Approaches to Asymmetric Click Chemistry

James Patrick Martin

This thesis is submitted in partial fulfilment of the requirements for the award of Master of Science.

25th September 2013

The University of East Anglia

School of chemistry

Abstract

CuAAC 'click' chemistry is an invaluable synthetic tool, with asymmetric examples are beginning to emerge. However no rugged asymmetric CuAAC system has to date been discovered.

This project aims to develop and utilize asymmetric CuAAC reactions in the synthesis of natural product mimicking macrocycles and heterohelicenes.

Acknowledgments

First, I would like to thank the Interreg program, IS:CE and AI-Chem, for funding the project. I would like to thank The University of East Anglia and the Université de Caen for the use of their laboratory facilities.

I would like to thank Prof. Phil Bulman Page and Dr. G. Richard Stephenson for their guidance, support and supervision. As well as Prof. Annie-Claude Gaumont and Dr. Carole Witulski-Alayrac for their guidance and support during my stay at LCMT, Université de Caen.

Next, I would like to thank the members of the organic chemistry department at The University of East Anglia, in particular, Dr. Yohan Chan, Mr. Ollie McGaw, Mr. Ian Strutt, and Mr Julien Doulcet.

Finally, I would like to thank everyone at LCMT, Université de Caen for their assistance and welcoming friendship while I was there, in particular, Mr. Romain Duwald, Mr. Pierre-François Vittoz, and Miss Pham Hoai Thu.

ABREVIATIONS

AIBN	azobisisobutyronitrile
Bu	butyl
CuAAC	copper-catalysed azide-alkyne cycloaddition
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
Et	ethyl
^{i}Pr	isopropyl
LDA	lithium diisopropylamide
Me	methyl
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
NMR	nuclear magnetic resonance spectroscopy
Ph	phenyl
Pr	isopropyl
Rbf	round-bottomed flask
^{t}Bu	tertiary butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPP	triphenylphosphine

CONTENTS

1.0 Introduction.

1.1 Copper-catalysed azide-alkyne cycloaddition reactions. 1

1.2 CuAAC mechanism. 2

1.3 CuAAC sources and ligands. 4

1.4 Asymmetric CuAAC. 7

1.5 CuAAC in the synthesis of macrocycles. 9

1.6 CuAAC in the synthesis of natural product analogues. 14

1.7 Carbohelicenes. 16

1.8 Carbohelicene syntheses. 17

1.9 Heterohelicene syntheses. 21

2.0 Results and Discussion.

2.1 Studies towards the asymmetric CuAAC reaction synthesis of macrocycles. 23

2.2 Studies towards the asymmetric CuAAC reaction synthesis of heterohelicenes. 29

3.0 Experimental.

3.1 Experimental procedures in the syntheses towards macrocycles. 37

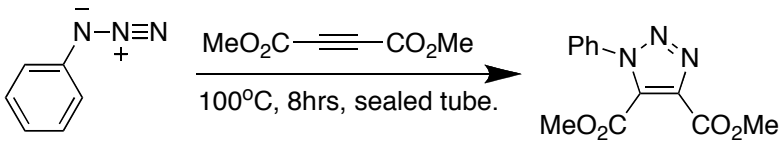
3.2 Experimental procedures in the syntheses towards heterohelicenes. 46

4.0 References. 55

1.0 Introduction.

1.1 Copper-catalysed azide-alkyne cycloaddition reactions.

In 1893, Arthur Michael reported the synthesis of 1,2,3-triazoles by heating alkyne diesters with phenyl azide[1] in a sealed tube at 100°C for 8 hours (scheme 1). The reaction then fell into obscurity, until rediscovered in 1961[2] by Rolf Huisgen, during his encompassing work on 1,3-dipolar cycloadditions, for whom this broad spectrum of reactions is named. Of the 1,3-dipolar cycloadditions, that between azides and alkynes is now so well known, the term 'Huisgen cycloaddition' has become somewhat synonymous with this specific reaction. While boasting perfect atom economy, the azide-alkyne Huisgen cycloaddition requires high temperatures, and, in the cases of non-symmetric alkynes, gives mixtures of the 1,2-substituted and 1,4-substituted 1,2,3-triazole isomers, limiting it's use in organic synthesis.

