]rotaxane 20m) cf. 25% 4m with 1 equiv. 1m; 97% ([2]rotaxane 4b) cf. 45% 4b with 1 equiv. 1b.

(ii) The significant reduction in reaction rate compared to that of the low macrocycle:Cu(I) ratio reactions. The largest effect on the rate is seen with the weakly copper-binding macrocycle 1m; the smallest effect on rate occurs for the strongly copper-binding macrocycle 1b. Again, this is strongly suggestive that the dominant mechanism of the CuAAC reaction under these conditions involves $\pi$-activation of the copper-$\sigma$-acetylide unit by a second, preferably ligandless for steric reasons, copper atom (i.e. I or II, Figure 2.9).

(iii) The formation of [3]rotaxane (in 33% yield using macrocycle 1m)—i.e. TWO macrocycles being threaded during the formation of ONE triazole ring. Molecular models show that this can most reasonably occur through the sort of bridged two copper atom intermediate III shown in Figure 2.1. Since such a doubly-bridged intermediate cannot occur with bidentate ligands (and no [3]rotaxane is observed with 1b) it seems likely that monodentate pyridine ligand-promoted CuAAC reactions proceed via doubly-bridged intermediates such as I (Scheme 2.9), the equivalent of intermediate B(ii) in Figure 2.1, whereas bidentate bipyridyl ligand-promoted CuAAC reactions proceed via simple $\pi$-coordinated complexes such as II (Scheme 2.9), the equivalent of intermediate A(ii) in Figure 2.1.
Scheme 2.9. The Effect of the Macrocycle:Cu(I) Ratio on the Active-Metal Template CuAAC Reaction. Reagents and conditions: i) 1a, 1m or 1b (10 equiv.), 2 (1 equiv.) and 3 (1 equiv.), [Cu(CH3CN)4](PF6) (1 equiv.), CH2Cl2, RT, 24 h (1a); 7 days (1m); 10 days (1b). ii) KCN, CH2Cl2/CH3OH. Product yields starting from macrocycle 1a: thread 5 (5%), [2]rotaxane 4a (90%), [3]rotaxane 20a (5%). Product yields starting from macrocycle 1a: thread 5 (5%), [2]rotaxane 4m (37%), [3]rotaxane 20m (33%). Product yields starting from macrocycle 1b: thread 5 (3%), [2]rotaxane 4b (97%), [3]rotaxane 20b (0%). In the reactive intermediates shown, the Cu-azide (orange) reacts with any of the Cu-alkyne units shown in green. L can be any non-reacting ligand, including other alkyne and azide groups.
The $^1$H NMR spectra of [2]rotaxane 4m and [3]rotaxane 20m are shown in Figure 2.7b and 2.7c, respectively. The resonances for the axle (H_{f-j}) of the rotaxanes are shifted upfield compared to the free non-interlocked thread 5 (Figure 2.7a). The effect is more pronounced in the [3]rotaxane (Figure 2.7c) than in the [2]rotaxane (Figure 2.7b). Due to the asymmetry of the thread, the $^1$H NMR spectrum of [3]rotaxane 20m (Figure 2.7c) displays non-equivalent but overlapping peaks for the two macrocycle components, which are double the intensity of the corresponding macrocycle signals in the [2]rotaxane.

![Figure 2.7. $^1$H NMR spectra (400 MHz, CDCl₃, 300 K) of a) triazole thread 5, b) [2]rotaxane 4m, c) [3]rotaxane 20m. The assignments correspond to the lettering shown in Scheme 2.9 and Figure 2.5.](image)

The solid state structure (Figure 2.8) confirmed the constitution of 20m as a [3]rotaxane. Although it may superficially appear that face-to-face π-stacking interactions might aid the relative orientation of the two macrocycles on the thread, in the solid state the aromatic rings of adjacent macrocycles are not co-planar and their separation (>3.8 Å) is somewhat greater than that typically associated with aromatic stacking interactions.
In conclusion, a monodentate, and analogous bidentate, macrocyclic ligand for use in active template reactions has been synthesized. The CuACC active template reaction with these ligands is an efficient protocol for the assembly of [2]rotaxane under both stoichiometric and catalytic conditions. While the presence of a ligand reduces the rate of reaction, the affinity of the metal for the ligand means that it is sequestered to a degree where the ligated reaction is competitive with, or dominates, the off-ligand reaction. The experimental evidence suggests external $\pi$-activation of Cu-acetylide by a second copper atom (which is not bound to a pyridyl ligand) in the presence of superstoichiometric copper. The surprising formation of [3]rotaxane with high monodentate macrocycle:copper ratios implies a doubly-bridged, two-copper intermediate, whereas it is likely that a simpler, $\pi$-coordinated intermediate is in operation in the presence of polydentate ligands. As well as the inherent efficiency of a metal performing two roles (templating and catalysis) in this highly efficient multi-component reaction, the reaction has also proved a useful experimental probe for the mechanism of the CuAAC reaction.
2.3 Experimental

General

Unless otherwise stated, all reagents were obtained from commercial sources and used without further purification, solvents were anhydrous and all reactions were carried out under an atmosphere of N$_2$ (g). Zinc powder was activated by washing with 1 M aqueous HCl, followed by H$_2$O, acetone and Et$_2$O and drying in vacuo. Sodium hydride was provided as a 60% dispersion in mineral oil.

2-Bromo-6-methylpyridine (6)

2-Aminopicoline (20.0 g, 185 mmol) was added portion-wise to HBr$_{(aq)}$ (48%, 100 mL) at RT, with vigorous stirring (no inert atmosphere was required). The reaction mixture was then cooled to –20 ºC and Br$_2$ (26.8 mL, 523 mmol) was added over 30 min. The resulting red/orange paste was allowed to stir at –20 ºC for 90 min after which time NaNO$_2$ (34.6 g, 501 mmol) in water (50 mL) was added. The reaction mixture was then allowed to warm to RT over 1 h and left to stir for 45 min. The reaction mixture was then cooled to –20 ºC and NaOH (133 g, 3.32 mol) in water (300 mL) was added slowly via a dropping funnel. The reaction mixture was then allowed to warm to RT and stirred for 18 h. The organic phase was extracted with EtOAc (3 x 50 mL) and the combined extracts were dried (MgSO$_4$) and concentrated under pressure. The resulting brown oil was purified by reduced pressure distillation (52 ºC, 3 mm Hg) to give 2-bromo-6-methylpyridine$^{109}$ (6) (21.9 g, 69%) as a yellow oil. $^1$H NMR (400 MHz; CDCl$_3$): δ = 7.41 (app-t, 1H, H$_B$), 7.27 (d, 1H, $J = 7.9$, H$_A$ or H$_C$), 7.09 (d, 1H, $J = 7.5$, H$_A$ or H$_C$), 2.52 (s, 3H, H$_D$).
**6,6'-Dimethyl-2,2'-dipyridyl (7)**

![Chemical Structure](image)

Triphenylphosphine (76.7 g, 292 mmol) was added to a solution of NiCl$_2$·6H$_2$O (17.4 g, 73.1 mmol) in DMF (315 mL) at RT. The resulting deep blue solution was heated to 50 °C and Zn powder (4.78 g, 73.1 mmol) was added. After 1 h the reaction mixture had turned red/brown and 6-bromopicoline (6) (12.6 g, 73.1 g) was added. After a further 1 h at 50 °C the DMF was removed under reduced pressure and aqueous NH$_3$ (17.5%, 100 mL) and CHCl$_3$ (100 mL) were added. The phases were separated and the aqueous phase further extracted with CHCl$_3$ (2 x 100 mL). The combined organic extracts were washed with H$_2$O (3 x 100 mL), dried (MgSO$_4$) and concentrated under reduced pressure. The resulting residue was redissolved in CHCl$_3$ (300 mL) and the product was extracted as the HCl salt using 1 M aqueous HCl (3 x 200 mL). The combined aqueous extracts were washed with CH$_3$Cl (3 x 200 mL), basified with NaOH then saturated with NaCl. The product was extracted with CHCl$_3$ (3 x 200 mL) and the combined organic extracts were dried (MgSO$_4$) and concentrated under reduced pressure to yield 2-methyl-6-(6-methylpyridin-2-yl)pyridine (7) (5.36 g, 80%) as a brown solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 8.17 (d, 2H, $J$ = 7.8, H$_A$), 7.67 (t, 2H, $J$ = 7.7, H$_B$), 7.13 (d, 2H, $J$ = 7.6, H$_C$), 2.62 (s, 6H, H$_D$).
2-(bromomethyl)-6-(6-(bromomethyl)pyridin-2-yl)pyridine (8)

Dibenzoyl peroxide (0.02 g, 0.1 mmol) was added to a solution of 

\[ \text{N-bromosuccinimide (0.41 g, 2.3 mmol) and bipyridyl (0.20 g, 1.1 mmol) in benzene (11 mL). The reaction mixture was heated at reflux for 18 h. Once cooled to RT, volatiles were removed } \text{in vacuo. The resulting residue was taken up in hot MeOH (20 mL). The remaining precipitate was collected by suction filtration to give 8 (0.15 g, 40%). as a white solid.} \]

\[ \text{1H NMR (400 MHz, CDCl}_3\text{): \( \delta = 8.09 \text{ (d, 2H, J = 7.8, HA)}, 7.59 \text{ (t, 2H, J = 7.7, HB)}, 7.06 \text{ (d, 2H, J = 7.6, HC)}, 2.54 \text{ (s, 4H, HD).} \]}

(4-allyloxyphenyl)methanol (10)

\[ \text{K}_2\text{CO}_3 \text{ (38.8 g, 0.28 mol) was added to a solution of 4-hydroxybenzyl alcohol (7.00 g, 56.3 mmol) in butanone (60 mL). Allyl bromide (4.9 mL, 56.6 mmol) was then added and the reaction mixture heated at reflux for 18 h. Once cooled to RT, volatiles were removed } \text{in vacuo and the product taken up in CH}_2\text{Cl}_2 \text{ (200 mL). H}_2\text{O (150 mL) was added and the phases separated. The aqueous phase was further extracted with CH}_2\text{Cl}_2 \text{ (200 mL) and the combined organic extracts were washed with H}_2\text{O (2 x 300 mL) and brine (150 mL), dried (MgSO}_4\text{) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (pet-EtOAc, 10:1) to give 10 (7.29 g, 79%) as a colourless oil.} \]

\[ \text{1H NMR (400 MHz; CDCl}_3\text{): \( \delta = 7.27 \text{ (d, 2H, J = 8.1, H}_D\text{ or H}_E\text{)}, 6.91 \text{ (d, 2H, J = 8.5, H}_D\text{ or H}_E\text{)}, 6.07 \text{ (m, 1H, H}_B\text{)}, 5.44 \text{ (dd, 1H, J = 17.3, 1.4, H}_A\text{-trans)}, 4.94 \text{ (dd, 1H, J = 10.5, 1.3, H}_A\text{-cis)}, 4.57 \text{ (s, 2H, H}_F\text{)}, 4.54 \text{ (d, 2H, J = 5.3, H}_C\text{)}, 2.45 \text{ (br-s, 1H, OH);} \]

\[ \text{13C NMR (100 MHz; CDCl}_3\text{): } \delta = 158.1, 133.3 \text{ (Cx2)}, 128.6, 117.7, 114.7, 68.8, 64.8; \text{ LREI+ve-} \]
MS: \( m/z = 164 \ [M]^+ \); HREI+ve-MS: \( m/z = 164.08334 \ [M]^+ \) (calc. for \( C_{10}H_{12}O_2 \ 164.08373 \)).

\[
\text{Method A}
\]

NaH (0.12 g, 3.0 mmol) was added to a solution of (4-(allyloxy)phenyl)methanol (10) (0.44 g, 2.7 mmol) in THF (12 mL) and the mixture was stirred until effervescence ceased. Dibromide 8 (0.41 g, 1.2 mmol) and NaI (cat.) were added and the reaction mixture was heated at reflux for 18 h. Once cooled to RT volatiles were removed \textit{in vacuo}. The residue was partitioned between \( CHCl_3/IPA \) (3:1, 25 mL) and \( H_2O \) (25 mL) and the phases were separated. The aqueous phase was further extracted with \( CHCl_3/IPA \) (3:1, 25 mL). The combined organic extracts were washed with \( H_2O \) (2 x 50 mL) and brine (25 mL), then dried (MgSO\(_4\)) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (gradient elution: 1. pet-EtOAc, 10:1 and 1% Et\(_3\)N, 2. pet-EtOAc, 5:1 and 1% Et\(_3\)N) to give 11 (0.30 g, 50%) as a white solid.

\[
\text{Method B}
\]

NaH (0.99 g, 24.7 mmol) was added to a suspension of 15.HCl (1.56 g, 6.17 mmol) in DMF (30 mL) at 0 °C and the mixture stirred until effervescence ceased. 1-Allyloxy-4-bromomethyl-benzene (16) (4.20 g, 24.7 mmol) was added, the cooling bath removed and the mixture was stirred at RT for 16 h. The reaction mixture was partitioned between \( H_2O \) (150 mL) and \( CHCl_3/IPA \) (3:1, 150 mL) and the layers separated. The aqueous phase was extracted with \( CHCl_3/IPA \) (3:1, 2 × 150 mL), the combined organic layers were dried (MgSO\(_4\)) and concentrated under reduced pressure.
pressure. The resulting residue was purified by column chromatography (gradient elution: 1. CH₂Cl₂, 2. CH₂Cl₂-acetone, 98:2) to give 11 (2.64 g, 84%) as a pale yellow solid. M.p. 86-90 ºC; ¹H NMR (400 MHz, CDCl₃): δ = 8.27 (d, 2H, J = 7.8, Hₐ), 7.80 (t, 2H, J = 7.8, Hₐ), 7.49 (d, 2H, J = 7.7, Hₗ), 7.32 (d, 4H, J = 8.6, Hₗ), 6.91 (d, 4H, J = 8.6, Hₖ), 6.05 (ddt, 2H, Jₕ = 17.3, 10.5, Jₖ = 5.3, Hₖ), 5.41 (ddt, 2H, Jₕ = 17.3, 1.6, Jₖ = 1.6, Hₖ-trans), 5.28 (ddt, 2H, Jₕ = 10.5, 1.4, Jₖ = 1.3, Hₖ-cis), 4.74 (s, 4H, Hₗ), 4.61 (s, 4H, Hₗ) 4.54 (dt, 4H, J = 5.3, 1.5, Hₖ); ¹³C NMR (100 MHz, CDCl₃): δ = 158.3, 158.2, 155.4, 137.4, 133.2, 130.3, 129.4, 121.2, 119.7, 117.7, 114.6, 73.0, 72.5, 68.8; LRFAB-MS (3-NOBA matrix): m/z = 509 [M+H]⁺; HRFAB-MS (3-NOBA matrix): m/z = 509.24403 [M+H]⁺ (calc. for C₃₂H₃₃N₂O₄ 509.24403).

![Diagram](image)

Aniline (1.85 mL, 20.4 mmol), then Pd(PPh₃)₄ (0.86 g, 0.74 mmol) were added to a solution of the diallyl ether, 11, (2.64 g, 5.20 mmol) in THF (6 mL) and the mixture stirred at 30 ºC for 2 h. The mixture was poured into H₂O (100 mL) and extracted with CHCl₃/IPA (3:1, 3 × 100 mL). The combined organic phases were dried (MgSO₄) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (gradient elution: CH₂Cl₂ to CH₂Cl₂:MeOH, 97:3) gave 12 (2.30 g, 88%) as a pale yellow oil which crystallized on standing. M.p. 128-130 ºC; ¹H NMR (400 MHz, CD₃OD): δ = 8.20 (d, 2H, J = 7.7, Hₐ), 7.84 (t, 2H, J = 7.8, 2H, Hₐ), 7.55 (d, 2H, J = 7.6, Hₗ), 7.22 (d, 4H, J = 8.6, Hₗ), 6.78 (d, 4H, J = 8.6, Hₗ), 4.90 (s, 2H, OH), 4.66 (s, 4H, Hₗ), 4.54 (s, 4H, Hₗ); ¹³C NMR (100 MHz, CD₃OD): δ = 159.6, 158.4, 156.7, 138.9, 130.9, 130.1, 122.8, 121.2, 116.2, 73.8, 73.6; LRFAB-MS (3-NOBA matrix): 429 [M+H]⁺.
6-bromopicolinaldehyde (13)\textsuperscript{112}

\[
\begin{align*}
\text{n-BuLi (1.6 M in hexanes, 53.3 mL, 85.3 mol) was diluted in THF (100 mL) and} \\
\text{cooled to –78 °C. To this n-BuLi solution, a solution of 2,6-dibromopyridine (20.0 g,} \\
\text{84.4 mol) in THF (75 mL) was added drop-wise — maintaining a temperature of} \\
\text{–78 °C — over 2 h. The resulting dark green solution was allowed to stir at –70 °C} \\
\text{for a further 30 min. DMF (10 mL) was added, causing an elevation in temperature} \\
\text{to 40 °C and a change in colour from green to blue. The reaction mixture was then} \\
\text{re-cooled to –78 °C for a further 30 min then allowed to warm to RT, with stirring,} \\
\text{over 2 h. MeOH (30 mL) was added, accompanied by a colour change to orange. Sat.} \\
\text{aqueous NaHCO}_3 (100 mL) was added and the mixture extracted with CH}_2\text{Cl}_2 (3 \times 200 \text{ mL}). The combined organic extractions were dried (Na}_2\text{SO}_4 \text{) and concentrated under reduced pressure to give the aldehyde 13 (13.50 g, 92\%) as a pale yellow oil,} \\
\text{which was used without further purification. }^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 9.98 \\
\text{(s, 1H, H}D\text{)}, \ 7.91 \text{ (d, 1H, } J = 6.6, \text{ H}C\text{)}, \ 7.73 \text{ (m, 2H, H}A\text{ and H}B\text{).}
\end{align*}
\]

1-Bromo-6-hydroxymethyl pyridine (14)

\[
\begin{align*}
\text{Aldehyde 13 (13.5 g, 78.0 mmol) was dissolved in MeOH (300 mL) and NaBH}_4 \\
\text{(4.00 g, 106 mmol) was added at 0 °C. The reaction mixture was allowed to warm to} \\
\text{RT then stirred for 1 h at RT. The reaction was quenched by carefully adding a little} \\
\text{H}_2\text{O and volatiles were removed } \textit{in vacuo.} \text{ The residue was partitioned between} \\
\text{CH}_2\text{Cl}_2 (300 mL) and water (300 mL) and the phases separated. The organic phase} \\
\text{was dried (Na}_2\text{SO}_4 \text{) and concentrated under reduced pressure. The resulting residue} \\
\text{was purified by column chromatography (CH}_2\text{Cl}_2 \text{ then Et}_2\text{O) to give alcohol 14 (10.1}
\end{align*}
\]
g, 68% from 2,6-dibromopyridine) as a white solid. $^1$H NMR (400 MHz, CDCl$_3$): $^{109}$ \(\delta = 7.51 \text{ (t, 1H, J = 7.5, H_B)}, 7.33 \text{ (d, 1H, J = 7.8, H_A)}, 7.29 \text{ (ddt, 1H, J_d = 7.3, 0.6, J_t = 0.6, H_C)}, 4.70 \text{ (d, 2H, J = 5.4, H_D)}$.

6,6'-bis(hydroxymethyl)-2,2'-dipyridyl hydrochloride (15)

\[\text{Zinc (5.67 g, 85.4 mmol) was added to solution of PPh}_3 \text{ (89.3 g, 340 mmol) and NiCl}_2 \cdot 6\text{H}_2\text{O (20.2 g, 85.4 mmol) in DMF (350 mL) and the resultant suspension was stirred for 1 h at 50 °C. (6-Bromo-pyridin-2-yl)-methanol (14) (16.0 g, 85.1 mmol) was added to the deep red suspension and the reaction mixture was stirred for 2 h at 50 ° then allowed to cool to RT. The mixture was poured into a mixture of conc. NH}_3 \text{ (250 mL), H}_2\text{O (250 mL) and sat. EDTA/K}_2\text{CO}_3 \text{ (100 mL) and extracted with CHCl}_3/\text{IPA (3:1, 4 × 500 mL). The combined organic phases were dried (MgSO}_4\text{) and concentrated under reduced pressure. The resulting residue was dissolved in CH}_2\text{Cl}_2 \text{ (500 mL) and HCl gas bubbled through the solution to give a white suspension. Suction filtration gave 15 as a white solid (8.8 g, 82%). M.p. 208 – 212 °C; }^1\text{H NMR (400 MHz, DMSO-}_d6\text{): }\delta = 8.38 \text{ (d, 2H, J = 7.9, H_A)}, 8.17 \text{ (t, 2H, J = 7.8, H_B)}, 7.72 \text{ (d, 2H, J = 7.8, H_C)}, 4.77 \text{ (s, 4H, H_D)}; ^{13}\text{C NMR (100 MHz, DMSO-}_d6\text{): }\delta = 170.7 \text{ (Cx2), 149.6, 131.6, 129.8, 72.7; LRESI-MS (MeOH): }m/z = 217 \text{ [M+H–Cl]}^+; \text{ HRESI-MS (MeOH): }m/z = 216.0887 \text{ (calc. for C}_{12}\text{H}_{12}\text{N}_2\text{O}_2 \text{ 216.08933).} \]
1-allyloxy-4-(bromomethyl)benzene (16)

Allylic ether 10 (6.00 g, 37 mmol) was dissolved in CH₂Cl₂ (50 mL) and HBrₐq (48%, 50 mL) was added. The mixture was concentrated under reduced pressure (to near dryness). The residue was partitioned between CH₂Cl₂ (100 mL) and H₂O (100 mL) and the phases were separated. The organic phase was washed with sat. K₂CO₃ (100 mL), H₂O (100 mL), brine (100 mL), then dried (MgSO₄) and concentrated under reduced pressure to give bromide 16 (5.75 g, 79%) as a brown solid, which was used without further purification. ¹H NMR (400 MHz; CDCl₃): δ = 7.33 (d, 2H, J = 8.7, H_D or H_E), 7.00 (d, J = 8.7, H_D or H_E), 6.09 (m, 1H, H_B), 5.46 (dd, 1H, J = 17.2, 1.5, H_A-trans), 5.34 (dd, 1H, J = 10.5, 1.4, H_A-cis), 4.55 (d, J = 5.3, H_C), 4.51 (s, 2H, H_F).