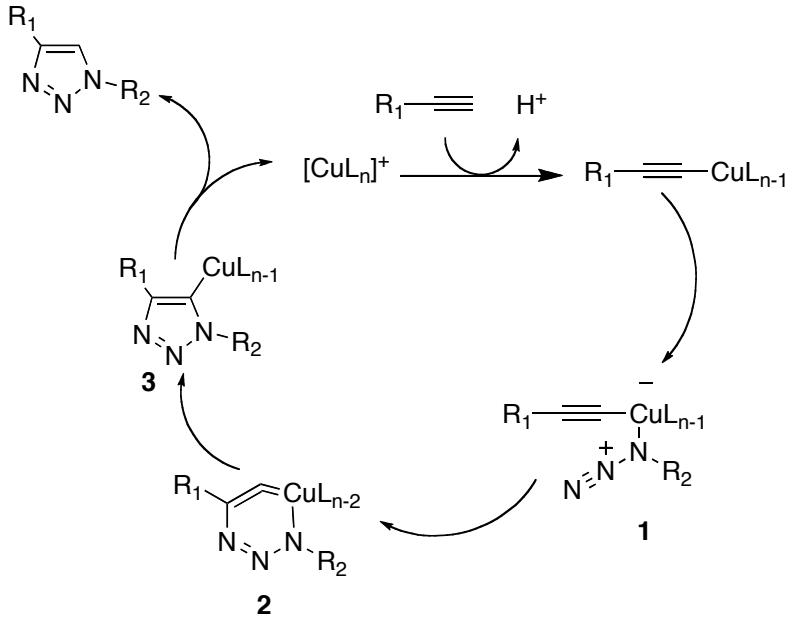


Scheme 1: *The triazole synthesis reported by Michael.*

The problems of the thermal azide-alkyne Huisgen cycloaddition were ironed out when Sharpless and Fokin[3] and Mendal[4], independently began working on metal catalysed azide-alkyne dipolar cycloadditions. They found that copper(I) salts catalysed the addition of azides to terminal alkynes at room temperature to give 1,4-substituted 1,2,3-triazoles as the sole product, often requiring no purification by column chromatography or recrystallization after workup, satisfying Sharpless' conditions to be included in the group of 'click' reactions.[5]

1.2 CuAAC Mechanism

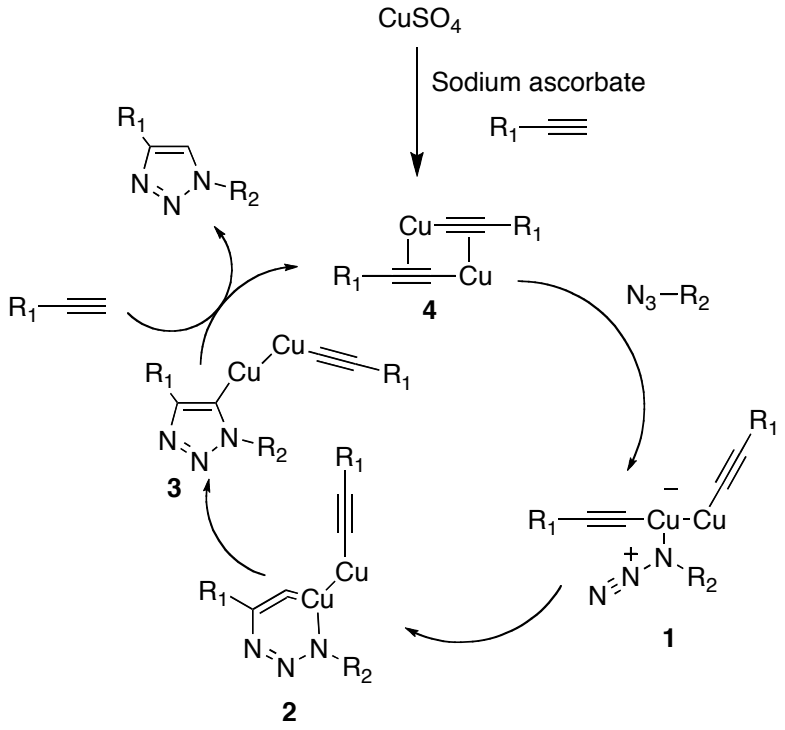
Despite the name, the mechanistic pathway of the copper-catalysed azide-alkyne cycloaddition (scheme 2) does not proceed via a concerted cycloaddition of the azide to the alkyne.[6] The alkynyl copper complex **1** is formed by C-H insertion of the terminal alkyne by copper, followed by coordination of the azide. Nucleophilic attack of the alkynyl π-bond to the terminal nitrogen of the azide gives an unusual 6-membered cyclic copper carbene **2**, elimination results in the 1,2,3-triazole as an organocuprate **3**, which undergoes further elimination to give the 1,4-substituted-1,2,3-triazole, and returning the copper catalyst.