2,6-bis(4-(allyloxy)benzylomethyl)pyridine (18)

NaH (1.02 g, 25 mmol) was added to a suspension of 2,6-pyridine dimethanol (1.90 g, 8.5 mmol) in DMF (100 mL) at 0 °C and the mixture was stirred until effervescence ceased. Bromide 16 (4.84 g, 21 mmol) was added and the mixture was stirred at RT for 16 h. The reaction mixture was partitioned between H₂O (250 mL) and CH₂Cl₂ (300 mL) and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (3 x100 mL). The combined organic extracts were washed
with H$_2$O (200 mL), brine (200 mL), dried (MgSO$_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (gradient elution: 1. CH$_2$Cl$_2$, 2. CH$_2$Cl$_2$-MeOH, 100:1) to give 18 (2.94 g, 80%) as a pale yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.77 (t, 1H, $J = 7.8$, H$_A$), 7.45 (d, 2H, $J = 7.8$, H$_B$), 7.37 (d, 4H, $J = 8.6$, H$_F$), 6.97 (d, 4H, $J = 8.7$, H$_E$), 6.13 (tdd, 2H, $J = 17.2$, 10.5, 5.3, H$_H$), 5.48 (ddm, 1H, $J_d = 17.24$, 1.53, H$_I$-trans), 5.36 (ddm, 2H, $J_d = 10.5$, 1.30, H$_I$-cis), 4.71 (s, 4H, H$_C$), 4.64 (s, 4H, H$_D$), 4.61 (dm, 4H, $J_d = 5.3$, H$_G$): $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 158.7, 157.7, 137.2, 133.2, 129.8, 129.5, 120.0, 117.7, 114.7, 72.8, 72.6, 68.8; LRESI-MS: m/z = 432 [M+H]$^+$; HRFAB-MS (3-NOBA matrix): m/z = 432.21678 (calc. for C$_{27}$H$_{30}$NO$_4$ 432.21748).

2,6-Bis(4-hydroxybenzyloxy)methyl pyridine (19)

Aniline (6.2 mL, 68 mmol), then Pd(PPh$_3$)$_4$ (2.8 g, 2.4 mmol) were added to a solution of diallyl ether 18 (25 g, 58 mmol) in THF (80 mL) and the mixture stirred at 30 ºC for 2 h. The mixture was partitioned between H$_2$O (500 mL) and CHCl$_3$/IPA (3:1, 500 mL). The organic phase was washed with H$_2$O (500 mL) then brine (500 mL), dried (MgSO$_4$) and the solvent concentrated under reduced pressure. The resulting residue was purified by column chromatography (gradient elution: 1. CH$_2$Cl$_2$, 2. CH$_2$Cl$_2$-acetone, 20:1) to give diphenol 19 (16.4 g, 78%) as a pale yellow solid. M.p. 53-57 ºC; $^1$H NMR (400 MHz, CD$_3$OD): $\delta$ = 7.79 (t, 1H, $J = 7.8$, H$_A$), 7.40 (d, 2H, $J = 7.8$, H$_B$), 7.19 (d, 4H, $J = 8.5$, H$_F$), 6.76 (d, 4H, $J = 8.5$, H$_E$), 4.56 (s, 4H, H$_C$), 4.50 (s, 4H, H$_D$); $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ = 159.0, 158.2, 139.1, 130.8, 129.8, 121.7, 116.0, 73.7, 72.9; LRESI-MS: m/z = 352 [M+H]$^+$; HRESI-MS: m/z = 374.13652 (calc. for C$_{27}$H$_{32}$O$_4$Na 374.13628).
K₂CO₃ (5.97 g, 43.2 mmol) was added to a solution of diphenol 19 (1.85 g, 4.32 mmol) in DMF (800 mL). 1,10-Dibromodecane (0.97 mL, 4.32 mmol) was added and the reaction mixture was stirred at 80 ºC for 24 h. After cooling to RT, DMF was removed in vacuo and the resulting residue taken up in CHCl₃/IPA (3:1, 300 mL) and H₂O (30 mL). The phases were separated and the aqueous phase extracted with CHCl₃/IPA (3:1, 200 mL). The combined organic extracts were washed with H₂O (200 mL) and brine (200 mL), dried (MgSO₄) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (gradient elution: 1. pet-EtOAc 10:1, 2. pet-EtOAc 4:1) to give macrocycle 1a (0.61 g, 29%) as a colourless solid. M.p. 61-62 ºC; ¹H NMR (400 MHz, CDCl₃): δ = 7.69 (t, 1H, J = 7.8, Hₐ), 7.36 (d, 2H, J = 7.8, H₉), 7.23 (d, 4H, J = 8.6, H₅), 6.80 (d, 4H, J = 8.6, H₆), 4.60 (s, 4H, H₇), 4.43 (s, 4H, H₈), 3.97 (t, 4H, J = 6.3, H₉), 1.73 (m, 4H, H₁₀), 1.22-1.48 (m, 12H, H₁₁, H₁₂ and H₁₃); ¹³C NMR (100 MHz, CDCl₃): δ = 158.7, 157.7, 137.1, 130.0, 129.2, 119.9, 114.5, 72.2, 71.2, 67.3, 29.3, 28.6, 28.5, 25.6. LRESI-MS: m/z = 490 [M+H]; HRESI-MS: m/z = 490.29552 [M+H]⁺ (calc. for C₃₁H₄₀O₄N₁ 490.29519).
K₂CO₃ (7.5 g, 48 mmol) was added to a stirred solution of diphenol 12 (2.06 g, 4.80 mmol) and 1,10-dibromodecane (1.44 g, 4.80 mmol) in DMF (2 L) and the mixture heated at 80 ºC for 16 h. The solvent was removed under reduced pressure and the residue was partitioned between H₂O (500 mL) and CH₂Cl₂ (500 mL) and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (3 × 500 ml). The combined organic layers were dried (MgSO₄) and the solvent removed under reduced pressure. The resulting residue was purified by column chromatography (gradient elution: pet-EtOAc 12:1 to 3:1) gave macrocycle 1b (0.85 g, 30%) as a colourless solid. M.p. 90-94°C; ¹H NMR (400 MHz, CDCl₃): δ = 8.04 (d, 2H, J = 7.7, HA), 7.72 (t, 2H, J = 7.8, HB), 7.40 (d, 2H, J = 7.6, HC), 7.19 (d, 4H, J = 8.5, HF), 6.76 (d, 4H, J = 8.6, HD), 4.66 (s, 4H, HE), 4.64 (s, 4H, HF), 3.91 (t, 4H, J = 6.5, HJ), 1.70 ( quint., 4H, J = 6.6, HI), 1.50-1.35 (m, 4H, HJ), 1.34-1.18 (m, 8H, HK, HL); ¹³C NMR (100 MHz, CDCl₃): δ = 158.6, 158.5, 155.6, 137.1, 129.8, 129.6, 121.2, 119.9, 114.4, 72.5, 72.1, 67.6, 29.2, 28.8, 28.6, 25.7; LRFAB-MS (3-NOBA matrix): m/z = 567 [M+H]⁺; HRFAB-MS (THIOG matrix): m/z = 567.32262 [M+H]⁺ (calc. for C₃₆H₄₃N₂O₄ 567.32228).
General Procedure for the Formation of ‘Click’ Rotaxanes

A solution of macrocycle, (1 equiv.), azide, (1 equiv.), alkyne, (1 equiv.) and [Cu(CH$_3$CN)$_4$](PF$_6$) (1.1 eq) in dry CH$_2$Cl$_2$ (5 mL) and under N$_2$ was stirred at room temperature for 24 h. The resulting mixture was diluted with CH$_2$Cl$_2$ (5 mL) and methanol (15 mL). Then a solution of KCN (10 equiv.) in methanol (2 mL) was added and the resulting suspension stirred vigorously for 1 h. Volatiles were removed \textit{in vacuo} and the residue was partitioned between water (15 mL) and CH$_2$Cl$_2$ (20 mL). The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic fractions were washed with water (10 mL) and brine (10 mL), then dried (MgSO$_4$) and concentrated under reduced pressure. Column chromatography and/or preparative TLC of the resulting residue afforded the pure rotaxane.

Spectroscopic data of the non-interlocked thread 5 generated during click reactions:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.61$ (s, 1H, $H_i$), 7.21 (d, 12H, $J = 8.52$, $H_b$, $H_n$), 7.03-7.11 (m, 16H, $H_c$, $H_d$, $H_m$, $H_l$), 6.82 (d, 2H, $J = 8.92$, $H_k$), 6.72 (d, 2H, $J = 8.89$, $H_e$), 5.17 (s, 2H, $H_j$), 4.59 (t, 2H, $J = 6.92$, $H_h$), 3.94 (t, 2H, $J = 5.53$, $H_f$), 1.23-1.43 (m, 2H, $J = 6.26$, $H_g$), 1.29 (s, 54H, $H_a$ and $H_o$). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 156.1$, 156.0, 148.3, 144.3, 144.0, 140.1, 132.3, 130.6, 124.0, 123.1, 113.2, 112.9, 63.7, 63.0, 61.9, 47.2, 34.2, 31.3, 29.9; HRFAB-MS (3-NOBA matrix): $m/z = 1130.75171$ (calcd. for C$_{80}$H$_{95}$N$_3$O$_2$, 1130.62920).
Following the general procedure, macrocycle \textbf{1a} (100 mg, 0.2 mmol) was reacted with alkyne \textbf{2} and azide \textbf{3} to give a crude yellow solid. Purification by column chromatography (CH$_2$Cl$_2$ then a gradient from 5 to 20 \% CH$_3$CN in CH$_2$Cl$_2$) gave rotaxane \textbf{4a} (180 mg, 54\%) as a colourless solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 7.50 (t, 1H, $J =$ 7.7, H$_A$), 7.31 (s, 1H, H$_I$), 7.22-7.30 (m, 14H, H$_B$, H$_b$ and H$_a$), 7.09-7.17 (m, 12H, H$_m$ and H$_n$), 7.08 (d, 2H, $J =$ 8.6, H$_i$), 7.04 (d, 2H, $J =$ 8.6, H$_o$), 6.97 (d, 4H, $J =$ 8.3, H$_e$), 6.77 (d, 2H, $J =$ 8.6, H$_h$), 6.56 (d, 4H, $J =$ 8.3, H$_F$), 6.48 (d, 2H, $J =$ 8.6, H$_o$), 4.91 (br s, 2H, H$_j$), 4.49 (br s, 4H, H$_D$), 4.31 (br s, 4H, H$_C$), 3.76-3.87 (m, 4H, HG), 3.71 (t, 2H, $J =$ 7.1, H$_h$), 3.34 (t, 2H, $J =$ 5.4, H$_j$), 1.61-1.73 (m, 4H, H$_H$), 1.54-1.62 (m, 2H, H$_g$), 1.34 (s, 27H, Ha or Ho), 1.33 (s, 27H, Ha or Ho), 1.17-1.41 (m, 12H, H$_I$, H$_i$ and H$_K$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 158.8, 157.7, 156.4, 146.4, 144.4, 144.3, 143.5, 139.9, 139.7, 137.3, 132.3, 132.1, 130.1, 130.0, 129.1, 124.2, 124.1, 123.6, 120.2, 114.4, 113.3, 113.1, 72.6, 71.4, 67.2, 64.0, 63.2, 61.6, 46.7, 34.4, 34.3, 31.5, 29.7, 29.5, 28.7, 25.8; LRESI-MS: $m/z =$ 1619 [M+H]$^+$; HRFAB-MS (3-NOBA matrix): $m/z =$ 1621.04087 (calcd. for $^{13}$C$_{12}$H$_{118}$N$_{135}$O$_6$, 1621.04152).
Following the general procedure, macrocycle 1b (9.9 mg, 17.4 μmol, 1.0 equiv.), azide 2 (10.2 mg, 17.4 μmol, 1.0 equiv.), alkyne 3 (10.4 mg, 19.2 μmol, 1.1 equiv.), [Cu(CH$_3$CN)$_4$](PF$_6$) (7.1 mg, 19.2 μmol, 1.1 eq) and KCN (11.4 mg, 0.17 mmol, 10 equiv.) gave the crude product as a mixture of rotaxanes 4b, thread 5 (45:65, by $^1$H NMR spectroscopy) and macrocycle 1b. Purification by column chromatography (Acetone-CH$_2$Cl$_2$; 4:96) followed by preparative TLC on alumina (3 elutions in Et$_2$O-pet; 1:1) gave the rotaxane 4b as a white solid (10 mg, 35%). M.p. 90-94 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ = 7.89 (d, 2H, J = 7.7, H$_A$), 7.43 (t, 2H, J = 7.7, H$_B$), 7.30-7.17 (m, 14H, H$_b$, H$_a$, H$_C$), 7.17-7.00 (m, 16H, H$_c$, H$_d$, H$_m$, H$_l$), 7.00-6.92 (m, 5H, H$_f$, H$_j$), 6.66 (d, 2H, J = 8.8, H$_k$), 6.54 (d, 4H, J = 8.5, H$_g$), 6.33 (d, 2H, J = 8.8, H$_e$), 4.81 (s, 2H, H$_j$), 4.54 (s, 4H, H$_D$), 4.51 (s, 4H, H$_E$), 3.75-3.66 (m, 6H, H$_H$, H$_h$), 3.24 (t, 2H, J = 5.6, H$_i$), 1.65-1.50 (m, 6H, H$_l$, H$_k$), 1.40-1.03 (m, 12H, H$_J$, H$_K$, H$_L$), 1.30 and 1.29 (2s, 54H, H$_a$, H$_o$); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 158.5, 158.1, 156.1, 148.2, 144.1, 144.0, 143.4, 139.8, 139.5, 137.1, 132.1, 131.9, 130.6, 129.6, 129.5, 124.0, 123.1, 121.5, 119.9, 114.2, 113.0, 112.7, 72.4, 72.2, 67.5, 63.6, 63.0, 61.5, 46.7, 34.2, 31.3, 29.6, 29.2, 28.7, 25.7; LRFAB-MS (3-NOBA matrix): m/z = 1698 [M+H]$^+$; HRFAB-MS (3-NOBA matrix): m/z = 1698.06527[M+H]$^+$ (calc. for $^{13}$C$_{12}$H$_{138}$N$_5$O$_6$ 1698.06807 [M+H]$^+$).
Following the general procedure, macrocycle 1m (29.0 mg, 60.4 μmol, 1.0 equiv.), azide 3 (35.5 mg, 60.4 μmol, 1.0 equiv.), alkyne 2 (36.0 mg, 66.4 μmol, 1.1 equiv.), [Cu(CH₃CN)₄](PF₆) (24.8 mg, 66.4 μmol, 1.1 eq) and KCN (40 mg, 0.66 mmol, 10 equiv.) gave the crude product as a mixture of rotaxane 4m, thread 5 (25:75, by ¹H NMR spectroscopy) and macrocycle 1m. Purification by column chromatography (CH₃CN-CH₂Cl₂-pet; 2.5:20:77.5) gave rotaxane 4m (15 mg, 14%) as a colourless solid. M.p. 130-132 °C; ¹H NMR (400 MHz, CDCl₃): δ = 7.73 (d, 4H, J = 8.8, Hc), 7.61 (t, 1H, J = 7.8, HA), 7.39 (d, 2H, J = 7.8, Hb), 7.22-7.18 (m, 12H, Hb, Ha), 7.10-7.03 (m, 16H, Ha, Hb, Hm, Hl), 6.89 (s, 1H, Hi), 6.82 (d, 4H, J = 8.8, Hb), 6.78 (d, 2H, J = 8.9, Hk), 6.66 (d, 2H, J = 8.9, Hl), 4.96 (s, 2H, Hj), 4.04 (t, 4H, J = 7.2, He), 4.00 (t, 2H, J = 7.1, Hb), 3.70 (t, 2H, J = 5.6, Hi), 1.97 (quint., 2H, J = 6.4, He), 1.60 (quint, 4H, J = 7.0, Hf), 1.33-0.98 (m, 24H, Hg, Hh, Hi, Hj, Hk, Hl), 1.30 and 1.29 (2s, 54H, Ha, Hb); ¹³C NMR (100 MHz, CDCl₃): δ = 158.9, 156.9, 156.2, 148.2, 144.0, 143.5, 139.8, 137.3, 132.5, 132.1, 130.7, 130.6, 128.8, 124.0, 123.2, 117.2, 115.3, 113.1, 112.8, 68.0, 63.9, 63.0, 61.7, 46.7, 34.2, 31.3, 30.1, 30.0, 29.6, 29.5, 28.2, 25.7; LRFAB-MS (3-NOBA matrix): m/z = 1617 [M+H]⁺; HRFAB-MS (3-NOBA matrix): m/z = 1617.0845 (calcd. for ¹³C₁₁₂H₁₃⁹N₄O₄, 1617.08299).
A solution of macrocycle 1m (170 mg, 0.35 mmol, 10 equiv.), azide 3 (20.6 mg, 35.0 μmol, 1.0 equiv.), alkyne 2 (19.0 mg, 35.0 μmol, 1.1 equiv.), [Cu(CH₃CN)₄](PF₆) (14.3 mg, 38.5 μmol, 1.1 eq) in CH₂Cl₂ (10 mL) and under N₂ was stirred at RT for 8 days. The solution was then refluxed for further 48 h then cooled to RT. The resulting mixture was diluted with CH₂Cl₂ (5 mL) and MeOH (15 mL). Then a solution of KCN (25 mg, 0.38 mmol, 10 equiv.) in MeOH (2 mL) was added and the resulting suspension stirred vigorously for 1 h. Solvents were evaporated (80 °C) and the residue was partitioned between water (15 mL) and CH₂Cl₂ (20 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic fractions were washed with water (10 mL) and brine (10 mL), then dried (MgSO₄) and concentrated under reduced pressure to give the crude product as a mixture of [2]rotaxane 4m, [3]rotaxane 19m, thread 5 (33:37:30, by ¹H NMR spectroscopy), macrocycle 1m, remaining azide 3 and alkyne 2, (75% overall conversion). Purification by preparative TLC on silica gel (3 elutions in CH₃CN-CH₂Cl₂-pet; 3.5:40:56.5) gave the [3]rotaxane 20m as a white solid (15 mg, 20%). M.p. 302-304 °C; ¹H NMR (400 MHz, CDCl₃): δ = 7.68 (m, 10H, Hc, Hc', Ha, Ha'), 7.37 (d, 4H, J = 7.8, Hb, Hb'), 7.20 -7.10 (m, 12H, Hn), 7.09 (s, 1H, Hi), 7.05-6.91 (m, 16H, Hc, Hm, Hd, Hl), 6.82 (d, 2H, J = 8.9, Hk), 6.74-6.65 (m, 8H, Hb, HD'), 6.46 (d, 2H, J = 8.9 Hz, Hc), 5.04 (s, 2H, Hi), 4.03-3.89 (m, 8H, Hb, HD'), 3.70 (t, 2H, J = 7.5 Hz, Hc), 3.50 (t, 2H, J = 5.7 Hz, Hc), 1.69 (br. quint., 2H, J = 6.7, Hg), 1.54 (br. quint, 2H, J = 7.35, Hf), 1.40-0.81 (m, 48H, HG, HG', HH, HH', HI, HI', HJ, HJ', HK, HK', HL, HL'), 1.27 and 1.26 (2s, 54H, Ha, Hb); ¹³C NMR (100 MHz, CDCl₃): δ = 158.9, 158.8, 156.8, 156.7, 156.2, 156.1,
LRFAB-MS (3-NOBA matrix): \( m/z = 2101 \ [M^+] \); HRFAB-MS (3-NOBA matrix): 
\[ m/z = 2102.41114 \ [M+H]^+ \] (calc. for \( ^{12}C_{145}^{13}CH_{182}N_{5}O_{6} \), 2102.41237 [M+H]^+).

Crystal data and structure refinement for 20m.

- **Empirical formula**: \( C_{146}H_{181}N_{5}O_{6} \)
- **Formula weight**: 2101.96
- **Temperature**: 173(2) K
- **Wavelength**: 1.54178 Å
- **Crystal system**: Triclinic
- **Space group**: P-1
- **Unit cell dimensions**: 
  - \( a = 14.0813(12) \) Å
  - \( \alpha = 84.390(4)^\circ \)
  - \( b = 19.2182(17) \) Å
  - \( \beta = 73.528(4)^\circ \)
  - \( c = 24.208(2) \) Å
  - \( \gamma = 83.845(4)^\circ \)
- **Volume**: 6230.5(10) Å\(^3\)
- **Z**: 2
- **Density (calculated)**: 1.120 Mg/m\(^3\)
- **Absorption coefficient**: 0.511 mm\(^-1\)
- **F(000)**: 2280
- **Crystal size**: 0.200 x 0.200 x 0.100 mm\(^3\)
- **Theta range for data collection**: 2.32 to 44.72°
- **Index ranges**: -12<=h<=12, -17<=k<=17, -22<=l<=22
- **Reflections collected**: 31202
- **Independent reflections**: 9695 [R(int) = 0.1469]
- **Completeness to theta = 25.00°**: 99.2 %
- **Absorption correction**: Multiscan
- **Max. and min. transmission**: 1.0000 and 0.0040
- **Refinement method**: Full-matrix least-squares on \( F^2 \)
- **Data / restraints / parameters**: 9695 / 16 / 1319
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<tr>
<td>R indices (all data)</td>
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Chapter 3: A Nickel-Copper-Mediated Alkyne Homocoupling Active Template


Acknowledgements
The following people are gratefully acknowledged for their contribution to this chapter: Nicholas Gowans and Pauline Fitzsimmonds investigated alternative active template conditions, not discussed here. José Berna synthesized alkyne 31 X-Ray quality crystals of 1b.NiCl2 were obtained by Dr. James Crowley and the structure was solved by Prof. Alexandra Slawin.
3.1 Introduction

Alkyne couplings have recently experienced renewed interest due to the electronic and optical properties of π-conjugated systems and, as a result, new methodology is constantly being developed to overcome the synthetic challenges presented by increasingly complicated systems.\textsuperscript{103} Since the first report of the reductive elimination of Cu(I)-acetylides in air by Glaser\textsuperscript{113} various modifications of the conditions have been reported.\textsuperscript{103,114-121} Alkyne homocouplings often involve the formation of Li-acetylides followed by transmetallation to the metal from which oxidative addition occurs. Such metallated alkynes have been generated from boron,\textsuperscript{122-124} tin,\textsuperscript{125} antimony,\textsuperscript{126} selenium,\textsuperscript{127} tellurium,\textsuperscript{128} and mercury.\textsuperscript{129}

Despite the widespread use of alkyne couplings as a synthetic tool, very little work has been done towards shedding light on the mechanism of these reactions. The generally accepted model of the Glaser coupling mechanism is that proposed by Bohlmann and co-workers in 1964.\textsuperscript{102} This model proposes the coordination of Cu(I) ions to the alkyne triple bond, activating it to deprotonation, followed by formation of a dinuclear Cu(II) acetylide complex which collapses to give the oxidatively coupled product (Scheme 3.1a).\textsuperscript{102} A Cu-catalyzed alkyne homocoupling to produce a [2]rotaxane has recently been reported by Saito and co-workers, in which tetrahedral complex 21.CuI catalyzes a Glaser coupling of alkyne 22 through the macrocyclic cavity (Scheme 3.1a) to give rotaxane 23 in 72% yield.\textsuperscript{107}

Palladium-promoted terminal alkyne couplings were first observed as a side-reaction during the coupling of terminal alkynes with aryl or vinyl halides.\textsuperscript{130} The reaction was later optimized by Rossi and co-workers, using a mixture of CuI and Pd(PPh\textsubscript{3})\textsubscript{4} as a catalyst for coupling aryl and alkyl alkynes.\textsuperscript{131} Since then, Pd-catalyzed alkyne couplings to give 1,4-disubstituted diynes have attracted considerable attention.\textsuperscript{132-144} The proposed mechanism for the Pd(II)-catalyzed coupling involves transmetallation of a Cu(I) acetylide (generated \textit{in situ} from a Cu(I) source, a terminal alkyne and an amine base) to give a dialkynyl Pd(II) species. Subsequent reductive elimination
gives the coupled product and a Pd(0) species which is reoxidized by I\(_2\) (Scheme 3.1, b).\(^{132}\) The Leigh group recently reported a Pd(II)-catalyzed active template alkyne homocoupling reaction to give [2]rotaxanes in high yield in the presence of catalytic quantities of Pd (Scheme 3.1b).\(^{145}\) The reaction is thought to proceed via \(\text{trans-1a}.\text{PdCl}_2(\text{MeCN})\): displacement of the \(\text{trans}\) Cl ligands by two Cu-acetyldes leads to a \(\text{trans}\) threaded complex which then undergoes \(\text{trans-cis}\) isomerization before reductive elimination can occur. With 1 equivalent of the Pd-macrocycle catalytic complex, \(\text{1a}.\text{PdCl}_2(\text{MeCN})\), and 2.5 equiv. of alkyne 24, rotaxane 25 is obtained in 43% yield. This was increased to 61% with 10 equiv. alkyne.\(^{145}\) By using only a catalytic quantity (0.05 equiv.) of the Pd-macrocycle complex (the remaining 0.95 equiv. is present as free macrocycle) the yield of rotaxane 25 could be increased to 90%.\(^{145}\) The origin of the high yields for this process can be explained by the orientation of the Cl ligands: they protrude from opposite faces of the macrocycle\(^{146}\) which leads to a high degree of selectivity for the threaded complex on transmetallation.\(^{145}\)

**Scheme 3.1.** a) Proposed mechanism of the Cu(I)-catalyzed Glaser coupling\(^{102}\) and its application to the synthesis of a [2]rotaxane\(^{107,a}\). b) Proposed mechanism of Pd-catalyzed oxidative homocoupling\(^{132}\) of terminal alkynes and its application to the synthesis of a [2]rotaxane.\(^{145}\) \(^{a}\)L = nitrogen ligand, for example, pyridine; a) X = Cl\(-\), OAc\(^-\); b) X = Cl.
In 1969 Rhee and co-workers observed the formation of a 1,4-diynone from the reaction of lithium phenylacetylide with \( \text{Ni(CO)}_4 \). Homocoupling of Li-acetylides in the presence of \( \text{NiCl}_2(\text{PPh}_3)_2 \) has been reported by Klein and co-workers and Whittall and co-workers (Scheme 3.2), while Ni(II)-promoted homocoupling of alkynes in supercritical water has also been described. However, compared to Cu- and Pd-mediated synthesis of 1,4-diynes, there has been relatively little study into the potential of nickel to promote the homocoupling of terminal alkynes.

Scheme 3.2. Ni(II)-promoted coupling of alkynyl lithium derivatives.

A very recent paper by Yin et al describes a Ni/Cu-co-catalyzed oxidative heterocoupling of terminal alkynes in the presence of TMEA as a ligand and \( \text{O}_2 \) as the oxidizing agent.

This chapter describes the first octahedral active-metal template: an unusual nickel-promoted reaction which couples ‘stoppered’ terminal alkynes through the centre of a bipyridyl macrocycle to give [2]rotaxanes in excellent yields.
3.2 Results and Discussion

When bipyridyl macrocycle 1b was employed in the Pd(II)-mediated active template alkyne homocoupling (vide supra) it was found to be significantly less efficient than monodentate pyridyl macrocycle 1a under stochiometric conditions: only 10% of the corresponding rotaxane was obtained with 2.5 equivalents of stoppered alkyne 24 and this could only be increased to 20% with 10 equivalents of 24. This was reasoned to be due to the square planar geometry of the Pd centre in a bidentate macrocycle not being conducive to threading during the transmetallation process. Indeed, in the solid state structure of complex 1b.PdCl2 the Cl ligands both protrude from the same face of the macrocycle (Figure 3.1) and thus transmetalation with a Cu-acetylide could be expected to lead predominantly to the unthreaded complex.

![Figure 3.1. X-ray crystal structure of complex 1b.PdCl2. Carbon atoms are shown in green, nitrogen atoms in blue, oxygen atoms in red, chloride atoms in light green, and the palladium in grey.](image)

Nickel is more geometrically flexible than palladium, as well as being inexpensive, readily available in a range of sources, and easily removed from the products of a reaction, and this led us to investigate the homocoupling of terminal alkynes mediated by macrocyclic bipyridyl complex, 1b.NiCl2. Literature on the preparation of complex 26.NiCl2 (see Scheme 3.3, vide infra) has reported a tetrahedral structure in the solid state. However, the solid state structure of complex 1b.NiCl2, determined by single crystal X-Ray diffraction, clearly shows that
in this system the Ni(II) centre exhibits a pseudooctahedral geometry, with the Ni centre coordinated to the benzylic ether oxygen atoms of the macrocycle (Figure 3.2). The Cl–Ni–Cl angle is 161°, with the Cl ligands pointing directly out of the plane of the bipyridyl unit on either side of the plane of the macrocycle. Therefore, unlike the corresponding Pd complex, \( \text{1b}.\text{NiCl}_2 \) seems ideally suited to an active template reaction in which the Cl ligands are replaced by acetylides prior to reductive elimination to form a substituted 1,4-diyne product.

![Figure 3.2. X-ray crystal structure of complex \( \text{1b}.\text{NiCl}_2 \), from a single crystal obtained from slow cooling in acetonitrile: a) viewed side-on; b) viewed along the Cl-Ni-Cl axis. Carbon atoms are shown in green, nitrogen atoms in blue, oxygen atoms in red, chloride atoms in pink, and the nickel in grey. Selected bond lengths [\( \text{Å} \)] and angles [deg]: N1-Ni 2.01, N2-Ni 2.02, O1-Ni 2.25, O2-Ni 2.41, Cl1-Ni 2.32, Cl2-Ni 2.33, N1-Ni-N2 79.8, O1-Ni-O2 131.7, Cl1-Ni-Cl2 161.4.](image)

6,6′-Dimethyl-2,2′-bipyridyl (26) and macrocycle \( \text{1b} \) were tested as ligands for a Ni(II)-promoted terminal alkyne coupling, using phenylacetylene as the substrate (Scheme 3.3). The \( \text{NiCl}_2 \) complexes were prepared \emph{in situ} by stirring equimolar quantities of ligand and \( \text{NiCl}_2.\text{DME} \) in THF at 80 °C. The reaction in the presence of \( \text{26.}\text{NiCl}_2 \) was unsuccessful (Scheme 3.3). By contrast, the control reaction, in which \( \text{NiCl}_2.\text{DME} \) was used without an added ligand, resulted in complete conversion to the homocoupled product (Scheme 3.3). We reasoned that the use of a softer nucleophile may result in formation of the required Ni(II)-diacetylide, and we were pleased to find that transmetalation of the Li-acetylide using CuI did indeed result in smooth
and quantitative homocoupling of the substrate in the presence of 23.NiCl₂ (Scheme 3.3). Only 5% coupling of Li-phenylacetylide was observed in the presence of 1b.NiCl₂, but once again, this increased to quantitative conversion upon addition of CuI (Scheme 3.3).

Scheme 3.3. Conditions for the Ni(II)-promoted homocoupling of phenylacetylene. Reagents and conditions: a) i) Phenylacetylene (0.05 mmol), n-BuLi (0.05 mmol), THF, –78 °C → 0 °C, ii) 23.NiCl₂ or 1b.NiCl₂ (0.025 mmol, in THF), –78 °C → RT, 80 °C for 18 h; or b) i) Phenylacetylene (0.05 mmol), n-BuLi (0.05 mmol), THF, –78 °C → 0 °C, ii) CuI (0.05 mmol), 0 °C, iii) 26.NiCl₂ or 1b.NiCl₂ (0.025 mmol, in THF), –78 °C → RT, 80 °C for 18 h. aFor the purposes of reactions, 26.NiCl₂ and 1b.NiCl₂ were prepared in situ from equimolar quantities of the appropriate ligand and NiCl₂.DME in THF at 80 °C. bCalculated from 1H NMR of the crude reaction mixture.

By using a terminal alkyne bearing a stoppering group larger than the cavity of the macrocycle, the reaction could be extended to the synthesis of a [2]rotaxane (Scheme 3.4). Treatment of a solution of acetylene 24 with an equimolar quantity of n-BuLi, to give the Li-acetylide in situ, followed by addition of CuI, gave the cuprate. Treatment of this cuprate with a solution of 1b.NiCl₂ resulted in formation of the [2]rotaxane 27 (48%), along with some of the non-interlocked thread 28 (Scheme 3.4).
Scheme 3.4. Synthesis of a [2]rotaxane by alkyne homocoupling in the presence of Ni(II) and Cu(I). Reagents and conditions: i) n-BuLi, CuI, 2 NiCl₂, THF, 80 ºC. Typical procedure is given in the Experimental section.

Characteristic upfield shifting of H₀ and H₆, of the rotaxane, in the ¹H NMR spectrum, relative to that of the free macrocycle, meant that the progress of reactions could easily be followed by ¹H NMR spectroscopy. Characteristic upfield shifting of the aromatic protons of the macrocycle (H₈, H₉, H₁₀ and H₁₁) and the protons in the axle (H₇, H₂, H₃, and H₄) confirm the interlocked nature of the product (Figure 3.3).
Unfortunately, the reaction proved to be capricious and in order to improve the yield and reliability of the reaction some optimization was carried out. Variation of the order of addition of reagents revealed addition of the CuI prior to addition of 1b.NiCl₂ to be the initial source of irreproducibility and low yields. Indeed, when the CuI was added last, the reaction became high yielding. Alkyne 24 (2.0 equiv.) was treated with n-BuLi (2.0 equiv) at –78 °C, followed by stirring at 0 °C for 30 min, to allow formation of the Li-acetylide. This solution was cooled to –78 °C, upon which a solution of 1b.NiCl₂ was added. Upon warming to RT, CuI (2.0 equiv.) was added and the reaction heated at 80 °C for 48 h. This protocol proved to be reproducible, giving rotaxane 27 in 67% isolated yield (Table 3.1, Entry 1), and as such these conditions were taken as the basis for further studies. Varying the quantity of CuI added showed that anything less that a stoichiometric quantity (with respect to 24) is detrimental to the yield (Table 3.1, Entries 2–4). Comparison of the total conversion of alkyne 24 to products (both rotaxane 27 and non-interlocked thread 28) however, shows that the reaction is selective for the interlocked product, but is slower when less Cu(I) is present (Table 3.1).
Table 3.1. The effect of the amount of Cu(I) present on the degree of coupling of alkyne 21 to produce rotaxane 22.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. 24</th>
<th>Equiv. 1b.NiCl₂</th>
<th>Equiv. Cu</th>
<th>Yield of rotaxane 27&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Total conversion of 24 to (27 + 28)&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.0</td>
<td>1.0</td>
<td>2.0</td>
<td>67%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>99%&lt;sup&gt;b&lt;/sup&gt; (32% of 28&lt;sup&gt;b&lt;/sup&gt;)</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.0</td>
<td>1.0</td>
<td>1.5</td>
<td>63%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&gt;99%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.0</td>
<td>1.0</td>
<td>1.0</td>
<td>32%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>52%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.0</td>
<td>1.0</td>
<td>0.5</td>
<td>23%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>27%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction carried out at 16.7 mM concentration with respect to 1b.NiCl₂; general experimental procedures can be found in the Experimental section. <sup>b</sup>Isolated yield. <sup>c</sup>Yield calculated from 1H NMR of the reaction mixture. <sup>d</sup>Relative to macrocycle 1b. <sup>e</sup>Relative to alkyne 24.

The importance of both metals to this reaction is illustrated by the poor yield of rotaxane when either nickel or copper is omitted from the reaction (Table 3.2, Entries 2 and 3). Comparison of the rate of reaction under the optimized conditions, with that of any background Cu-catalyzed coupling, shows that the reaction is assisted greatly by the presence of the nickel. After 48 h at 80 °C the bimetallic system has reached its maximum conversion to products (Table 3.2, Entry 1) while the corresponding reaction in the absence of Ni(II) has only formed 13% of rotaxane 27 and 45% non-interlocked thread 28 (Table 3.2, Entry 2), showing that the Cu-mediated reaction is both much slower and exhibits low selectivity for formation of interlocked over non-interlocked product. The presence of Ni(II) is essential for rotaxane formation in an appreciable yield in the same timeframe.
It was particularly pleasing to see that a 2-fold increase in the amount of alkyne used resulted in a near-quantitative yield of [2]rotaxane 27 (Table 3.2, Entry 5). No coupling was observed in the absence of $n$-BuLi (Table 3.2, Entry 4).

### Table 3.2. Experiments to determine the conversion of alkyne 24 to rotaxane 27 and non-interlocked thread 28 under a range of conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. 24</th>
<th>Equiv n-BuLi</th>
<th>Equiv 1b</th>
<th>Equiv NiCl$_2$.DME</th>
<th>Equiv Cu</th>
<th>Conversion to rotaxane 27$^d$</th>
<th>Total conversion of 24 to (27 + 28)$^e$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^a$</td>
<td>2.0</td>
<td>2.0</td>
<td>1.0</td>
<td>1.0</td>
<td>2.0</td>
<td>67$^b$,f</td>
<td>99$^b$,f (32$^c$)</td>
</tr>
<tr>
<td>2$^a$</td>
<td>2.0</td>
<td>2.0</td>
<td>1.0</td>
<td>-</td>
<td>2.0</td>
<td>13$^c$,f</td>
<td>46$^c$,f</td>
</tr>
<tr>
<td>3$^f$</td>
<td>2.0</td>
<td>2.0</td>
<td>1.0</td>
<td>1.0</td>
<td>-</td>
<td>5$^c$,f</td>
<td>5$^c$,f</td>
</tr>
<tr>
<td>4$^{a,f}$</td>
<td>2.0</td>
<td>-</td>
<td>1.0</td>
<td>1.0</td>
<td>2.0</td>
<td>0$^c$,f</td>
<td>0$^c$,f</td>
</tr>
<tr>
<td>5$^{a,f}$</td>
<td>4.0</td>
<td>2.0</td>
<td>1.0</td>
<td>2.0</td>
<td>2.0</td>
<td>95$^{b,k}$</td>
<td>66$^{e}$</td>
</tr>
</tbody>
</table>

$^a$ Reaction carried out at 16.7 mM concentration with respect to 1b; general experimental procedures can be found in the Experimental section. $^b$ Isolated yield. $^c$ Yield calculated from $^h$H NMR of the reaction mixture. $^d$ Relative to macrocycle 1b. $^e$ Relative to alkyne 24. $^f$ Where macrocycle 1b and NiCl$_2$.DME are both present, these were added as the previously described solution of the complex 1b.NiCl$_2$. $^h$ After 86 h at 80 °C. $^i$ After 48 h at 80 °C.

In order to demonstrate substrate scope the reaction to was applied to stoppered propargylic ether, 2, and an aryl alkyne, 31, to produce rotaxanes 29 and 32 respectively along with the corresponding non-interlocked threads (Scheme 3.5). Rotaxane 29 was produced in 85% yield which was particularly pleasing as stopper 2 could not be coupled by the Pd(II)-catalyzed reaction due to the propargylic group being cleaved in the presence of palladium.$^{156}$ The aryl alkyne 31 coupled to give rotaxane 32 in 31% yield.
Scheme 3.5. Ni/Cu-mediated active template homocoupling of a stoppered propargylic ether (2) and an aryl alkyne (31) to give [2]rotaxanes. Reagents and conditions: i) n-BuLi, CuI, THF, –78 °C→80 °C. Typical procedure is given in the Experimental section.

Characteristic upfield shifting of H_B, H_C, H_D, H_E, H_F, H_G and H_H (of the macrocycle of the rotaxane) and H_e and H_f (of the axle of the rotaxane) in the 1H NMR spectrum confirms the interlocked nature of the rotaxane 29 (Figure 3.4).

For rotaxane 32 a fairly dramatic upfield shift of the aromatic axle protons H_g and H_h is observed, relative to those of the non-interlocked thread (Figure 3.5). H_e and H_f also experience some upfield shifting (Figure 3.5).
Figure 3.4. Partial $^1$H NMR spectra (400 MHz, CDCl$_3$, 300 K) of a) macrocycle 1b, b) [2]rotaxane 29, c) thread 30. The assignments correspond to the lettering shown in Scheme 3.5.

Figure 3.5. Partial $^1$H NMR spectra (400 MHz, CDCl$_3$, 300 K) of a) macrocycle 1b, b) [2]rotaxane 32, c) thread 33. The assignments correspond to the lettering shown in Scheme 3.5.
The proposed mechanism for this reaction is that of a bimetallic system, where the Cu(I) displaces the Ni(II) from the macrocyclic cavity to form a bimetallic, 4-membered intermediate \( \text{II} \), from which nickel can be reductively eliminated (Scheme 3.6). Such a mechanism explains the increased reliability of the reaction when the copper source was added last, giving the Ni(II)-diacetylide intermediate complex \( \text{I} \) time to form first.

\[ \text{Scheme 3.6}. \text{Proposed mechanism for the Ni(II)/Cu(I)-mediated assembly of [2]rotaxanes.} \]
In earlier experiments with phenylacetylene, no conversion to the homocoupled product was observed in the absence of CuI (Scheme 3.3). Using the mechanism proposed in Scheme 3.6, this can be explained by the failure of nickel to eliminate from the intermediate Ni-diacetylide, when ligated by a bipy ligand. This ‘switching off’ of the reaction by a bipyridyl ligand is not entirely surprising, given that phosphine-ligated Ni(II)-diacetylide species are known to be isolatable and stable in air and above room temperature.\textsuperscript{149,157-160} Nitrogen-containing ligands are harder donors than their phosphine counterparts, leading to a less electron-rich complex, which may explain the apparent stability of the complex, and subsequent degradation back to the starting alkyne upon removal of the metal.

A change of colour from pale yellow (proposed intermediate I) to deep orange, upon addition on Cu(I), is an indication of the formation of intermediate II, in which it is proposed Cu(I) is coordinated to the macrocycle. Heating an equimolar solution of macrocycle 1b and CuI also gives a deep orange solution in THF, whereas 1b.NiCl\textsubscript{2} gives a pink solution in the same solvent.

No reaction occurs in the absence of n-BuLi (Table 3.2, Entry 4). It is known that Cu-acetylides can form in the absence of strong base, as Cu-activation of the triple bond decreases the pK\textsubscript{a} of the acetylenic proton sufficiently. Therefore if formation of a Cu-acetylide was the necessary first step, we would expect to observe some degree of rotaxane formation in the absence of base. This is not the case however.

To produce a truly ‘traceless’ rotaxane, rotaxane 27 was subjected to hydrogenation conditions to give a rotaxane with a C\textsubscript{10} aliphatic chain in the axle (Scheme 3.7). Rotaxane 34 has minimal functionality in the thread and showcases the ability of the active template strategy to produce structures which could not be synthesized using traditional passive transition metal templates, which require recognition motifs on each component.
Scheme 3.7. Hydrogenation of the triple bonds in rotaxane 27. Reagents and conditions:
i) Pd/C, H₂, THF, RT, 83%.