Scheme 2: *The initially proposed CuAAC mechanism.*

Computational studies show that the activation energy of azide-alkyne cycloadditions, in which the copper catalyst acts as a π-Lewis acid, is higher than the classic copper free Huisgen 1,3-dipolar cycloaddition of azides to alkynes. However, it has been proposed that initially η^2-coordination of copper to the alkyne occurs, but rather than activating the alkyne towards cycloaddition with the azide, coordination lowers the pKa of the alkynyl proton, assisting with the C-H insertion of copper.[6]

In 2010 Heaney published a revision of this mechanism,[7] providing experimental and computational evidence for dimeric alkynyl cuprate ladderanes **4** as the active catalytic species, explaining their observation that mono-click products from CuAAC reactions of alkynes with bis-azides are rarely isolated as a second copper acetylide is in close proximity to the second azide, facilitating quick reaction. This observation could, however, also be explained by the ligation of the triazoles to the copper acetylides, once again bringing the reactive species together in close proximity.



Scheme 3: *Revised CuAAC mechanism.*

1.3 CuAAC Copper Sources and Ligands.

The active catalytic species may be generated from many sources. Copper metal may be used, often in the form of powder. Copper turnings[3] have also seen used, as well as, in the case of flow chemistry, the material from which the flow reactor tubing is made.[8]

The copper(I) species may also be generated by the reduction of copper(II) salts, most notably copper(II) sulfate by sodium ascorbate.[3] The advantage of these catalyst sources is the avoidance of the disproportionation of Cu^{I} to Cu^{0}/Cu^{II}, as well as not requiring the exclusion of oxygen, which would otherwise oxidise copper(I) to the catalytically inactive copper(II).

Copper(I) salts, such as copper chloride and copper iodide, however, it has been noted by Fokin[9] in a review of CuAAC chemistry that copper(I) iodide should be avoided in the use of CuAAC reactions as the iodide anion may act as a bridging ligand for the copper, interfering with the catalytic process. The use of copper(I) iodide may also result in the formation of iodoalkynes, and subsequently iodotriazoles. While the direct use of copper(I) salts requires the exclusion of oxygen from the reaction, it is the obvious choice should the use of ligands be desired in the reaction.