Tetrahedral81 and square planar145,161,162 metal-macrocycle complexes have been used in active template reactions and here the first octahedral metal complex for active template reactions has been described, based on the Ni(II)-mediated homocoupling of alkynes. This represents a cheap, high-yielding and general synthesis of such rotaxanes, using a readily accessible macrocycle. As well as the efficiency of the protocol, the reaction itself has proven to be under investigated and its mechanism is non-trivial. The addition of Cu(I) to a Ni(II) coupling system achieves a high degree of homocoupling that would not be possible in a simple bipyridyl-Ni(II) system.
3.3 Experimental

General

Unless otherwise stated, all reagents were obtained from commercial sources and used without further purification, solvents were anhydrous and all reactions were carried out under an atmosphere of $N_2(g)$.

![NiCl$_2$.DME](image)

NiCl$_2$.DME (38.8 mg, 0.18 mmol) was added to a solution of macrocycle 1b (100 mg, 0.18 mg) in MeCN (7 mL). The solution was gently heated until everything had dissolved and the resulting pink solution was allowed to cool to RT. The resulting solid (81 mg, 65%) was collected by suction filtration and was not purified further. Single crystals, suitable for x-ray diffraction, were grown by slow cooling of a saturated solution of this crude product in MeCN.

**General Experimental Procedure for the Ni/Cu Active Template Reaction to produce [2]Rotaxane**

A solution of alkyne (2.0 or 4.0 equiv.) in THF (1 mL) was cooled to $–78 \, ^\circ\text{C}$ and treated with a solution of $n$-BuLi (2.0 equiv) in THF (1 mL) and the resulting mixture was allowed to stir at 0 ºC for 30 min. The mixture was re-cooled to $–78 \, ^\circ\text{C}$ and a solution of complex 1b.NiCl$_2$ (1.0 equiv.) – prepared by dissolving an equimolar quantity of 1b and NiCl$_2$.DME in THF (1 mL) at 80 ºC – was added slowly. The reaction mixture was removed from the $–78 \, ^\circ\text{C}$ bath and CuI (2.0 equiv.) was added, which resulted in an immediate colour change from pale yellow to orange. The reaction mixture was heated at 80 ºC in a sealed microwave vial for
86 h. Once cooled to RT, the reaction was diluted with CH₂Cl₂ (5 mL) and washed with a basic saturated EDTA solution, (2 x 10 mL). The combined organic extracts were washed with brine (5 mL). The organic phase was dried (Na₂SO₄) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (gradient elution: petrol-CH₂Cl₂ (70:25) to petrol-CH₂Cl₂-MeCN (70:25:4)) to give the desired rotaxane.

Following the general procedure, alkyne 24 (110 mg, 0.20 mmol) and macrocycle 1b (28.4 mg, 0.05 mmol) were reacted to give rotaxane 27 (81 mg, 95%) as a colourless solid. ¹H NMR (400 MHz, CDCl₃): δ = 8.02 (d, J = 7.6, 2H, Hₐ), 7.51 (dd, J = 7.8 7.6, 2H, Hₖ), 7.28 (d, J = 7.8, 2H, Hₐ), 7.16 (d, J = 8.6, 12H, Hₖ), 7.00 (d, J = 8.6, 12H, Hₖ), 6.96 (d, J = 8.6, 4H, Hₖ), 6.86 (d, J = 8.9, 4H, Hₖ), 6.54 (d, J = 8.6, 4H, Hₖ), 6.32 (d, J = 8.9, 4H, Hₖ), 4.51 (s, 4H, Hₕ), 4.49 (s, 4H, Hₕ), 3.69 (t, J = 6.6, 4H, Hₕ), 3.44 (t, J = 6.0, 4H, Hₕ), 2.02 (t, J = 7.0, 4H, Hₕ), 1.56-1.41 (m, 8H, Hₕ, Hₕ), 1.23 (s, 54H, Hₕ), 1.21-1.06 (m, 12H, Hₕ, Hₕ, Hₕ); ¹³C NMR (100 MHz, CDCl₃): δ =158.6, 158.2, 156.4, 155.3, 148.2, 144.2, 139.3, 137.0, 134.7, 132.0, 130.7, 129.7, 124.0, 121.3, 119.6, 114.4, 112.8, 72.4, 72.2, 67.6, 65.8, 65.6, 64.2, 63.0, 34.3, 31.4, 29.4, 28.9, 28.8, 28.0, 25.8, 15.8; LRFAB-MS (3-NOBA matrix): m/z = 1707 [M+H]+; HRFAB-MS (3-NOBA matrix): m/z = 1707.08219 [M+H]+ (calc. for ¹²C₁₁₉¹³C₁₄H₁₄₁N₂O₆ 1707.08232).
The following thread, 28, was formed as a by-product in the rotaxane-forming reaction.

![Diagram of 28]

M.p. 140 °C (decomp.); $^1$H NMR (400 MHz, CDCl$_3$): δ 7.23 (d, $J = 8.6$, 12H, H$_b$), 7.08 (d, $J = 8.6$, 12H, H$_c$), 6.75 (d, $J = 8.9$, 4H, H$_d$), 6.76 (d, $J = 9.0$, 4H, H$_e$), 4.01 (t, $J = 6.0$, 4H, H$_i$), 2.47 (t, $J = 6.9$, 4H, H$_h$), 1.98 (m, 4H, H$_g$), 1.30 (s, 54H, H$_a$); $^1$C NMR (100 MHz, CDCl$_3$): δ = 156.5, 148.2, 144.1, 139.6, 132.2, 130.7, 124.0, 112.9, 76.6, 65.9, 65.7, 63.0, 34.3, 31.4, 28.2, 16.1; LRFAB-MS (glycerol matrix): $m/z = 1139 \,[M]^+$; HRFAB-MS (glycerol matrix): $m/z = 1138.75907 \,[M]^+$ (calc. for C$_{64}$H$_{98}$O$_2$ 1138.75668).

![Diagram of 29]

Following the general procedure, alkyne 2 (109 mg, 0.20 mmol) and macrocycle 1b (28.4 mg, 0.05 mmol) were reacted to give rotaxane 29 (70 mg, 85%) as a colourless solid. M.p 113-118 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ = 8.00 (d, 2H, $J = 7.5$, H$_A$), 7.45 (t, 2H, $J = 7.8$, H$_b$), 7.23 (m, 14H, H$_b$ and H$_c$), 7.05 (d, 12H, $J = 8.6$, H$_c$), 7.02 (d, 4H, $J = 8.6$, H$_d$), 6.94 (d, 4H, $J = 8.9$, H$_e$), 6.58 (d, 4H, $J = 8.6$, H$_e$), 6.41 (d, 4H, $J = 8.9$, H$_G$), 4.58 (s, 4H, H$_{DE}$), 4.56 (s, 4H, H$_{DE}$), 3.73 (t, 4H, $J = 6.7$, H$_H$), 1.57
(quint., 4H, $J = 6.9$, $H_1$), 1.20 (m, 68H, $H_i$, $H_j$, $H_k$, $H_a$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 158.5$, 158.1, 155.2, 148.2, 144.0, 140.1, 137.0, 132.4, 132.0, 130.6, 129.7, 124.0, 121.3, 119.6, 114.3, 112.8, 74.6, 72.4, 72.2, 70.6, 67.6, 63.0, 55.6, 34.2, 31.3, 29.2, 28.7, 28.6, 25.6; HRFAB-MS (3-NOBA matrix): $m/z = 1651.02068$ [M+H]$^+$ (calc. for $^{12}$C$_{115}^{13}$C$_1$H$_{133}$N$_2$O$_6$ 1651.01972).

The following thread, 30, was formed as a by-product in the rotaxane-forming reaction.

![Diagram of 30](image)

M.p. 265 °C (decomp.); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.23$ (d, 12H, $J = 8.5$, $H_b$), 7.10 (d, 4H, $J = 8.9$, $H_d$), 7.07 (d, 12H, $J = 8.5$, $H_c$), 6.80 (d, 4H, $J = 8.9$, $H_e$), 4.72 (s, 2H, $H_f$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 155.3$, 148.3, 143.9, 140.7, 132.3, 130.6, 124.0, 113.2, 74.7, 70.9, 63.0, 56.2, 34.2, 31.3; LREI-MS: $m/z = 1084$ [M]$^+$.
Following the general procedure, alkyne 31 (121 mg, 0.20 mmol) and macrocycle 1b (28.4 mg, 0.05 mmol) were reacted to give rotaxane 32 (28 mg, 31%) as a colourless solid. M.p. 132-134 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.92 (d, 2H, $J$ = 7.7, H$_A$), 7.49 (t, 2H, $J$ = 7.7, H$_B$), 7.28 (d, 2H, $J$ = 7.9, H$_C$), 7.24 (d, 12H, $J$ = 8.6, H$_b$), 7.21 (d, 4H, $J$ = 8.2, H$_g$), 7.09 (d, 12H, $J$ = 8.6, H$_d$), 7.06 (d, 4H, $J$ = 8.6, H$_d$), 7.03 (d, 4H, $J$ = 8.9, H$_f$), 6.98 (d, 4H, $J$ = 8.3, H$_h$), 6.62 (d, 4H, $J$ = 8.6, H$_c$), 6.59 (d, 4H, $J$ = 8.9, H$_g$), 4.6 (s, 4H, H$_f$), 4.53 (s, 4H, H$_{DE}$), 4.54 (s, 4H, H$_{DE}$), 3.74 (t, 4H, $J$ = 6.5, H$_{HI}$), 1.55 (m, 4H, H$_I$), 1.28 (br-m, 66H, H$_J$, H$_K$, H$_L$, H$_a$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 158.5, 158.2, 156.3, 155.1, 148.2, 144.1, 139.8, 138.2, 136.9, 132.3, 132.1, 130.7, 129.7, 129.6, 127.0, 124.0, 121.0, 120.7, 119.5, 114.3, 113.1, 81.5, 74.0, 72.3, 71.9, 68.9, 67.5, 63.0, 34.2, 31.3, 29.6, 29.4, 28.9, 28.7; LRFAB-MS (3-NOBA matrix): m/z = 1803 [M]$^+$. 

The following thread, 33, was produced as a by-product in the reaction.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.54 (d, 4H, $J$ = 8.3, H$_g$), 7.40 (d, 4H, $J$ = 8.3, H$_b$), 7.23 (d, 12H, $J$ = 8.6, H$_b$), 7.09 (m, 16H, H$_c$ and H$_d$), 6.82 (d, 4H, $J$ = 9.0, H$_c$), 5.04
Pd/C (30.0 mg of a 10% w/w dispersion) was added to a solution of rotaxane 27 (150 mg, 0.09 mmol) in THF (5 mL) and the reaction mixture was allowed to stir at RT for 2 h, under an atmosphere of H₂ (g). After this time the reaction mixture was diluted with CH₂Cl₂ (20 mL), filtered through a layer of celite, and concentrated under reduced pressure to afford 34 as a white solid (120 mg, 83%). M.p. 75 °C (decomp.); ¹H NMR (400 MHz, CDCl₃): δ = 7.99 (d, 2H, J = 7.7 Hz, Hₐ), 7.47 (t, 2H, J = 7.8 Hz, Hₜ), 7.23 (m, 14H, H₆ and Hₐ), 7.05 (m, 16H, Hₐ and Hₜ), 6.93 (d, 4H, J = 8.9, Hₜ), 6.58 (d, 4H, J = 8.6, H₂), 6.40 (d, 4H, J = 8.9, Hₐ), 4.57 (d, 8H, J = 8.1, Hₐ and Hₜ), 3.72 (t, 4H, J = 6.6, H₂), 1.56 (m, 8H, Hₜ and H₝), 1.30 (app-s, 68H, H₉, Hₐ, Hₐ, H₈, H₈, H₉, H₉, H₉, H₈); ¹³C NMR (100 MHz, CDCl₃): δ = 158.5, 158.1, 155.2, 148.2, 144.0, 140.1, 137.0, 132.0, 130.6 (2xC), 129.7, 129.5, 124.0, 121.3, 119.6, 114.3, 112.8, 74.6, 72.4, 72.2, 70.6, 67.5, 62.9, 55.6, 34.2, 29.2, 28.7, 28.6, 25.5.; LRESI-MS (3-NOBA matrix): m/z = 1714 [M⁺]; HRFAB-MS (3-NOBA matrix): m/z = 1715.14086 [M+H⁺]⁺ (calc. for C₁₁₀H₁₄⁹¹³CN₂O₆ 1715.14492).
Crystal data and structure refinement for **1b.NiCl₂**

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<tr>
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Chapter 4: Doubly-Threaded [3]Rotaxanes from a Single Active Template Binding Site


Acknowledgements
The following people are gratefully acknowledged for their contribution to this chapter: The crystal structure of complex 35PdCl2(MeCN) was solved by Prof. Alexandra Slawin.
4.1 Introduction

The minimum number of individual, covalently bonded, components in a mechanically interlocked molecular architecture is 1 (e.g. lariats and knots). The simplest catenanes and rotaxanes are [2]rotaxanes and [2]catenanes, where two covalently bonded components are kinetically bound by one mechanical bond (Chapter 1, Figure 1.1). Template strategies have allowed increasingly elaborate structures to be assembled by the generation of multiple mechanical bonds within a molecule. The assembly of rotaxanes and catenanes with multiple mechanically bonded components have been described and several syntheses of topologically complex Borromeates have been reported. Rotaxanes and catenanes with multiple mechanical bonds linking 2 covalently bonded components have also been synthesized.

The majority of [n]rotaxanes (where \( n > 2 \)) consist of \( n \)-1 rings encircling one thread (be it a linear or a branched thread, Figure 4.1 a and b). The synthesis of such multi-ring rotaxanes normally requires at least one binding site on the thread per macrocycle (that is a minimum of \( n - 1 \) templates per \( n \) interlocked components). The Leigh group have recently reported a Pd(II) passive template for clipping up to 3 macrocycles (or as many as the thread will accommodate) onto a thread containing just one ligation site.

[n]Rotaxanes consisting of multiple threads passing through one ring are much less common. Loeb and co-workers have described a [3]rotaxane with an axle threaded through each cavity of a bis-macrocycle (Figure 4.1c), while several non-stoppered pseudorotaxanes with multiple components have been reported. However, there has only been one report of a true [n]rotaxane with >1 thread encircled by one macrocycle: Anderson and coworkers utilized the hydrophobic effect to synthesize both homo- and hetero- [3]rotaxanes, with both threads passing through a \( \gamma \)-cyclodextrin macrocycle. Sauvage and co-workers recently described an Fe(II) passive template which passed two identical threads through the same ring.
(Figure 4.1,d) and used a CuAAC reaction to stopper the threads. However the structure formed was not a true rotaxane as it dethreaded upon demetallation.


Here an active template route to doubly threaded [3]rotaxanes that requires just one active template binding site within the macrocycle is described. By designing a bifurcated macrocycle with a ligating bridging unit, an active template reaction can take place through each cavity, generating a [3]rotaxane. (Figure 4.2).

Figure 4.2. The active template strategy to a [3]rotaxane. The metal, shown in grey, coordinates to the binding site, which bridges the macrocycle. It can then promote formation of a covalent bond through both cavities of the macrocycle, generating a doubly-threaded [3]rotaxane.
4.2 Results and Discussion

The design of bifurcated macrocycle 35 (Figure 4.3) incorporates one monodentate, 2,6-disubstituted pyridine binding site, and two cavities. A CPK model showed that, with a C_{14} alkyl chain, the cavities are large enough to accommodate a simple alkyl thread, but small enough to prevent the stoppers passing through. The benzylic ether linkages provide a degree of flexibility around the binding site.

![Figure 4.3. A bifurcated macrocycle, with a bridging ligating site.](image)

Macrocycle 35 could be synthesized in nine steps from 2,6-dihydroxybenzoic acid (Scheme 4.1). From this commercially available starting material, 2,2-dimethyl-5-hydroxy-4-oxo-benzo-1,3-dioxin (36) was synthesized according to a literature procedure.\(^{203}\) The second phenol was protected with an allyl group, giving 37, before acetal cleavage to give phenol 38. This phenol was alkylated and the ester group was reduced to give alcohol 39. A double Williamson reaction between alcohol 39 and 2,6-bis(bromomethyl)pyridine gave 40, which was deprotected using Pd(PPh\(_3\))\(_4\) to give bisphenol 41. The first cavity was created by a Williamson macrocyclization reaction between 41 and tetradecane-1,14-ditosylate (which was prepared in 3 steps, from the diacid). The second ring closure was achieved using RCM of 42 to give 43. Compound 43 was purified before hydrogenation to give the target compound, macrocycle 35.
Scheme 4.1. Synthesis of macrocycle 35. Reagents and conditions: i) Allyl bromide, NaI, K$_2$CO$_3$, butanone, Δ, 75%; ii) K$_2$CO$_3$, MeOH, 86%; iii) 1. 8-Bromoctene, K$_2$CO$_3$, butanone, Δ, 2. LiAlH$_4$, THF, 0 ºC→RT, 62%; iv) NaH, 2,6-bis(bromomethyl)pyridine, DMF, 0 ºC→RT, 60%; v) Pd(PPh$_3$)$_4$, aniline, THF, 30 ºC, 71%; vi) Tetradecane-1,14-ditosylate, K$_2$CO$_3$, DMF, 100 ºC, 60%; vii) Grubbs 1, CH$_2$Cl$_2$, 64%; viii) Pd/C, H$_2$ (g), THF, 96%.

Obtaining a single crystal of 35 proved difficult, so a small amount of the corresponding palladium complex, 35.Pd(MeCN) was synthesized and single crystals were grown by slow cooling of a solution of 35.Pd(MeCN) in acetonitrile. From the crystal structure (Figure 4.4) it can be seen that the macrocycle is reasonably flat, with the pyridine bridging unit bent back into one of the cavities. From the side-view (Figure 4.4b) it can be seen that due to the (almost 180º) Cl-Pd-Cl axis being orthogonal to the plane of the macrocycle, approach of active template substrates from either face of the cavity should lead to interlocking upon covalent bond formation using the previously described Pd-mediated active template homocoupling of acetylenes.
However, subjecting a catalytic quantity of this complex to Pd(II)-catalyzed homocoupling active template reaction conditions\(^{145,204}\) proved unsuccessful; only a trace of [2]rotaxane could be seen by \(^1H\) NMR and no [3]rotaxane was observed. It was therefore decided focus on the CuAAC active template reaction (described in Chapter 2) as it is a robust reaction that doesn’t require a large excess of stoppers.

![Figure 4.4. X-Ray crystal structure of 35.PdCl\(_2\)(MeCN), from a single crystal obtained from slow cooling in acetonitrile. Carbon atoms are shown in grey, nitrogen atoms in blue, oxygen atoms in red, chlorine atoms in green and the palladium in pink. Selected bond angles [Å] and angles [deg]: a) N1-Pd 2.02, N2-Pd 2.01, Cl1-Pd 2.28, Cl2-Pd 2.29, Cl1-Pd-Cl2 178.0.](image)

Dual-cavity macrocycle 35 was submitted to standard CuAAC active template reaction conditions (Scheme 4.2). Stirring macrocycle 35 with a stoichiometric quantity of \([\text{Cu(CH}_3\text{CN)}_4]PF_6\) and 5 equiv. of alkyne 2 and azide 3 in dichloroethane at 70 °C furnished 41% of [2]rotaxane 45 after 36 h (Table 4.1, entry 1). However, only 10% of the desired [3]rotaxane 47a/b could be seen by \(^1H\) NMR and could not be isolated from the crude mixture (Table 4.1, Entry 1). The low yield of [3]rotaxane can be rationalized by the supposition that, following formation of the [2]rotaxane, the second cavity is more restricted and less able to cope with the transition states required for the CuAAC reaction to take place (see Chapter 2).
Scheme 4.2. CuAAC active template reaction through each cavity of a bifurcated macrocycle, affording [2]- and [3]rotaxane. Reagents and conditions: i) 1. [Cu(CH3CN)4](PF6), ClCH2CH2Cl, 70 ºC, 2. EDTA/NH3.

Table 4.1. Conversion of 35 and 44 to rotaxane under the conditions shown in Scheme 4.2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Macrocycle</th>
<th>Equiv. 2&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Equiv. 3&lt;sup&gt;a&lt;/sup&gt;</th>
<th>[2]Rotaxane/ yield</th>
<th>[3]Rotaxane/ yield&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Total conversion of 2 and 3 to products&lt;sup&gt;c&lt;/sup&gt;</th>
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<td>1</td>
<td>35</td>
<td>5.0</td>
<td>5.0</td>
<td>45/41&lt;sup&gt;de&lt;/sup&gt;</td>
<td>47a+b/10&lt;sup&gt;e&lt;/sup&gt;</td>
<td>&gt;99&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>5.0</td>
<td>5.0</td>
<td>46/57&lt;sup&gt;df&lt;/sup&gt;</td>
<td>48a+b/40&lt;sup&gt;de&lt;/sup&gt;</td>
<td>92&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>10.0</td>
<td>10.0</td>
<td>46/14&lt;sup&gt;de&lt;/sup&gt;</td>
<td>48a+b/86&lt;sup&gt;de&lt;/sup&gt;</td>
<td>90&lt;sup&gt;c&lt;/sup&gt;</td>
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</table>

<sup>a</sup>Where more than 5.0 equiv. stoppers are used, stoppers were added potion-wise, 5.0 equiv. every 24 h.  
<sup>b</sup>Yield based on quantity of macrocycle.  
<sup>c</sup>Calculated from <sup>1</sup>H NMR of the reaction mixture.  
<sup>d</sup>Isolated yield.  
<sup>e</sup>After 36 h.  
<sup>f</sup>After 24 h.  
<sup>g</sup>After 48 h.  
<sup>h</sup>Rotaxane products plus non-interlocked thread 5.
It was reasoned that a larger cavity would increase the yield of both [2] and [3] rotaxane, therefore macrocycle 44, which benefits from an extra 4 CH₂ groups in each of the alkyl chains, was synthesized in eight steps from 38 (Scheme 4.3). The synthesis differs slightly from that of 35 in that both cavities were closed using an RCM reaction. The reason for using a Williamson macrocyclization for the first cavity closure in the synthesis of 35 was the high cost of 8-bromoocdecene. The 10-bromodecene required here, however, was much cheaper. A CPK model showed that the cavities of 44 are still small enough to prevent it passing over the stoppers.

**Scheme 4.3.** Synthesis of bifurcated macrocycle 44. Reagents and conditions: i) 1. 10-bromodecene, K₂CO₃, butanone, Δ, 2. LiAlH₄, THF, 0 ºC→RT, 52%; ii) NaH, 2,6-bis(bromomethyl)pyridine, DMF, 0 ºC→RT, 57%; iii) Pd(PPh₃)₄, aniline, THF, 30 ºC, 96%; iv) Grubbs 1, CH₂Cl₂, 47%; v) Pd/C, H₂ (g), THF, >99%; vi) 10-bromodecene, K₂CO₃, butanone, Δ, 56%, vii) Grubbs 1, CH₂Cl₂, 83%; viii) Pd/C, H₂ (g), THF, 98%.
Treating macrocycle 44 with CuPF₆ and 5.0 equiv. of each stopper furnished 57% [2]rotaxane 46 and 40% of [3]rotaxane 48a/b after only 24 h (Table 4.1, entry 2). Even more impressive is that by increasing the equivalents of each stopper to 10, a yield of 86% [3]rotaxane 48a/b (Table 4.1, entry 3) is achieved. It is important to note that while 10 equiv. of stopper are used relative to macrocycle, this is 5.0 equiv. relative to each cavity, making this a very efficient reaction that is comparable with the original CuAAC active template reaction (with a single cavity macrocycle) in terms of yield (Chapter 2).

The partial ¹H NMR spectrum of rotaxane 45 is shown in Figure 4.5 and the signals show upfield shifting relative their non-interlocked components, as is characteristic of interlocked molecules. The signals of CH₂ groups H C and H D have been significantly split by the presence of the thread, as was observed in the original CuAAC template rotaxane (rotaxane 4, Chapter 2).

Macrocycle 35 exhibits C₂ᵥ symmetry. The mirror plane in the plane of the pyridine ring means that the aromatic protons, Hₑ are chemically equivalent. Upon [2]rotaxane formation, this plane of symmetry is lost, resulting in splitting of the aromatic signals, Hₑ into two distinct doublets as the protons are now chemically different (Hₑ and Hₑ', Scheme 4.2). The signal for HＧ is also split due to this loss of symmetry (Figure 4.5b).
Figure 4.5. Partial $^1$H NMR spectra of a) macrocycle 35, b) [2]rotaxane 47, and c) non-interlocked thread 5. The lettering corresponds to that shown in Scheme 4.2.

This splitting of H$_E$ and H$_G$ is also observed in the $^1$H NMR of [2]rotaxane 46 (Figure 4.6). A major feature of the [3]rotaxane is that H$_E$ and H$_{E'}$ and H$_G$ and H$_{G'}$ become chemically equivalent again. The result is one signal for each in the $^1$H NMR spectrum (Figure 4.6c).

[3]Rotaxane 48 is formed as 2 co-conformational isomers. The syn isomer, 48a has both azide stoppers are on the same face of the macrocycle and both alkyne stoppers on the other. This isomer exhibits $C_{2v}$ symmetry. The anti isomer, 48b has $C_{2h}$ symmetry.
The only manifestation of this difference in topological symmetry properties in the $^1$H NMR spectrum is the doubling up of the signals of H_e and H_k (Figure 4.7). It can be seen that each signal now consists of two overlapping doublets in a ratio of approximately 2:1. Unfortunately it was not possible to identify which set of signals correspond to which isomer, and therefore deduce the degree of formation of one isomer over the other.
The synthetic utility of the active template strategy for the synthesis of mechanically interlocked molecules had been demonstrated by extending it, for the first time, to the synthesis of a [3]rotaxane where two threads pass through the same macrocycle. Two mechanical bonds have been generated using a single active template binding site and this could be a starting point for many more sophisticated active template syntheses, to generate more topologically demanding structures.
4.3 Experimental

General

Unless otherwise stated, all reagents were obtained from commercial sources and used without further purification, solvents were anhydrous unless otherwise stated. Dichloroethane was reagent grade and not anhydrous. All reactions were carried out under an atmosphere of N₂, unless otherwise stated. 2,6-Bis(bromomethyl)pyridine and 2,2-dimethyl-5-hydroxy-4-oxo-benzo-1,3-dioxin were prepared following literature procedures. Tetradecane-1,14-ditosylate was prepared in 3 steps, from the diacid, following literature procedures.

5-Allyloxy-2,2-dimethyl-1,3-benzodioxin-4-one (37)

Ally bromide (8.9 mL, 102.3 mmol) and NaI (cat.) were added to a solution of 2,2-dimethyl-5-hydroxy-4-oxo-benzo-1,3-dioxin (13.24 g, 68.2 mmol) and K₂CO₃ (47.13 g, 341 mmol) in butanone (200 mL) and the reaction mixture heated at reflux for 18 h. The reaction mixture was allowed to cool to RT and CH₂Cl₂ (100 mL) and water (100 mL) were added. The phases were separated and the aqueous phase was further extracted with CH₂Cl₂ (2 x 100 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL), dried (Na₂SO₄) and evaporated under reduced pressure. The resulting residue was purified by column chromatography (pet-CH₂Cl₂, 2:1) to give acetonide (12.03 g, 75%) as a white solid. M.p 45-49 °C; ¹H NMR (400 MHz, CDCl₃): ²⁰⁹ δ = 7.4 (t, 1H, J = 8.4, H₈), 6.59 (d, 1H, J = 8.5, H₄ or H₆), 6.53 (dd, 1H, J = 8.2, 0.5, H₆ or H₈), 6.12-6.02 (m, 1H, H₅), 5.56 (app-dd, 1H, Jₐ = 17.3, 1.6, Hₐ-trans), 5.32 (app-dd, 1H, J₉ = 10.6, 1.4, H₉-cis), 4.67 (dt, 2H, J₉ = 4.8, J₇ = 1.6, H₇), 1.69 (s, 6H, H₈); LRFAB-MS (3-NOBA matrix): m/z = 234 [M]⁺.
2-(Allyloxy)-6-hydroxybenzoic acid (38)

Acetonide 37 (4.00 g, 17.0 mmol) was dissolved in MeOH (100 mL) and K$_2$CO$_3$ (23.0 g, 170 mmol) was added. No inert atmosphere was required. The reaction mixture was allowed to stir at RT for 18 h. Water (300 mL) and CH$_2$Cl$_2$ (200 mL) were added and the phases separated. The aqueous phase was re-extracted with CH$_2$Cl$_2$ (2 x 100 mL) and the combined extracts washed with brine (200 mL) and dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give methyl ester 38 (3.06 g, 86%) as a pale orange solid which was used without further purification.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 11.52 (s, 1H, OH), 7.31 (app-t, 1H, H$_B$), 6.60 (dd, 2H, $J$ = 8.3, 0.7, H$_A$ or H$_C$), 6.40 (d, 2H, $J$ = 8.3, H$_A$ or H$_C$), 6.10-6.01 (m, 1H, H$_E$), 5.53 (app-dd, 1H, $J$ = 17.2, 1.7, H$_F$-trans), 5.31 (dd, 1H, $J$ = 10.7, 1.6, H$_F$-cis), 4.56 (dt, 1H, $J_d$ = 4.3, $J_t$ = 1.6, H$_D$), 4.00 (s, 3H, H$_G$).

(2-(allyloxy)-6-(oct-7-enyloxy)phenyl)methanol (39)

8-Bromoctene (4.40 mL, 26.0 mmol) was added to a solution of 38 (4.55 g, 22.0 mmol) and K$_2$CO$_3$ (15.0 g, 109 mmol) in butanone (150 mL) and the reaction mixture was heated at reflux for 18 h. Volatiles were removed in vacuo and the residue was partitioned between CH$_2$Cl$_2$ (200 mL) and H$_2$O (100 mL). The phases were separated and the aqueous phase was further extracted with CH$_2$Cl$_2$ (100 mL). The combined organic extracts were washed with brine (200 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The resulting oil was added to a suspension of LiAlH$_4$ (2.00 g, 43.4 mmol) in THF (200 mL) at 0 °C and the reaction mixture was allowed to stir at RT for 4 h. The reaction mixture was cooled back down to 0 °C
and 10 M aqueous NaOH was added slowly, with vigorous stirring, until a white precipitate formed. This finely divided precipitate was removed by suction filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by column chromatography (pet-EtOAc, 10:1) to give alcohol 39 (3.94 g, 62%) as a colourless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.16$ (t, 1H, $J = 8.3$, H$_B$), 6.54 (d, 1H, $J = 8.3$, H$_A$ or H$_C$), 6.53 (d, 1H, $J = 8.3$, H$_A$ or H$_C$), 6.06 (m, 1H, H$_E$), 5.82 (m, 1H, H$_N$), 5.41 (ddt, 1H, $J_d = 17.3$, 1.6, $J_t = 1.6$, H$_{F-trans}$), 5.28 (ddt, 1H, $J_d = 10.6$, 1.4, $J_t = 1.3$, H$_{F-cis}$), 5.00 (ddt, 1H, $J_d = 17.1$, 1.9, $J_t = 1.6$, H$_{O-trans}$), 4.94 (dm, 1H, $J_d = 10.2$, H$_{O-cis}$), 4.84 (s, 2H, H$_G$), 4.56 (dt, 2H, $J_d = 5.2$, $J_t = 1.5$, H$_D$), 3.99 (t, 2H, $J = 6.5$, H$_H$), 2.62 (br-s, 1H, OH), 2.07 (m, 2H, H$_M$), 1.81 (m, 2H, H$_I$), 1.42 (m, 6H, H$_J$, H$_K$, H$_L$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 157.8$, 157.2, 138.8, 133.0, 128.8, 117.3, 114.2, 104.8, 104.7, 69.1, 68.3, 55.0, 33.6, 29.1, 28.7 (C$_x$3), 25.9; LRESI-MS: $m/z = 308$ [M+NH$_4$]$^+$; HRESI-MS: $m/z = 308.22244$ [M+NH$_4$]$^+$ (calc. for C$_{18}$H$_{30}$O$_3$N$_1$ 308.22202).

2,6-bis((2-(allyloxy)-6-(oct-7-enyloxy)benzyloxy)methyl)pyridine (40)

NaH (1.40 g, 58.4 mmol) was added to a solution of alcohol 39 (5.65 g, 19.5 mmol) in DMF (150 mL) at 0 ºC. After 30 min 2,6-bis(bromomethyl)pyridine$^{205}$ (2.2 g, 7.8 mmol) was added and the reaction mixture was allowed to warm from 0 ºC to RT and stirred for 18 h. A small amount of water was added slowly to quench excess NaH, and the solvent was removed in vacuo. Column chromatography of the resulting residue (gradient elution: 1. CH$_2$Cl$_2$, 2. CH$_2$Cl$_2$-EtOAc, 50:1) gave 40 (3.22 g, 60%) as a pale yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.62$ (t, 1H, $J = 7.7$, H$_A$), 7.44 (d, 2H, $J = 7.7$, H$_B$), 7.19 (t, 2H, $J = 8.3$, H$_E$), 6.53 (d, 2H, $J = 8.3$, H$_E$ or H$_G$), 6.52 (d, 2H, $J = 8.3$, H$_E$ or H$_G$), 6.12-6.01 (m, 2H, H$_Q$), 5.87-5.76 (m, 2H, H$_N$),
5.39 (ddt, 2H, $J_d = 17.2$, $J_t = 1.6$, $H_{R-trans}$), 5.24 (ddt, 2H, $J_d = 10.6$, $J_t = 1.5$, $H_{R-cis}$), 4.98 (dd, 2H, $J_d = 17.1$, $J_t = 2.0$, $H_{O-trans}$), 4.92 (app-d, 2H, $J_d = 10.2$, $H_{O-cis}$), 4.77 (s, 4H, $H_C$), 4.70 (s, 4H, $H_D$), 4.56 (dt, 4H, $J_d = 5.1$, $J_t = 1.5$, $H_P$), 3.97 (t, 4H, $J = 6.5$, $H_H$), 2.04 (m, 4H, $H_M$), 1.78 (m, 4H, $H_I$), 1.39 (m, 12H, $H_J$, $H_K$, $H_L$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 159.0, 158.7, 158.5, 139.0, 136.7, 133.5, 129.7, 129.6, 119.4, 117.0, 114.9, 114.3, 105.0, 104.9, 73.2, 69.3, 68.5, 61.4, 33.7, 29.3, 28.8, 25.9; LRESI-MS: $m/z = 685$ [M+H]$^+$; HRESI-MS: $m/z = 684.42586$ (calc. for C$_{43}$H$_{58}$NO$_6$ 684.42533).

2-(((6-((2-hydroxy-6-(oct-7-enyloxy)benzyloxy)methyl)pyridin-2-yl) methoxy)methyl)-3-(oct-7-enyloxy)phenol (41)

Pd(PPh$_3$)$_4$ (9.20 mg, 0.08 mmol) was added to a solution of bis-allyl-protected diphenol 40 (350 mg, 0.51 mmol) and aniline (0.2 mL, 2.04 mmol) in THF (2 mL). The reaction mixture was stirred at 30 ºC for 4 h. Water (10 mL) and 3:1 CHCl$_3$-IPA (10 mL) were added and the phases separated. The aqueous phase was further extracted with CHCl$_3$:IPA (2 x 20 mL) and the combined organic extracts were washed with water (20 mL) and brine (20 mL) and concentrated under reduced pressure. Column chromatography of the resulting residue (gradient elution: 1. pet, 2. pet-EtOAc, 10:1) gave diphenol 41 (230 mg, 71%) as a colourless oil. $^1$H NMR (400 MHz, CDCl$_3$-CD$_3$OD, 3:1): $\delta$ = 7.58 (t, $J = 7.7$, $H_A$), 7.22 (d, $J = 7.7$, $H_B$), 6.95 (t, $J = 8.2$, $H_F$), 6.35 (d, $J = 7.7$, $H_E$ or $H_G$), 6.26 (d, $J = 8.2$, $H_E$ or $H_G$), 5.69-5.58 (m, 2H, $H_N$), 4.82 (ddt, 2H, $J_d = 17.1$, $J_t = 2.0$, $J_i = 1.6$, $H_{O-trans}$), 4.76 (app-d, 2H, $J_d = 10.2$, $H_{O-cis}$), 4.69 (s, 4H, $H_C$), 4.62 (s, 4H, $H_D$), 3.78 (t, $J = 6.5$, $H_H$), 1.88 (m, 4H, $H_M$), 1.61 (m, 4H, $H_I$), 1.23 (m, 12H, $H_J$, $H_K$, $H_L$); $^{13}$C NMR (100 MHz, CDCl$_3$-CD$_3$OD, 3:1): $\delta$ = 157.7, 157.3, 157.1, 153.8, 138.6, 137.5, 129.3, 120.0,
113.8, 111.2, 108.6, 102.7, 71.5, 68.0, 62.9, 33.3, 28.8, 28.4, 25.6; LRESI-MS: $m/z = 604 \, [M]^+$; HRESI-MS: $m/z = 604.36277 \, [M]^+$ (calc. for C$_{37}$H$_{50}$NO$_6$ 604.36326).

Tetradecane-1,14-ditosylate$^{207}$ (550 mg, 1.02 mmol) was added to a solution of diphenol 41 (616 mg, 1.02 mmol) and K$_2$CO$_3$ (1.41 g, 10.2 mmol) in DMF (2 L) and the reaction mixture was heated at 100 °C for 18 h. Volatiles were removed in vacuo and 3:1 CHCl$_3$-IPA (200 mL) and water (200 mL) were added and the phases were separated. The aqueous phase was extracted with 3:1 CHCl$_3$:IPA (2 x 100 mL) and the combined organic phases were washed with water (100 mL) and brine (100 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Column chromatography of the resulting residue (pet-EtOAc, 10:1) gave compound 42 (814 mg, 60%) as a pale yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.63 (t, 1H, $J = 7.7$, HA), 7.46 (d, 2H, $J = 7.7$, HB), 7.19 (t, 2H, $J = 8.3$, HF), 7.18 (d, 4H, $J = H_E$ and $H_G$), 5.85-5.75 (m, 2H, $H_N$), 4.98 (ddt, 2H, $J_d = 17.1$, 1.8, $J_t = 1.6$, $H_O$-trans), 4.92 (app-d, 2H, $J_d = 10.1$, $H_O$-cis), 4.75 (s, 4H, $H_C$), 4.73 (s, 4H, $H_D$), 3.98 (m, 8H, $H_H$ and $H_P$), 2.07-2.03 (m, 4H, $H_M$), 1.84-1.74 (m, 8H, $H_I$ and $H_Q$), 1.64-1.61 (m, 4H, $H_L$), 1.54-1.43 (m, 8H, $H_Q$ and $H_J$), 1.41-1.32 and 1.29-1.21 (2 x m, 28H, $H_J$, $H_K$, $H_R$, $H_S$, $H_T$, $H_U$, $H_V$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 159.0, 158.9, 158.8, 139.0, 136.6, 129.6, 119.2, 114.6, 114.3, 104.5, 104.4, 73.5, 68.5, 68.4, 61.6, 33.7, 29.4, 29.3 (C$_x$2), 29.2 (C$_x$3), 28.8 (C$_x$2), 26.2, 25.9; LRESI-MS: $m/z = 799 \, [M+H]^+$; HRESI-MS: $m/z = 798.56471$ (calc. for C$_{51}$H$_{76}$O$_6$N 798.356672).
Dialkene 42 (470 mg, 0.59 mmol) in degassed CH₂Cl₂ (25 mL) was added to a solution of Grubb’s 1 catalyst (49 mg, 59.0 µmol) in degassed CH₂Cl₂ (600 mL) and the reaction mixture was allowed to stir at RT for 18 h. Ethyl vinyl ether (3 mL) was added and volatiles removed in vacuo. Column chromatography of the resulting residue (CH₂Cl₂) gave 43 (290 mg, 64%) as a colourless solid. M.p. 114-117 °C; ᵃ¹H NMR (400 MHz, CDCl₃): δ = 7.64 (t, 1H, J = 7.7, H₄), 7.47 (d, 2H, J = 7.7, H₃), 7.18 (t, 2H, J = 8.3, H₂), 6.52 (d, 4H, J = 8.4, H₀ and H₁), 4.43-4.41 (m, 1.8H, H₄-major), 5.39-5.37 (m, 0.2H, H₄-minor), 4.75 (s, 4H, H₂), 3.98 (t, 8H, J = 5.9, H₃ and H₄), 2.05-1.95 (m, 4H, H₅), 1.85-1.77 (m, 8H, H₆ and H₇), 1.58-1.50 (m, 8H, H₈ and H₉), 1.34 (br-m, 12H, H₁₀, H₁₁ and H₁₂), 1.30 (br-m, 12H, H₁₃, H₁₄, H₁₅); ᵃ¹³C NMR (100 MHz, CDCl₃): δ = 159.0, 158.9, 158.8, 136.6, 130.3, 129.6, 119.1, 114.4, 104.3 (Cx2), 73.7, 68.4 (Cx2), 61.7, 32.5, 29.5 (Cx4), 29.4, 29.2 (Cx2), 29.1, 26.4, 26.3; LRESI-MS: m/z = 770 [M]⁺; HRESI-MS: m/z = 770.53396 (calc. for C₄₉H₇₂O₆N 770.53542).
Pd/C (27.0 mg of a 10% w/w dispersion) was added to a solution of 43 (270 mg, 0.35 mmol) in THF (25 mL). The reaction mixture was allowed to stir under an atmosphere of H₂ (g) for 5 h. The reaction mixture was filtered through celite and volatiles were remove in vacuo to give macrocycle 35 (260 mg, 96%) as a white solid. M.p. 85-88 ºC; ¹H NMR (400 MHz, CDCl₃): δ = 7.65 (t, 1H, J = 7.7, Hₐ), 7.47 (d, 2H, J = 7.7, H₇B), 7.19 (t, 2H, J = 8.3, H₉), 6.52 (d, 4H, J = 8.4, H₅), 4.76 (s, 4H, H₆C), 4.75 (s, 4H, H₈D), 3.98 (t, 8H, J = 6.0, H₉G), 1.80 (m, 8H, H₉H), 1.53 (m, 8H, H₉I), 1.32 (m, 32H, H₉J, H₉K, H₉L, H₉M); ¹³C NMR (100 MHz, CDCl₃): δ = 159.0, 158.9, 136.6, 129.6, 119.0, 114.5, 104.3, 73.8, 68.4, 61.8, 29.5, 29.4, 29.3, 29.2 (Cx2), 26.3; LRESI-MS: m/z = 773 [M+H]⁺; HRESI-MS: m/z = 772.55340 (calc. for C₄₉H₇₄O₆N₇ 772.55107).