Ligands allow the tailoring of metal catalysed reactions to specific substrates, conditions, and reactions. Altering selectivity, improving turnover and stability, and increasing, or decreasing, activity. While investigation into the use of ligands in CuAAC is far from complete and remains somewhat disorderly, progress is being made. Of particular note among the ligands that have seen use in CuAAC is tris(benzyltriazolyl)methyl amine **5** (figure 1), synthesised by the CuAAC reaction of trispropargylamine and benzyl azides, as a chelating ligand reported by Fokin in 2004.[10] This class of tridentate ligand (figure 1) not only stabilised copper(I) towards oxidation and disproportionation, but also accelerated the reaction rate.[11] Further development of this class of ligand focused on increasing their water solubility. In 2008, Finn and co-workers, designing conditions for CuAAC bioconjugation reactions, employed a simple modification of the tris(benzyltriazolyl)methyl amine ligand **6** in which the benzyl moieties were

furnished with para-carboxylates, increasing the water solubility of the copper-ligand complex, for use in the in-situ electrochemical reduction of copper(II) salts. In 2009, furthering the previous work on bioconjugation CuAAC reactions, Finn reported[12] the use of another water soluble analogue of this ligand class, tris(3-hydroxypropyltirazolylmethyl)amine, THPTA **7**.

The same year, Pericàs and co-workers also reported on the synthesis and application of a tris(triazolyl) ligand, tris(triazolyl)methanol[11] **8**, synthesised by the CuAAC reaction of benzyl azide with tris(alkynyl)carbinol. The resulting complex with copper(I) chloride was used in a range of CuAAC reactions performed in the standard butanol/water solvent system.