(2-(allyloxy)-6-(dec-9-enyloxy)phenyl)methanol (49)

Phenol 38 (2.58 g, 12.4 mmol), K₂CO₃ (8.60 g, 62.0 mmol) and 1,10-dibromodecene (3.0 mL, 14.9 mmol) were reacted and the resulting residue treated with LiAlH₄, as described for 39, to give 49 (2.06 g, 52%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.16 (t, 1H, J = 8.3, H₉B), 6.54 (d, 1H, J = 8.3, H₉A or H₉C), 6.53 (d, 1H, J = 8.3, H₉A or H₉C), 6.12-6.01 (m, 1H, H₅), 5.87-5.76 (m, 1H, H₉P), 5.41 (ddt, 1H, J₉d = 17.3, 1.6, J₉t = 1.6, H_{9-trans}), 5.28 (ddt, 1H, J₉d = 17.3, 1.6, J₉t = 1.6, H_{9-trans}), 4.93 (app-d, 1H, J₉d = 10.2, 1H, H_{9-cis}), 4.84 (s, 2H,
Alcohol 49 (649 mg, 2.04 mmol), 2,6-bis(bromomethyl)pyridine (246 mg, 0.93 mmol) and NaH (150 mg, 6.14 mmol) were reacted as described for 40. Column chromatography (gradient elution: 1. CH$_2$Cl$_2$, 2. CH$_2$Cl$_2$-EtOAc 50:1) gave 50 (390 mg, 57%) as a pale yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.62$ (t, 1H, $J = 7.7$, HA), 7.44 (d, 2H, $J = 7.7$, HB), 7.18 (t, 2H, $J = 8.3$, HF), 6.54 (d, 2H, $J = 6.1$, HE or HG), 6.52 (d, 2H, $J = 6.3$, HE or HG), 6.08-5.99 (m, 2H, HS), 5.85-5.75 (m, 2H, HP), 5.41 (ddt, 2H, $J_d = 17.3$, 1.6, $J_t = 1.6$, H$_t$-trans), 5.24 (ddt, 2H, $J_d = 10.6$, 1.5, $J_t = 1.4$, H$_t$-cis), 4.98 (ddt, 2H, $J_d = 17.1$, 2.1, $J_t = 1.6$, H$_O$-trans), 4.92 (app-d, 2H, $J_d = 10.2$, H$_O$-cis), 4.77 (s, 4H, HC), 4.71 (s, 4H, HD), 4.56 (dt, 4H, $J_d = 5.1$, $J_t = 1.5$, HR), 3.98 (t, 4H, $J = 6.5$, H$_H$), 2.05-2.00 (m, 4H, H$_O$), 1.81-1.74 (m, 4H, H$_I$), 1.47-1.23 (m, 20H, H$_I$, H$_J$, H$_K$, H$_L$, H$_M$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 158.9, 158.6, 158.4, 139.2, 136.6, 133.4, 129.6, 119.3, 117.0, 114.7, 114.1, 104.8 (Cx2), 73.1, 69.2, 68.4, 61.3, 33.7, 29.4, 29.3, 29.2, 29.0, 28.8, 26.0; LRSEI-MS: $m/z = 740$ [M+H]$^+$. HRESI-MS: $m/z = 740.48847$ (calc. for C$_{47}$H$_{68}$O$_6$N 740.48847).
2-(((6-((2-(dec-9-enyloxy)-6-hydroxybenzyloxy)methyl)pyridin-2-yl)methoxy)methyl)-3-(dec-9-enyloxy)phenol (51)

Bis-allyl protected diphenol 50 (1.45 g, 1.96 mmol) was treated with Pd(PPh₃)₄ (0.34 g, 0.29 mmol) and aniline (0.7 mL, 7.84 mmol) as described for 41. Column chromatography (gradient elution: 1. pet-EtOAc, 10:1, 2. pet-EtOAc, 5:1) gave diphenol 51 (1.24 g, 96%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃-CD₃OD, 3:1): δ = 7.54 (t, 1H, J = 7.8, Hₐ), 7.20 (d, 2H, J = 7.7, H₈), 6.91 (t, 2H, J = 8.2, H₆), 6.31 (d, 2H, J = 8.1, H₇ or H₉), 6.23 (d, 2H, J = 8.2, H₆ or H₇), 5.65-5.55 (m, 2H, HP₂), 4.78 (ddt, 2H, J₆ = 17.1, 1.7, H₆-trans), 4.72 (app-d, 2H, J₄ = 10.2, H₆-cis), 4.65 (s, 4H, H₃), 4.58 (s, 4H, H₄), 3.75 (t, 4H, J = 6.5, H₅), 1.85-1.81 (m, 4H, H₀), 1.61-1.54 (m, 4H, H₁), 1.27-1.09 (m, 20H, H₂, H₃, H₄, H₅, H₆, H₇, H₈, H₉); ¹³C NMR (100 MHz, CDCl₃-CD₃OD, 3:1): δ = 157.8, 157.3, 157.1, 138.7, 137.5, 129.3, 119.9, 113.6, 111.3, 108.5, 102.7, 71.4, 68.0, 62.7, 33.3, 29.0, 28.9, 28.8, 28.6, 28.5, 25.6; LRESI-MS: m/z = 661 [M+H]+; HRESI-MS: m/z = 660.42554 (calc. for C₄₁H₅₈O₆N 660.42586).
Dialkene 51 (1.24 g, 1.88 mmol) in degassed CH₂Cl₂ (50 mL) was added to a solution of Grubbs 1 catalyst (155 mg, 0.19 mmol) in degassed CH₂Cl₂ (500 mL) and the reaction allowed to stir at RT for 24 h. A second portion of Grubb’s 1 catalyst (155 mg, 0.19 mmol) was added and the reaction mixture allowed to stir for a further 24 h. Ethyl vinyl ether (2 mL) was added and volatiles were removed in vacuo. Column chromatography of the resulting residue (pet-EtOAc, 4:1) gave 52 (533 mg, 47%) as a brown oil. ¹H NMR (400 MHz, CDCl₃): δ = 8.64 (br-s, 2H, OH), 7.75 (t, 1H, J = 7.7, HA), 7.32 (d, 2H, J = 7.7, HB), 7.13 (td, 2H, J = 8.2, 2.3, HF), 6.56 (d, 2H, J = 7.9, HG or HE), 6.04 (d, 1.4H, HG or HE-major), 6.39 (d, 0.6H, J = 7.8, HG or HE-minor), 5.36-5.32 (m, 2H, H₅-mixture of cis and trans), 4.93 (s, 2.8H, H₆-major), 4.91 (s, 1.2H, H₆-minor), 4.84 (s, 4H, HPD), 3.94-3.89 (m, 4H, HH), 2.02-1.97 (m, 1H, H₀-minor), 1.96-1.92 (m, 3H, H₀-major), 1.74-1.65 (m, 4H, H₁), 1.43-1.24 (m, 20H, H₂, H₃, H₄, HM, HΝ); ¹³C NMR (100 MHz, CDCl₃): δ = 157.8, 157.2, 157.0, 137.9, 130.3, 129.4, 120.1, 110.7, 109.5, 103.0, 72.1, 68.2, 65.1, 32.3, 29.3, 29.2, 29.0, 28.5, 26.1; LRESI-MS: m/z: 633 [M+H]⁺; HRESI-MS: m/z = 632.39600 (calc. for C₃₀H₄₅O₆N 632.39456).
Pd/C (89 mg of a 10% w/w dispersion) was added to a solution of 52 (613 mg, 0.84, 0.97 mmol) in THF (40 mL). The reaction mixture was allowed to stir under an atmosphere of H₂ (g) for 8 h. The reaction mixture was filtered through celite and volatiles were removed in vacuo to give macrocycle 53 (611 mg, 99%) as a brown oil. ¹H NMR (400 MHz, CDCl₃): δ = 8.63 (br-s, 1H, OH), 7.75 (t, 1H, J = 7.7, HA), 7.32 (2H, d, J = 7.7, HB), 7.13 (t, 2H, J = 8.2, H₆), 6.56 (d, 2H, J = 7.7, H₉), 6.41 (d, 2H, J = 8.2, H₈), 4.94 (s, 4H, H₀), 4.84 (s, 4H, H₀), 3.94 (t, 4H, J = 5.9, H₃), 3.76-3.73 (m, 4H, H₁), 1.87-1.84 9 (m, 4H, H₁), 1.75-1.68 (m, 4H, H₁), 1.45-1.37 (m, 4H, H₁), 1.32-1.24 (m, 16H, H₆, H₀, H₀, H₀); ¹³C NMR (100 MHz, CDCl₃): δ = 157.8, 157.2, 157.1, 137.9, 129.4, 120.0, 110.7, 109.5, 103.0, 72.1, 68.2, 65.1, 29.3, 29.2, 29.1, 29.0, 29.0, 26.1, 25.5; LRESI-MS: m/z = 634 [M⁺]; HRESI-MS: m/z = 634.41005 (calc. for C₃₉H₅₆O₆N 634.41021).
NaH (61.4 mg, 2.56 mmol) was added to a solution of diphenol 53 (540 mg, 0.85 mg) in DMF (15 mL) at 0 ºC. After 10 minutes, 10-bromodecene (1.03 mL, 5.11 mmol) was added and the reaction was allowed to warm from 0 ºC to RT then stirred for a further 18 h at RT. A few drops of water were carefully added to quench the reaction then the reaction mixture was filtered through celite. EtOAc (100 mL) and H2O (100 mL) were added and the phases separated. The aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with H2O (2 x 100 mL) then brine (100 mL), dried (Na2SO4) and concentrated under reduced pressure. Column chromatography of the resulting residue (pet-EtOAc, 9:1) gave 54 (433 mg, 56%) as a yellow oil. 1H NMR (400 MHz, CDCl3): δ = 7.39 (t, 1H, J = 7.9, HA), 7.47 (d, 2H, J = 7.7, H9), 7.19 (t, 2H, J = 8.3, Hf), 6.52 (d, 4H, J = 8.4, Hg and Hg), 4.98 (ddt, 2H, J1 = 17.2, 1.8, J1 = 1.5, Hz-trans), 4.75 (app-d, 2H, J1 = 10.2, Hz-cis), 4.73 (s, 4H, HC), 3.97 (t, 8H, J = 6.3, HH and HQ), 2.05-1.99 (m, 4H, HX), 1.83-1.73 (m, 8H, H1 and HK), 1.50-1.17 (m, 48H, HJ, HK, HL, HM, HN, HP, HS, HT, HU, HV and HW); 13C NMR (100 MHz, CDCl3): δ = 158.9 (Cx2), 158.7, 139.0, 136.5, 129.5, 125.4, 119.2, 114.1, 104.5 (Cx2), 73.3, 68.5, 68.4, 61.5, 34.0, 33.7, 32.7, 29.4, 29.3 (Cx2), 29.1, 29.0, 28.9, 28.8 (2xC), 28.6, 28.1, 26.1, 26.0.; LRESI-MS: m/z = 911 [M+H]+; HRESI-MS: m/z = 910.69197 (calc. for C59H92O6N 910.69192).
A solution of 54 (433 mg, 475 μmol) in degassed CH₂Cl₂ (50 mL) was added to a solution of Grubb’s I catalyst (391 mg, 47.5 μmol) in degassed CH₂Cl₂ (500 mL). The reaction mixture was allowed to stir under an atmosphere of N₂(g) for 18 h. Ethyl vinyl ether (1 mL) was added to quench the catalyst and volatiles were removed in vacuo. Column chromatography of the resulting residue (pet-EtOAc, 9:1) gave 55 (350 mg, 83%) as a colourless solid. M.p. 92-95 ºC; ¹H NMR (400 MHz, CDCl₃): δ = 7.64 (t, 1H, J = 7.7, H₄), 7.48 (d, 2H, H₆), 7.19 (t, 2H, J = 8.3, H₅), 6.52 (d, 4H, J = 8.4, H₈ and H₉), 5.38-5.34 (m, 2H, Hᵥ- mixture of cis and trans), 4.74 (s, 8H, H₇ and H₈), 3.97 (td, 8H, Jₐ = 6.2, J₉ = 1.7, H₈ and H₉), 2.02-1.97 (m, 4H, Hᵥ), 1.84-1.77 (m, 8H, H₇ and H₈), 1.50-1.44 (m, 8H, H₄ and H₅), 1.38-1.29 (m, 40H, Hᵥ, H₇, H₈, H₉, H₁₀, H₉, H₁₀, H₁, H₂, H₃, H₄, H₅, H₆, H₇, H₈), 158.9 (C₂x), 158.7, 136.7, 130.4, 129.6, 119.3, 114.4, 104.4 (C₂x), 73.5, 68.5, 68.5, 61.6, 32.2, 29.4 (3xC), 29.3, 29.2, 29.1 (3xC), 29.0, 28.9 (2xC), 28.8, 28.4, 26.0; LRESI-MS: m/z = 883 [M+H]+; HRESI-MS: m/z = 882.65983 (calc. for C₅₇H₈₈O₆N 882.66062).
Pd/C (41 mg of a 10% w/w dispersion) was added to a solution of 55 (340 mg, 385 μmmol) in THF (20 mL) and the reaction mixture allowed to stir for 5 h under an atmosphere of H2 (g). The reaction mixture was filtered through celite and evaporated under reduced pressure to give macrocycle 44 (334 mg, 98%) as a white solid. M.p. 73-76 °C; 1H NMR (400 MHz, CDCl3): δ = 7.65 (t, 1H, J = 7.7, HA), 7.48 (d, 2H, J = 7.7, HB), 7.19 (t, 2H, J = 8.3, H1), 6.52 (d, 4H, J = 8.4, HE), 4.76 (s, 4H, HC), 4.75 (s, 4H, HD), 3.97 (t, 8H, J = 6.4, HG), 1.84-1.77 (m, 8H, HH), 1.51-1.44 (m, 8H, HI), 1.37-1.25 (m, 52H, HJ, HK, Hl, HM, HN, HO); 13C NMR (100 MHz, CDCl3): δ = 158.9, 158.7, 136.7, 129.6, 119.3, 114.4, 104.4, 73.5, 68.5, 61.7, 29.3, 29.1, 29.0, 28.8 (2xC), 28.7, 26.0; LRESI-MS: m/z = 885 [M+H]+; HRESI-MS: m/z = 884.67693 (calc. for C57H90NO 884.67627).
A solution of macrocycle 35 (50.0 mg, 65 μmol) in CH₂Cl₂ (2.5 mL) was added to a solution of trans-PdCl₂(MeCN)₂ (16.9 mg, 65 μmol) in MeCN (2.5 mL) and the resulting solution stirred for 1 h at RT. Volatiles were removed in vacuo to leave 35.PdCl₂(MeCN) as a yellow/orange solid, which was not purified. Single crystals, suitable for X-ray diffraction, were grown by slow cooling of a saturated solution of this crude product in MeCN.


Alkyne (5.0 equiv.) and azide (5.0 equiv.) were added to a solution of macrocycle (1.0 equiv.) and [Cu(CH₃CN)₄](PF₆) (1.0 equiv.) in ClCH₂CH₂Cl. The solution was heated to 70 °C and allowed to stir at this temperature for 36 h. To increase the yield of [3]rotaxane over [2]rotaxane, a further 5.0 equiv. of alkyne and 5.0 equiv. of azide were added after 24 h and the reaction mixture stirred for an additional 24 h at 70 °C. The reaction mixture was then allowed to cool to RT and diluted with CH₂Cl₂ (100 mL). This organic phase was washed with a basic saturated EDTA solution (3 x 100 mL), H₂O (100 mL) then brine (100 mL). The organic phase was dried (Na₂SO₄) and concentrated under reduced pressure. Column chromatography gave the [2]- and/or [3]rotaxane.
Following the general procedure, alkyne 2 (51.5 mg, 95 μmol), azide 3 (56.0 mg, 95 μmol) and macrocycle 35 (15.0 mg, 19 μmol) were reacted in ClCH₂CH₂Cl (2 mL). Column chromatography (gradient elution: pet-Et₂O, 1. 20:1, 2. 10:1, 3. 5:1, 4. 4:1, 5. 3:1) gave [2]rotaxane 45 (15 mg, 41%) as a colourless film. ¹H NMR (400 MHz, CDCl₃): δ = 7.68 (s, 1H, H₉), 7.33 (t, 1H, J = 7.7, H₆), 7.22 (dd, 12H, J = 8.7, 2.5, H₇ and H₈), 7.17 (d, 2H, J = 7.7, H₉), 7.10 (d, 12H, J = 8.4, H₉ and H₈), 7.05 (m, 6H, H₉, H₈ and H₁₀), 6.77 (d, 2H, J = 8.9, H₁₁), 6.69 (d, 2H, J = 8.9, H₁₁), 6.44 (d, 2H, J = 8.3, H₁₂ or H₁₂′), 6.36 (d, 2H, J = 8.4, H₁₂ or H₁₂′), 4.85 (s, 2H, H₁₃), 4.70 (s, 4H, H₁₄), 4.56 (s, 4H, H₁₅), 4.18 (t, 2H, J = 7.9, H₁₆), 3.93 (t, 4H, J = 5.5, H₁₇ or H₁₇′), 3.78 (t, 2H, J = 5.5, H₁₈), 3.71 (td, 4H, J₁ = 7.4, J₂ = 2.4, H₁₉ or H₁₉′), 2.10-2.03 (m, 2H, H₂₀), 1.78-1.71 (m, 4H, H₁₉ or H₁₉′), 1.63-1.56 (m, 4H, H₁₉ or H₁₉′), 1.54-1.46 (m, 4H, aliphatic CH), 1.29 (m, 54H, H₂₁ and H₂₂), 1.27-1.26 (m, 18H, aliphatic CH), 1.15 (br-m, 18H, aliphatic CH); ¹³C NMR (100 MHz, CDCl₃): δ = 159.1, 158.6, 157.8, 156.4, 156.4, 148.1 (Cx₂), 144.2, 143.3, 139.4, 139.3, 136.4, 132.0, 132.0, 130.7 (Cx₃), 129.6, 123.9 (Cx₂), 120.5, 114.2, 113.1, 113.0, 104.3, 104.0, 73.8, 68.9, 68.0, 64.3, 63.0, 61.7, 61.6 (2xC), 47.0, 34.2 (Cx₂), 29.7, 29.6 (Cx₃), 29.5, 29.4, 29.3, 29.1 (Cx₂) 28.7, 26.4, 25.8; LRESI-MS 1904 [M+H]⁺ HRFAB-MS (3-NOBA matrix): m/z = 1903.30073 [M+H]⁺ (calc. for C₁₂₈H₁₆₉¹³CN₄O₈ 1903.29740).
Following the general procedure, alkyne 2 (307 mg, 565 μmol), azide 3 (332 mg, 565 μmol) and macrocycle 44 (100 mg, 113 μmol) were reacted in ClCH₂CH₂Cl (4 mL). Column chromatography (gradient elution: 1. CHCl₃, 2. CHCl₃ with 0.5→3% acetone) gave [2]rotaxane 46 (131 mg, 57%) as a colourless solid; ¹H NMR (CDCl₃, 400 MHz): δ = 7.67 (s, 1H, H₉), 7.32 (t, 1H, J = 7.6, H₈), 7.21 (dd, 12H, J = 7.2, 2.3, H₆ and H₇), 7.17 (d, 2H, J = 7.7, H₈), 7.08 (d, 16H, J = 8.6, H₉, H₁₀, H₁₁, H₁₂), 7.05 (t, 2H, J = 8.8, H₉), 6.78 (d, 2H, J = 8.9, H₁₂), 6.68 (d, 2H, J = 8.9, H₁₀), 6.45 (d, 2H, J = 8.4, H₁₁ or H₁₃), 6.37 (d, 2H, J = 8.3, H₁₁ or H₁₃), 4.95 (s, 2H, H₁₁), 4.69 (s, 4H, H₁₂), 4.58 (s, 4H, H₁₀), 4.24 (t, 2H, J = 7.6, H₁₂), 3.90 (s, 4H, J = 6.3, H₁₃ or H₁₃'), 3.79-3.73 (m, 6H, H₁₂, H₁₃ or H₁₃'), 2.12-2.05 (m, 2H, H₁₁), 1.76-1.72 (m, 4H, H₁₂ or H₁₃), 1.61-1.56 (m, 4H, H₁₀ or H₁₁), 1.48-1.41 (m, 8H, H₁₀), 1.28 (d, 54H, J = 1.4, H₁₂ and H₁₃), 1.25-1.24 (m, 48H, H₁₃, H₁₁, H₁₂, H₁₃, H₁₄, H₁₅, H₁₆); ¹³C NMR (100 MHz, CDCl₃): δ = 158.9, 158.7, 158.2, 156.3, 148.1 (Cx₂), 144.1 (Cx₂), 139.6 (Cx₂), 136.6 (Cx₂), 132.1, 132.0, 130.6, 129.6, 124.0 (Cx₂), 119.9, 114.2 (Cx₂), 113.1, 113.0, 104.4, 104.2, 73.5, 68.7, 68.4, 64.1 (Cx₂), 61.7, 53.0, 47.1, 44.4, 34.2 (Cx₂), 31.3 (Cx₂), 29.6, 29.4, 29.3, 29.2, 29.0, 28.9, 28.9, 28.8, 28.8, 26.0, 25.7; LRESI-MS: m/z = 2015 [M]⁺ and 2016 [M+H]⁺; HRESI-MS: m/z = 2015.4307 (calc. for C₁₃₇H₁₈₆N₄O₈ 2015.42707, C₁₃₆¹³CH₁₈₅N₄O₈ 2015.42260).
Following the general procedure, alkyne 2 (307 mg, 565 μmol), azide 3 (332 mg, 565 μmol) and macrocycle 48a/b (100 mg, 113 μmol) were reacted in ClCH₂CH₂Cl (4 mL). After 24 h a further portion of alkyne 2 (307 mg, 565 μmol) and azide 3 (332 mg, 565 μmol) were added and the reaction mixture was allowed to stir for a
further 24 h. Column chromatography (gradient elution: 1. CHCl₃, 2. CHCl₃ with 0.5→3% acetone) gave [3]rotaxane 48, as a mixture of isomers 48a and 48b, (31.4 mg, 86%) as a white solid. M.p. 131-133 ºC; ¹H NMR (400 MHz, CDCl₃): δ = 7.52 (s, 2H, H₉), 7.21-7.18 (m, 24H, H₆ and H₈), 7.07 (dm, 24H, J₄ = 8.6, H₄ and H₆ₐ), 7.04 – 9.97 (m, 10H, H₅, H₇ and H₈), 6.72 and 6.71 (2 x d, 4H, J = 8.9, H₄ and H₆), 6.60 and 6.59 (2 x d, 4H, J = 8.9 and 8.8, H₅ and H₆), 6.32 (d, 4H, J = 8.4, H₅), 4.86 (s, 4H, H₅), 4.67 (s, 4H, H₆), 4.44 (s, 4H, H₇), 4.17 (t, 4H, J = 7.2, H₈), 3.72 (t, 8H, J = 6.9, H₉), 3.68 (t, 4H, J = 5.9, H₁₀), 2.04-1.98 (m, 4H, H₁₁), 1.61-1.52 (m, 8H, H₁₂), 1.27 (d, 108H, J = 2.4, H₁₃). ¹³C NMR (100 MHz, CDCl₃): δ = 158.8, 157.7, 156.2, 148.1 (2xC), 144.1 (2xC), 143.5, 139.6, 139.5, 136.5, 132.0, 132.0, 130.6, 130.6, 129.7 (2xC), 124.0 (2xC), 123.3, 120.2, 114.1, 113.0, 112.9, 104.3, 73.4, 68.6 (2xC), 65.8, 64.0, 63.0, 61.8, 61.6, 47.1, 41.3 (2xC), 34.2 (2xC), 31.3, 29.8, 29.6, 29.4, 29.4, 29.3, 29.1, 29.0, 25.8, 20.4; LRESI-MS: m/z = 3146 [M]⁺ and 3147 [M+H]⁺; HRESI-MS: m/z = 3146.16929 (calc. for C₁₂₆¹³CH₂₈₁₁N₇O₁₀ 3146.17285).

Crystal data and structure refinement for 35.PdCl₂(MeCN)

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Independent reflections: 9,169 \( [R\text{(int)} = 0.0490]\)

Completeness to theta = 25.00\(^\circ\): 99.8\%

Absorption correction: Multiscan

Max. and min. transmission: 1.0000 and 0.9288

Refinement method: Full-matrix least-squares on \( F^2 \)

Data / restraints / parameters: 9,169 / 40 / 562

Goodness-of-fit on \( F^2 \): 1.070

Final R indices \([I > 2\sigma(I)]\): \( R1 = 0.0855, wR2 = 0.2288 \)

R indices (all data): \( R1 = 0.0928, wR2 = 0.2379 \)

Extinction coefficient: 0.0020(7)

Largest diff. peak and hole: 1.716 and -1.139 e.Å\(^{-3}\)
Chapter 5: Towards Active Template Carbene Transformations

Acknowledgements
The following people are gratefully acknowledged for their contribution to this chapter: Dr. S. Goldup synthesized hydrazone 71 and complex 99. CuCl. Stewart Franklin and Louise Hogg synthesized 4-(tris(4-tert-butylphenyl)methyl)phenol (56). Luca Pignataro synthesized stoppers 80, 81 and 82. Paul McGonigal and Roy McBurney synthesized macrocycle 75. Paul McGonigal and Dr. Stephen Goldup synthesized macrocycle 99.
5.1 Introduction

Diazocarbonyl compounds, such as diazoesters, ketones and amides, form metallocarbenes (carbenoids) with transition metals, providing very useful synthetic intermediates which can undergo various transformations (Figure 5.1).²¹⁰ A range of transition metals have been demonstrated to facilitate transfer of the carbene to a π- or σ-bond and judicious choice of ligand promotes the desired reaction pathway.²¹⁰

Figure 5.1. Possible reactions of electron-poor metallocarbenes.²¹⁰

A [2+1] cycloaddition between the non-bonding electrons of the metallocarbene and the π-electrons of an alkene gives a cyclopropane (Figure 5.2a). This reaction has attracted a great deal of synthetic interest, particularly in the development of asymmetric catalysts.²¹¹ The most commonly used transition metals for this reaction are Cu, Rh, Ru and Co.²¹¹ The ligands employed in cyclopropanations of metallocarbenes are normally semicorrin, bisoxazoline or pybox derived,²¹⁰ although the use of chiral bipyridyl ligands for Cu has been described.¹⁵⁶,²¹²,²¹³ There has also been one report of the use of a chiral, macrocyclic bisoxazoline ligand for Cu-catalyzed cyclopropanation.²¹⁴
The insertion of carbenes into C-H and Si-H bonds is an extremely important tool in organic synthesis.\textsuperscript{215,216} Most reported examples of C-H insertion focus on intramolecular processes, due to the relatively low reactivity of this bond, and will not be covered in this chapter.

Intramolecular metallocarbene insertion into N-H bonds has proved to be a useful reaction for the preparation of β-lactams and other cyclic systems.\textsuperscript{217} Intermolecular N-H insertions (Figure 5.2b) have been achieved using ruthenium,\textsuperscript{218} rhodium,\textsuperscript{219-221} copper\textsuperscript{222,223-226} and silver\textsuperscript{222,225} While Cu-catalysts normally have nitrogen donor ligands, Nolan and co-workers have recently developed efficient copper\textsuperscript{227} and gold\textsuperscript{228} catalysts with N-heterocyclic carbene (NHC) ligands. Insertions into O-H bonds are somewhat less well studied and less success had been achieved with stereochemical control of these reactions.\textsuperscript{229,230}

![Figure 5.2.](image)

**Figure 5.2.** Simplified representation of a) addition of a metallocarbene to an alkene to furnish a substituted cyclopropane, b) insertion of a metallocarbene into an X-H bond (X = C, Si, N, O).

While the vast majority of recent work on carbene transformations has focussed on stereocontrol, here attempts to develop an active template reaction based on carbene transfer from a diazoester stopper are described and as such the stereochemical outcome of the reaction is not significant. The potential of cyclopropanation and X-H insertion reactions were investigated, and various ligands were tested in the active template synthesis of rotaxanes.
5.2 Results and Discussion

Synthesis of a Stoppered Carbene Source

It was necessary to synthesize a stoppered α-diazoester compound for use as a carbene precursor for active template reactions. This was initially attempted via introduction of diazo functionality into compound 57 (Scheme 5.1). Following a literature procedure, this was first carried out using Et₃N as the base and p-toluenesulfonyl azide as the diazo source. Unfortunately no disappearance of the α-protons was observed (by ¹H NMR of the crude product) and the only product observed was the starting phenol. Substitution of NaH for Et₃N led to no improvement, nor did substitution of methyl sulfonyl azide for p-toluene sulfonyl azide.

Scheme 5.1. Reagents and conditions: i) acetoacetic acid, DMAP, EDCI, CH₂Cl₂, 0 ºC→RT, 74%; ii) Et₃N or NaH, TsN₃ or MsN₃, THF, RT.

Since phenolic ester 57 appears unstable to the reaction conditions, an analogous alkyl ester, 60, was synthesized (Scheme 5.2). However, only starting material, 60, plus some alcohol, 59, was observed following treatment with Et₃N and TsN₃.

Scheme 5.2. Reagents and conditions: i) 1-bromopropanol, K₂CO₃, butanone, Δ, 81%; ii) acetoacetic acid, DMAP, EDCI, CH₂Cl₂, 0 ºC→RT, 53%; ii) Et₃N, TsN₃, THF, RT.
Coupling of Boc-Gly to either an aniline or phenol derived stopper could be achieved and subsequent deprotection afforded the amine salts 64 and 68 (Scheme 5.3 and 5.4 respectively). Unfortunately it wasn’t possible to convert either of these to the corresponding diazoesters.\(^{232}\) For these reactions commercially available trityl phenol (62, Scheme 5.3) and trityl aniline (66, Scheme 5.4) were used to test the methodology.

Scheme 5.3. Reagents and conditions: i) Boc-Gly, EDCI, DMAP, 0 °C→RT, 57%; ii) TFA, CH\(_2\)Cl\(_2\), 66%; iii) NaNO\(_2\), H\(_2\)SO\(_4\) (5% aq.), H\(_2\)O, CH\(_2\)Cl\(_2\), -10 °C→RT.\(^{232}\)

Scheme 5.4. Reagents and conditions: i) Boc-Gly, EDCI, DMAP, 0 °C→RT, 62%; ii) HCl (5 M in MeOH), RT, >99%; iii) NaNO\(_2\), H\(_2\)SO\(_4\) (5% aq.), H\(_2\)O, CH\(_2\)Cl\(_2\), -10 °C→RT.\(^{232}\)

Following a re-examination of the literature a successful route was found (Scheme 5.5). Hydrazine 71 was obtained by stirrign tosyl hydrazide (70) with glyoxylic acid in THF at RT.\(^{233}\) Treatment of 71 with oxalyl chloride and a catalytic quantity of DMF resulted in formation of the acid chloride, 72, which was reacted with alcohol 59 to give the required diazoester stopper, 73 in 80% yield.\(^{234}\)

Scheme 5.5. Reagents and conditions: i) THF, RT, 95% ii) (COCl)\(_2\), DMF (cat.), RT, 90%; iii) \(N,N\)-dimethylaniline, Et\(_3\)N, RT, 80%. 

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\(^{232}\) Vicki E. Ronaldson, 2009  Chapter 5
Studies Towards Carbene Transformations with Bipy Ligands

It was decided to test macrocycle 1b as a ligand for the Cu(I)-catalyzed cyclopropanation of the carbene transfer from 73 to a stoppered styrene, 74. Reactions were carried out in CDCl₃ and monitored by ¹H NMR. Unfortunately the reaction was unsuccessful and ¹H NMR of the reaction mixture showed that none of alkene 74 had been consumed (Table 5.1, Entry 1). A range of conditions were screened, including varying the Cu source and the ligand, but these also proved unsuccessful (Table 5.2, Entries 2-6). When CuOTf was used (Table 5, Entry 6) decomposition of macrocycle 1b was observed.

Table 5.1. Attempted Cu-mediated cyclopropanation reaction of a styrene stopper and a diazoester stopper, in the presence of an acyclic and a macrocycle bipy ligand.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Cu Source</th>
<th>Consumption of alkene 74%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>1b</td>
<td>CuPF₆</td>
<td>0%</td>
</tr>
<tr>
<td>2a</td>
<td>26</td>
<td>CuPF₆</td>
<td>0%</td>
</tr>
<tr>
<td>3a</td>
<td>1b</td>
<td>CuAc</td>
<td>0%</td>
</tr>
<tr>
<td>4a</td>
<td>1b</td>
<td>CuCl</td>
<td>0%</td>
</tr>
<tr>
<td>5a</td>
<td>1b</td>
<td>CuCl (with 1 eq. AgNO₃)</td>
<td>0%</td>
</tr>
<tr>
<td>6a</td>
<td>1b</td>
<td>CuCl (with 1 eq. Na[BArF]⁺)</td>
<td>0%</td>
</tr>
<tr>
<td>7a</td>
<td>1b</td>
<td>CuOTf</td>
<td>0%</td>
</tr>
</tbody>
</table>

In all reactions, 1.0 equiv. 73, 1.0 equiv. 74 and 1.0 equiv. of either 1b or 26 were used. Diazoester 73 was added by syringe pump over 1 h and the final concentration of each reagent was 0.025 M. Degree of consumption of alkene determined by ¹H NMR of reaction mixture. Reagents and conditions: i) Cu source (1.0 equiv.), CDCl₃, 18h, RT. R = (⁵BuC₆H₄)₃CC₆H₄.
Studies Towards Carbene Transformations with Pybox Ligands

Following the lack of success using a bipyridyl macrocycle, attention was turned to a pybox derived macrocycle. Macrocycle 75 (Figure 5.3) could be obtained within the laboratory as it had been synthesized by co-workers for another project. The acyclic analogue (76) of this macrocycle is commercially available. Macrocycle 75 was synthesized as the 1R2R enantiomer of the trans diastereomer, due to availability of commercial starting materials. The acyclic analogue purchased was the 1S2S enantiomer. However, as the stereochemical outcome of the reaction is not relevant to these studies, the stereochemistry of the ligand is not significant.

![Figure 5.3. A pybox derived macrocyclic ligand, 75, and its commercially available acyclic analogue, 76.](image)

Stirring 1 equiv. of 75 with 1 equiv. of CuOTf overnight at RT showed that, unlike macrocycle 1b, pybox macrocycle 75 is stable to CuOTf. It was decided to first of all test the macrocycle-copper complex with commercially available substrates. Complete conversion to the desired product was observed for the reaction between styrene and ethyl diazoacetate (Table 5.2, entry 1), showing that the complex is active. Reacting styrene with diazoester 73 gave 45% consumption of alkene (Table 5.2, Entry 2) and reacting ethyl diazoacetate with alkene 74 gave 44% consumption of alkene (Table 5.2, Entry 3). Unfortunately, the reaction between stoppers 73 and 74 failed to result in any consumption of the alkene component, both in the presence of macrocycle 75 and pybox ligand 76 (Table 5.2, Entries 4 and 5).
Table 5.2. Attempted Cu-mediated cyclopropanation of stoppered and commercially available alkenes and diazoesters in the presence of pybox ligands.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Diazoester</th>
<th>Ligand</th>
<th>Expected product</th>
<th>Consumption of alkene&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Styrene</td>
<td>Ethyl diazoacetate</td>
<td>75</td>
<td></td>
<td>&gt;99%</td>
</tr>
<tr>
<td>2</td>
<td>Styrene</td>
<td>73</td>
<td>75</td>
<td></td>
<td>45%</td>
</tr>
<tr>
<td>3</td>
<td>74</td>
<td>Ethyl diazoacetate</td>
<td>75</td>
<td></td>
<td>44%</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>73</td>
<td>76</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>74</td>
<td>73</td>
<td>75</td>
<td></td>
<td>0%</td>
</tr>
</tbody>
</table>

Reagents and conditions: Alkene (1.0 equiv.), diazoester (1.0 equiv.), ligand (1.0 equiv.), CuOTf (1.0 equiv.), CDCl<sub>3</sub>, RT, 18 h. R = (tBuC<sub>6</sub>H<sub>4</sub>)<sub>3</sub>CC<sub>6</sub>H. Diazoester 73 was added by syringe pump over 1 h and the final concentration of each reagent was 0.025 M.<sup>a</sup>Degree of consumption of alkene determined by <sup>1</sup>H NMR of the reaction mixture.

When using diazoester 73 as a substrate, degradation of this α-diazoester was observed, giving a messy <sup>1</sup>H NMR spectrum, even when none of the alkene was consumed. This suggested that either intra- or intermolecular reaction of the diazoester was competing with, and dominating, the desired cycloaddition. No coupling of the α-diazo carbonyls, was observed. It is well known that α-diazocarbonyl compounds will insert intramolecularly into the C-H bonds of aliphatic chains and where possible the 5-membered ring is favoured.<sup>217</sup> However, C-H bonds adjacent to an ether oxygen are more activated towards insertion than unactivated aliphatic carbons and the presence of an ether oxygen can direct formation of a 6-membered ring over the 5-membered ring.<sup>235</sup> It is possible that the
phenolic ether oxygen in stopper 73 activates the adjacent carbon to C-H insertion, which competes with the desired cyclopropanation reaction (Scheme 5.6).

Scheme 5.6. Possible reaction pathways of diazoester 73 following metallocarbene formation: a) Cycloaddition with an alkene to form a cyclopropane; b) intramolecular C-H insertion at the activated C-H.

It was reasoned that a longer aliphatic spacer unit between the activated C-H and the diazoester group could help circumvent this problem. Diazoester 78 was synthesized in the same way as 73, using a hexanol functionalized stopper (Scheme 5.7).

Scheme 5.7. Reagents and conditions: i) 6-Bromohexanol, K₂CO₃, NaI, butanone, Δ, 82%; ii) 1. (COCl)₂, DMF (cat.), RT, 2. N,N-dimethyl aniline, Et₃N, RT, 71%.

Unfortunately reacting diazoester 78 with alkene stopper 74 in the presence of ligand 76, under the conditions outlined in Table 5.2, resulted in no consumption of the alkene and apparent decomposition of the diazoester.
Studies Towards Carbene Transformations with N-Heterocyclic Carbene Ligands

Due the lack of success with nitrogen ligands, attention was turned to an N-heterocyclic carbene (NHC) ligand. NHCs have attracted a great deal of attention as organocatalysts in recent years. These persistent, so-called Arduengo carbenes also have synthetic utility as ligands in TM-catalyzed reactions. Nolan and co-workers have recently shown that NHC complexes $79.\text{CuCl}^{238}$ and $79.\text{AuCl}^{228}$ (Figure 5.4) are effective catalysts for carbene transfer reactions from ethyl diazoacetate.

![Figure 5.4. A Cu- and Au-NHC catalyst for carbene transfer reactions.](image)

Complexes $79.\text{CuCl}$ and $79.\text{AuCl}$ were synthesized from the commercially available imidiazolium salt of $79$ according to literature procedures, and tested with a variety of stoppered substrates that were available in the laboratory. Insertion into the O-H of phenol $56$, alcohol $59$ and acid $80$ using $79.\text{CuCl}$ were unsuccessful (Table 5.3, Entries 1-3). Stoppered aniline $81$ furnished no insertion product in the presence of $79.\text{CuCl}$ or $79.\text{AuCl}$ (Table 5.3, Entries 4 and 5). The more electron-poor aniline stopper, $82$ was also unreactive in the presence of $79.\text{AuCl}$ (Table 5.3, Entry 7) but promisingly showed quantitative conversion to the insertion product, $87$, in the presence of $79.\text{CuCl}$ (Table 5.3, Entry 6). Column chromatography gave 71% of the isolated product, $87$. This was a promising result and the next step was to carry out the reaction using a macrocyclic ligand.
Table 5.3. Reaction of diazoester 73 with a variety of OH and NH containing substrates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Catalyst</th>
<th>Insertion product</th>
<th>Conversion to product$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R-OH</td>
<td>79.CuCl</td>
<td><img src="image1.png" alt="Image" /></td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>R-OH-OH</td>
<td>79.CuCl</td>
<td><img src="image2.png" alt="Image" /></td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>R-OH-OH</td>
<td>79.CuCl</td>
<td><img src="image3.png" alt="Image" /></td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>R-CH$_2$NH$_2$</td>
<td>79.CuCl</td>
<td><img src="image4.png" alt="Image" /></td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>81</td>
<td>79.AuCl</td>
<td>86</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>82</td>
<td>79.CuCl</td>
<td>87</td>
<td>&gt;99% (71%)$^b$</td>
</tr>
</tbody>
</table>

$^a$Consumption of starting material determined by $^1$H NMR of the reaction mixture.

$^b$Compound purified but it was not possible to get it completely clean. Reagents and conditions: diazoester stopper 73 (64.0 µmol), amine or alcohol stopper (117 µmol), catalyst (32 µmol) CH$_2$Cl$_2$ (1 mL), 80 °C, 18 h.

Macrocycle 99 had been synthesized within the group with the intention of using it in organocatalyzed active template reactions. Although synthesized by a co-worker, the synthetic route has been included for completeness (Scheme 5.8). The CuCl complex of 99 could be generated by stirring the imidazolium salt with KO$^t$Bu for 30 min, then adding CuCl, as described in the literature for 79.CuCl.239
Scheme 5.8. Reagents and conditions: i) I$_2$ (1.0 equiv.), pyridine-dioxane (1:1), 0 °C → RT, 88%; ii) Oxaldehyde, formic acid, n-PrPH, 70 °C, 81%; iii) Paraformaldehyde, HCl (in dioxane, THF, RT, 62%; iv) H$_2$SO$_4$ (conc.), MeOH, Δ, 77%; v) 1-Bromo pentene, K$_2$CO$_3$, NaI, butanone, Δ, 90%; vi) LiAlH$_4$, THF, 0 °C → RT, 80%; vii) CBr$_4$, PPh$_3$, CH$_2$Cl$_2$, RT, 76%; viii) Zn, I$_2$, NMP, 80 °C then I-NHC-I, LiBr, PEPPSI, NMP-THF, RT, 78%; ix) Grubbs 1, CH$_2$Cl$_2$, RT, 88%; x) H$_2$, Pd/C, EtOH, 85%.

Diazooester 73, aniline 82 and 99.CuCl were reacted under the same conditions used to form the thread (Scheme 5.9). Unfortunately none of the expected rotaxane, 100, was observed. Interestingly however, 70% thread was observed by $^1$H NMR analysis of the crude reaction mixture. While it was disappointing that no rotaxane was observed, it was encouraging to see that macrocyclic complex 99.CuCl catalyzes N-H insertion.
Scheme 5.9. Attempted rotaxane formation by carbene insertion in the presence of a Cu-NHC macrocycle complex. Unfortunately none of rotaxane 100 was observed, but 70% conversion to thread 87 was observed. \textsuperscript{a}Conversion to product calculated from \textsuperscript{1}H NMR of the reaction mixture. Reagents and conditions: i) 73 (64.0 μmol), 82 (117 μmol), 99.CuCl (32 μmol) CH\textsubscript{2}Cl\textsubscript{2} (1 mL), 80 °C, 18 h.
Figure 5.5 shows the $^1$H NMR of thread 87, (isolated from the reaction with complex 79. CuCl). The NH peak, which integrates to 1H, can be seen at around 4.7 ppm and H$_k$ gives rise to a doublet, due to coupling with NH.

![Figure 5.5. $^1$H NMR spectrum of thread 87. Assignments correspond to the lettering in Scheme 5.9.](image)

**Future Work**

Normally when thread, but no rotaxane, is formed in an active template reaction it is due to a combination of the metal ion spending time free in solution (rather than bound inside the macrocyclic cavity) and the ‘off-ligand’ (that is when the metal is not bound to the macrocycle) reaction occurring faster than the rotaxane forming reaction. In the CuAAC active template reaction the rate of ‘off-ligand’ thread formation was found to be greater than the rate of reaction through the macrocyclic cavity. However, the high-affinity of the copper for the macrocyclic binding site meant that rotaxane formation could compete with non-interlocked thread formation (see Chapter 2). Binding of a transition metal to the C2 carbon of an NHC leads to the formation of a very strong metal–carbon bond. Unlike classic metal-ligand coordinative bond, those to NHCs do not undergo fast insertion or reductive elimination reactions and so NHCs are relatively reliable spectator ligands.\textsuperscript{240} It is
therefore unlikely that in the presence of a macrocyclic NHC ligand-metal complex thread formation is catalyzed by free metal in solution. One possible explanation for thread formation is that the metal is bound *exo* to the macrocyclic cavity (Figure 5.6). Catalysis of the insertion reaction outside the macrocyclic cavity would lead to non-interlocked product.

![Figure 5.6. Complex 99.CuCl with the CuCl pointing out of the macrocyclic cavity.](image)

Design of a macrocycle with a more rigid cavity may circumvent this problem. An example of such a macrocycle is shown in Figure 5.7.

![Figure 5.7. An NHC precursor with a more restricted cavity than 99, to reduce the chance of exo binding of the metal.](image)

A CPK model of macrocycle 101 shows the cavity is still large enough to accommodate a thread molecule. In addition to transition metal mediated carbene transfer from α-diazo compounds, NHC macrocycles could also be utilized in organocatalysis as to date, no organocatalytic active template reaction have been developed.
5.3 Experimental

General

Unless otherwise stated, all reagents were obtained from commercial sources and used without further purification, solvents were anhydrous and all reactions were carried out under an atmosphere of N₂ (g). p-toluenesulfonyl azide, methylsulfonyl azide, p-toluenesulfonyl hydrazide, CuCl, and AuCl₂ were prepared according to literature procedures.

4-(Tris(4-tert-butylphenyl)methyl)phenyl 3-oxobutanoate (57)

EDCI (1.03 g, 6.6 mmol) was added to a solution of acetoacetic acid (0.50 g, 4.2 mmol) and 4-(tris(4-tert-butylphenyl)methyl)phenol (56) (1.42 g, 2.8 mmol) and DMAP (0.78 g, 6.6 mmol) in CH₂Cl₂ (40 mL) at 0 °C. The reaction mixture was allowed to stir for 18 h at RT. The reaction mixture was then washed with 1 M aqueous HCl (3 x 50 mL), sat. aqueous NaHCO₃ (3 x 50 mL), and H₂O (50 mL). The organic phase was dried (MgSO₄) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (gradient elution: 1. pet-EtOAc 10:1, 2. pet-EtOAc 5:1) to yield ester 57 (1.00 g, 59%) as a colourless solid. M.p. 204-206 °C; ¹H NMR (400 MHz; CDCl₃): δ = 7.23 (m, 8H, Hc and Hd), 7.00 (d, J = 8.4, Hb), 6.91 (d, 2H, J = 8.8, He), 4.75 (s, 2H, Hf), 2.11 (s, 3H, Hg), 1.22 (s, 27H, Ha); ¹³C NMR (100 MHz; CDCl₃): δ = 170.3, 166.5, 148.5, 147.9, 145.4, 143.6, 132.3, 130.7, 124.2, 99.7, 63.4, 60.8, 34.3, 31.4, 20.5; LRFAB-MS (3-NOMA matrix): m/z = 589 [M+H]+; HRFAB-MS (3-NOBA matrix): m/z = 589.36820 [M+H]+ (calcd. for C₄₁H₄₉O₃, 589.36817).
3-(4-(Tris(4-tert-butylphenyl)methyl)phenoxy)propan-1-ol (59)

K₂CO₃ (4.50 g, 32.5 mmol) was added to a solution of 4-[tris-(4-tert-butylphenyl)methyl]phenol (56) (3.30 g, 6.50 mmol) and 1-bromopropanol (0.86 mL, 9.80 mmol) in butanone (160 mL). The reaction mixture was heated at reflux for 24 h. After cooling, volatiles were removed in vacuo. The residue was dissolved in CH₂Cl₂ (100 mL). The organic layer was washed with H₂O (2 x 100 mL) and brine (100 mL), dried (MgSO₄), and concentrated under reduced pressure. The residue was re-dissolved in hot MeOH (200 mL) and the remaining precipitate filtered off. The filtrate was concentrated under reduced pressure to yield alcohol 59 (2.96 g, 81%) as a colourless solid. M.p. 290-292 °C. ¹H NMR (400 MHz, CDCl₃): δ = 7.23 (d, 6H, J = 8.6, Hb), 7.08 (d, 8H, J = 8.6, Hc, Hd), 6.77 (d, 2H, J = 8.9, He), 4.10 (t, 2H, J = 5.9, Hf), 3.86 (q, 2H, J = 4.8, Hh), 2.04 (m, 2H, Hg), 1.30 (s, 27H, Ha). ¹³C NMR (100 MHz, CDCl₃): δ = 156.4, 148.2, 144.0, 139.8, 132.2, 130.6, 124.0, 112.9, 65.7, 63.0, 60.7, 34.2, 31.9, 31.3. LRFAB-MS (3-NOBA matrix): m/z = 562 [M⁺].
3-(4-(Tris(4-tert-butylphenyl)methyl)phenoxy)propyl 3-oxobutanoate (60)

EDCI (100 mg, 0.5 mmol) was added to a solution of acetoacetic acid (63.0 mg, 0.5 mmol), alcohol 59 (20.0 mg, 0.4 mmol) and DMAP (63.0 mg, 0.5 mmol) in CH$_2$Cl$_2$ (5 mL) at 0 °C. The reaction mixture was allowed to stir for 18 h at RT. The reaction mixture was then washed with 1 M aqueous HCl (3 x 20 mL), sat. aqueous NaHCO$_3$ (3 x 20 mL) then H$_2$O (20 mL). The organic phase was dried (MgSO$_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (pet-EtOAc 5:1) to yield ester 60 (119 mg, 53%) as a colourless solid. M.p. 165 °C (decomp); $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ = 7.24 (d, 6H, $J = 8.6$, H$_b$), 7.09 (d, 2H, $J = 9.0$, H$_d$), 7.09 (d, 6H, $J = 8.6$, H$_c$), 6.76 (d, 2H, $J = 8.9$, H$_e$), 4.61 (s, 2H, H$_i$), 4.38 (t, 2H, $J = 6.3$, H$_h$), 4.02 (t, 2H, $J = 6.0$, H$_f$), 2.15 (s, 3H, H$_j$), 2.13 (quint., 2H, $J = 6.2$, H$_g$), 1.31 (s, 27H, H$_a$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 200.4, 170.3, 167.7, 157.3, 156.4, 148.2, 144.0, 139.7, 132.2, 130.6, 124.0, 112.8, 63.7, 63.0, 62.3, 60.6, 34.2, 31.3; LRFAB-MS (3-NOBA matrix): $m/z = 647$ [M$^+$]; HRFAB-MS (3-NOBA matrix): $m/z = 647.40924$ [M+H$^+$] (calc. for C$_{44}$H$_{55}$O$_4$ 647.41004).
4-Tritylphenyl 2-((tert-butoxycarbonyl)acetate (63)

![Chemical Structure of 63](image)

Boc-Gly (0.58 g, 3.3 mmol) was added to a solution of 4-trityl phenol (1.00 g, 3.0 mmol) in CH$_2$Cl$_2$ (50 mL). EDCI (0.63 g, 3.3 mmol) was added, then the solution was cooled to 0 °C and DMAP (0.55 g, 4.5 mmol) was added. The reaction mixture was allowed to warm to RT and stirred for 18 h. After this time the reaction mixture was washed with 1 M aqueous HCl (3 x 50 mL), sat. aqueous NaHCO$_3$ (3 x 50 mL) and H$_2$O (50 mL). The organic phase was dried (MgSO$_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (pet-EtOAc, 10:1) to give 63 (0.84 g, 57%) as a white foam. $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ = 7.14 (m, 17H, H$_a$, H$_b$, H$_c$ and H$_d$), 6.92 (d, 2H, $J$= 8.8, H$_e$), 5.00 (br-s, 1H, NH), 4.07 (d, 2H, $J$= 5.5, H$_f$), 1.39 (s, 9H, H$_g$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 167.3, 162.2, 153.4, 148.2, 146.4, 132.1, 131.0, 127.5 (2xC), 126.0, 120.0, 57.4, 42.6, 28.2, LRFAB-MS (3-NOBA matrix): $m/z$ = 494 [M+H]$^+$; HRFAB-MS (3-NOBA matrix): $m/z$ = 494.23317 [M+H]$^+$ (calc. for C$_{32}$H$_{32}$NO$_4$, 494.23313).

2-oxo-2-(4-tritylphenoxy)ethanaminium 2,2,2-trifluoroacetate (64)

![Chemical Structure of 64](image)

Boc-protected amine 63 (1.20 g, 2.4 mmol) was dissolved in CH$_2$Cl$_2$ (10 mL) and trifluoroacetic acid (10 mL) and allowed to stir at RT for 1 h. The reaction mixture was concentrated under reduced pressure to leave the salt 64 (0.81 g, 66%), which was used without further purification.
Tert-butyl 2-oxo-2-(4-tritylphenylamino)ethylcarbamate (67)

Boc-Gly (0.58 g, 3.3 mmol) was added to a solution of 4-trityl aniline (1.01 g, 3.0 mmol) in CH₂Cl₂ (50 mL). EDCI (0.63 g, 3.3 mmol) was added then the solution was cooled to 0 °C and DMAP (0.55 g, 4.5 mmol) was added. The reaction mixture was allowed to warm to RT and stirred for 18 h. After this time the reaction mixture was washed with 1 M aqueous HCl (3 x 50 mL), sat. NaHCO₃ (3 x 50 mL) and H₂O (50 mL). The organic phase was dried (MgSO₄) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (pet-EtOAc, 5:1) to give 67 (0.89 g, 62%) as a white foam; ¹H NMR (400 MHz; CDCl₃): δ = 7.39 (d, 2H, J = 8.7, 2H, He), 7.16-7.24 (m, 17H, Ha, Hb, Hc and Hd), 3.90 (d, 2H, J = 5.8, Hf), 1.47 (s, 9H, Hg).

2-Oxo-2-(4-tritylphenylamino)ethanaminium chloride (68).

Boc-protected amine 67 (0.88 g, 1.8 mmol) was dissolved in HCl (5 M in MeOH, 10 mL) and the resulting solution left to stir at RT for 18 h. The reaction mixture was concentrated under reduced pressure to leave the salt 68 (0.80 g, >99%) as a colourless solid which was used without further purification. ¹H NMR (400 MHz; CDCl₃): δ = 7.47 (d, 2H, J = 8.8, He), 7.16-7.24 (m, 17H, Ha, Hb, Hc and Hd), 3.49 (s, 2H, Hf).
Oxalyl chloride (0.65 mL, 7.7 mmol) was added to a solution of hydrazone (1.46 g, 7.0 mmol) in CH₂Cl₂ (60 mL). Two drops of DMF were added and the reaction mixture was allowed to stir at RT for 2 h, after which time the previously cloudy solution had turned clear. Volatiles were removed in vacuo. The resulting pale yellow oil (acid chloride, 1.64 g) was dissolved in CH₂Cl₂ (20 mL) and added to a solution of alcohol (3.54 g, 6.30 mol) in CH₂Cl₂ (20 mL). N,N-dimethyl aniline (4.00 mL, 31.5 mmol) was added at 0 °C. After stirring for 30 min at 0 °C, Et₃N (7.40 mL, 53.0 mmol) was added (still at 0 °C) and the reaction mixture was then left to stir at RT for 90 min. After this time the reaction mixture was diluted with CH₂Cl₂ (30 mL), washed with a saturated aqueous solution of citric acid (50 mL), H₂O (50 mL) and brine (50 mL). The organic phase was dried (Na₂SO₄) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (gradient elution: pet-CH₂Cl₂, 3:1, 2:1, 1:2) to give diazoester (2.50 g, 67% from 59) as a pale yellow solid. M.p. 185-186 °C; \(^1\)H NMR (400 MHz, CDCl₃): \(\delta = 7.23 \text{ (d, 6H, } J = 8.6, \text{ H}_b), 7.08 \text{ (d, 8H, } J = 8.6, \text{ H}_c \text{ and H}_d), 6.75 \text{ (d, 2H, } J = 8.9, \text{ H}_e), 4.74 \text{ (br-s, 1H, H}_i), 4.36 \text{ (t, 2H, } J = 6.3, \text{ H}_g), 4.01 \text{ (t, 2H, } J = 6.1, \text{ H}_f), 2.12 \text{ (quint., 2H, } J = 6.2, \text{ H}_h); ^{13}\text{C NMR (100 MHz, CDCl₃): } \delta = 156.4, 148.2, 144.0, 139.7, 132.2, 130.6 \text{ (2xC), 124.0, 112.8, 63.9, 63.0, 61.7, 46.0, 34.2, 31.3, 28.8; LRFAB-MS (3-NOBA matrix): } m/z = 630 \text{ [M]^+; HRFAB-MS (3-NOBA matrix): } m/z = 648.4158 \text{ [M+NH}_4]^+ \text{ (calc. for C}_{42}\text{H}_{54}\text{N}_{3}\text{O}_3 648.4150).}
3-(4-(tris(4-tert-butylphenyl)methyl)phenoxy)propyl 4-vinylbenzoate (74)

A solution of alcohol 59 (1.00 g, 1.72 mmol) and 4-vinylbenzoic acid (310 mg, 2.06 mmol) in CH₂Cl₂ (50 mL) was cooled to 0 °C. EDCI (430 mg, 2.25 mmol) and DMAP (210 mg, 1.72 mmol) were added. The resulting mixture was allowed to stir overnight at RT. The reaction was quenched by addition of H₂O. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (hexane-EtOAc 9:1) to give 74 (0.67 g, 56%) as a colourless solid. M.p. 180-183 °C. ¹H NMR (400 MHz, CDCl₃): δ = 7.91 (d, 2H, J = 8.3, Hᵢ), 7.36 (d, 2H, J = 8.3, Hⱼ), 7.14 (d, 6H, J = 8.5, Hₖ), 7.00 (d, 6H, J = 8.5, Hₗ), 7.00 (d, 2H, J = 8.8, Hₘ), 6.69 (d, 2H, J = 8.8, Hₙ), 6.66 (dd, 1H, J = 17.6, 10.9, Hₖ), 5.77 (d, 1H, J = 17.6, H₋trans), 5.29 (d, 1H, J = 10.9, H₋cis), 4.43 (t, 2H, J = 6.2, Hₜ), 4.02 (t, 2H, J = 6.1, Hᵣ), 2.16 (tt, 2H, J = 6.2, 6.1, Hᵣ), 1.21 (s, 27H, Hᵥ). ¹³C NMR (100 MHz, CDCl₃): δ = 166.3, 156.6, 148.3, 144.1, 142.0, 139.8, 136.0, 132.3, 130.7, 129.9, 129.4, 126.1, 124.3, 116.5, 113.0, 64.3, 63.1, 61.9, 34.3, 31.4, 28.9; LRFAB-MS (3-NOBA matrix): m/z = 693 [M⁺]; HRFAB-MS (3-NOBA matrix): m/z = 692.4226 [M⁺] (calc. for C₄₉H₅₆O₃ 692.4230).
Acid chloride 72 was generated from 71 as described for compound 73. A solution of this (3.3 mmol in 13.2 mL) was treated with alcohol 77 (1.99 g, 3.30 mmol) and N,N-dimethyl aniline (2.10 mL, 16.5 mmol) at 0 °C. After stirring for 30 min at 0 °C, Et3N (4.60 mL, 33.0 mmol) was added (still at 0 °C) and the reaction mixture was then left to stir at RT for 90 min. After this time the reaction mixture was diluted with CH2Cl2 (20 mL), washed with a saturated aqueous solution of citric acid (30 mL), H2O (50 mL) and brine (30 mL). The organic phase was dried (Na2SO4) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (gradient elution with pet-CH2Cl2, 3:1, 2:1, 1:2) to give diazoester 78 (1.58 g, 71% from 77) as a pale yellow solid. M.p. 145-147 °C; 1H NMR (400 MHz, CDCl3): δ = 7.22 (d, 6H, J = 8.7, Hb), 7.08 (dm, 8H, Jd = 8.7, Hc and Hd), 6.75 (d, 2H, J = 9.0, He), 4.72 (br-s, 1H, Hl), 4.17 (td, 2H, Jt = 6.6, Jd = 1.8, Hk), 3.93 (t, 2H, J = 6.4, Hf), 1.82-1.74 (m, 2H Hg), 1.71-1.63 (m, 2H, Hj), 1.51-1.38 (m, 4H, Hh and Hi), 1.30 (s, 27H, Ha); 13C NMR (100 MHz, CDCl3): δ = 156.8, 148.2, 144.1, 139.3, 132.1, 130.6 (Cx2), 123.9, 112.8, 67.5, 64.8, 64.7, 62.9, 34.2, 31.3, 29.1, 28.7, 25.7, 25.6.; LRFAB-MS (3-NOBA matrix): m/z = 673 [M]+.
Complex 79.CuCl (15.6 mg, 0.032 mmol) was added to a solution of aniline 82 (80.0 mg, 0.177 mmol) and diazoester 73 (40 mg, 0.064 mmol) in CH_2Cl_2 (1mL). The reaction mixture was heated at 80 °C in a sealed microwave vial for 18 h. After cooling to RT, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with a 17.5% solution of NH_3 saturated with EDTA (2 x 10 mL) then H_2O (10 mL). The combined aqueous washings were re-extracted with CH_2Cl_2 (10 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography of the resulting residue (10:1, pet-Et_2O) gave thread 87 (29.6 mg, 72%) as a pale brown solid. It could be seen from the ^1H NMR spectrum that the product still contained impurities, however the relevant signals are listed: ^1H NMR (400 MHz, CDCl_3): δ = 7.87 (d, 2H, J = 8.7, H_i), 7.22 (d, 12H, J = 8.6, H_b), 7.07 (d, 16H, J= 8.6, H_c and H_d), 6.78-6.73 (m, 4H, H_e and H_o), 6.54 (d, 2H, J = 8.8, H_j), 4.71 (t, 1H, J = 5.0, NH), 4.46-4.39 (m, 4H, H_h and H_l), 4.07 (t, 2H, J= 6.1, H_f), 4.01 (t, 2H, J= 5.9, H_n), 3.94 (d, 2H, J = 5.1, H_k), 2.24-2.10 (m, 4H, H_g and H_m), 1.29 (s, 54H, H_a and H_s). LRFAB-MS (3-NOBA matrix): m/z = 1286 [M+H]^+; HRFAB-MS (3-NOBA matrix): m/z = 1284.80187 (calc. for C_{89}H_{106}NO_6 1284.0202).
References and Notes


(7) IUPAC Compendium of Chemical Terminology - the Gold Book (http://goldbook.iupac.org/index.html). Date of access 26/01/09.


(85) The Cu(I)-catalyzed terminal alkyne-azide cycloaddition is often referred to as the ‘Sharpless copper click reaction’ or the ‘Sharpless-Huisgen alkyne-azide cycloaddition’. However, Sharpless gives Fokin the credit for the idea and recognition of the copper catalysis of this reaction at Scripps [Rouhi, A. M. *Chem. Eng. News* **2004**, *82*, 63-65.]. The initial work at Scripps was carried out shortly after, and without knowledge of, the first paper (Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057-3064) describing the Cu(I)-catalyzed alkyne-azide cycloaddition (on solid supported resins) had been submitted by Meldal and co-workers.
(86) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. Angew. Chem. Int. Ed. 2002, 41, 2596-2599.


(90) Lewis, W. G.; Magallon, F. G.; Fokin, V. V.; Finn, M. G. J. Am. Chem. Soc. 2004, 126, 9152-9153.


(93) If the [2+3] cycloaddition were the preferred mechanism of the Cu-catalyzed reaction, the structures A–C shown in Figure 2.1 would still be relevant as reactive intermediates.


(95) Ahlquist, M.; Fokin, V. V. Organometallics 2007, 26, 4389-4391.


(97) In this thesis the phrases ‘ligandless’ and ‘ligand-free’ are used to describe copper that is not bound to the macrocyclic pyridine ligands added to the CuAAC reactions to generate the active-template synthesis. As discussed in the text, any Cu(I) that is not coordinated to pyridine units will be complexed by molecules of acetonitrile, azide, alkyne, water or other donor atoms present.


(104) Note: Cu(I)-acetylides are generally complex extended multi-atom aggregates, at least in the solid state and in the absence of good nitrogen ligands (see ref 98). The types of reactive intermediates shown in Figure 2.1 are not meant to be precise or definitive structures—indeed, some of them (e.g. A(ii) and B(ii)) are very closely related—but rather are meant to illustrate different (possible) features of the putative reactive intermediate.

(105) The standard reactions conditions use one equivalent of each reagent and low temperatures to minimize the background, uncatalyzed, thermal cycloaddition. These conditions were chosen to allow the relative efficacy of the different macrocycles in promoting rotaxane formation to be assessed.


(108) Macrocycle **1m** was chosen for this study because it is a rather poor ligand, due to the steric crowding around the pyridine nitrogen and the π- electron density presented to the low oxidation state copper from the adjacent aromatic rings. The rather weak Cu(I) binding affinity—meaning there is more ligandless Cu(I) present in solution than many of the other macrocycles shown in Figure 2.5—is most likely the reason for the modest yield of rotaxane using 1 equiv. of this macrocycle. It was reasoned that the yield should be improved by increasing the macrocycle:copper ratio.
(109) This compound was commercially available but, due to cost, was prepared in the lab.


(155) The formation of a thick yellow paste indicated the presence of the Cu-acetylide species, which exist as complex aggregates (see ref. 98).


(198) Molokanova, O.; Vysotsky, M. O.; Cao, Y. D.; Thondorf, I.; Bohmer, V. Angew. Chem. Int. Ed. 2006, 45, 8051-8055.


(204) Reaction carried out under stoichiometric conditions (see ref. 145): 1 equiv. macrocycle 35, 1 equiv. Pd-trans-Cl2(MeCN)2, 10 equiv. alkyne 24, 0.25 equiv. Cul, 2 mL DIPA.


Appendix I: Published Work