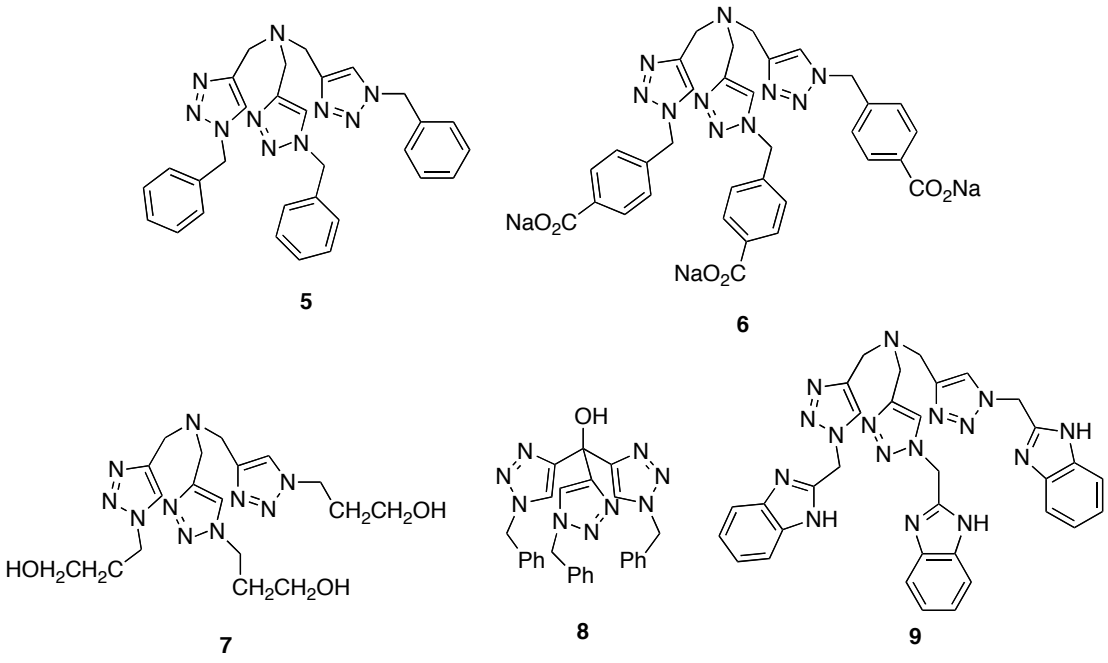


Figure 1: *Tris(triazolyl) ligands synthesised by CuAAC*

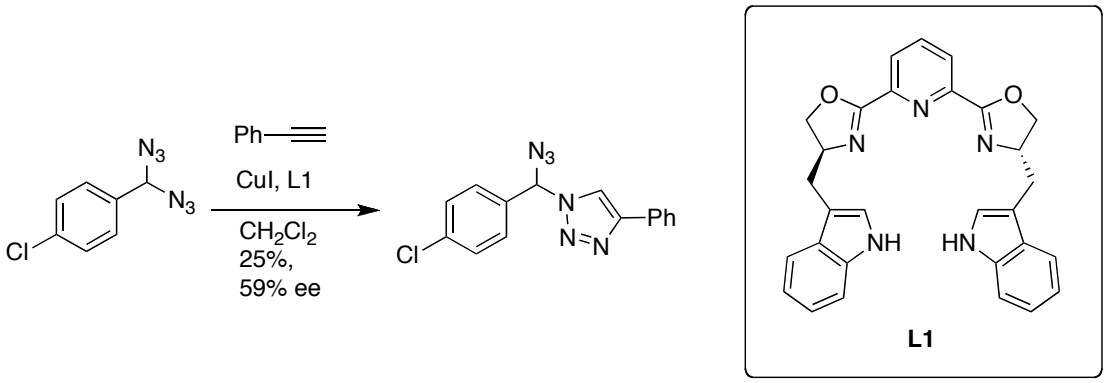
The structurally related tris(2-benzimidazolylmethyl)amine ligand **9** reported by Finn and co-workers highly accelerated the rate of CuAAC reaction. Their standard screening reaction gave only 10% conversion after 1 hour, while the introduction of the ligand to the reaction resulted in 100% conversion after 1 hour.

As well as reaction rate acceleration and catalyst stabilisation, another practical benefit of the use of ligands in CuAAC reactions is the solubility of the copper

complexes in organic solvents. In 2003, Santoyo–González and co-workers reported the use of copper(I) phosphine complexes, specifically, tris(triphenylphosphine)copper(I) bromide and tris(triethyl phosphite)copper(I) iodide, in the catalysis of the cycloaddition reaction of azides with sugar-derived alkynes performed in toluene.[13]

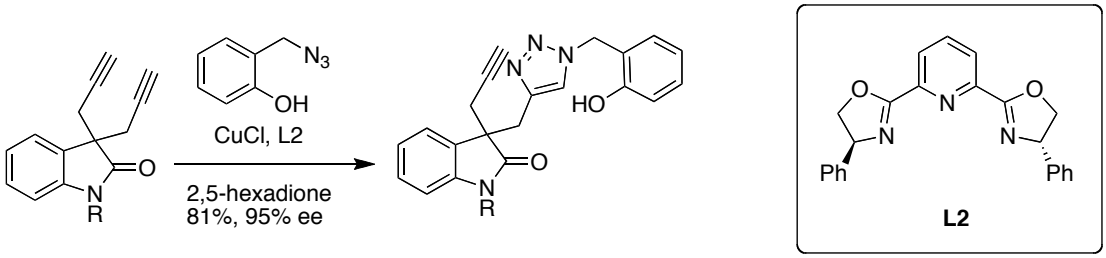
1.4 Asymmetric CuAAC

Reports of asymmetric CuAAC reactions are few, with three known examples, all of which focus on the desymmetrization of bis-functionality. The first example[14] was the kinetic resolution of bis-azides in the presence of chiral bis-oxazoline and bis-oxazolinylpyridine ligands (scheme 4).



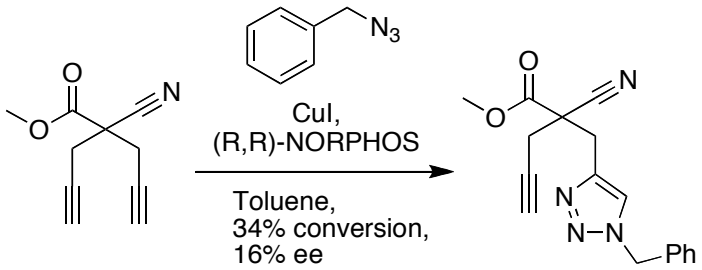
Scheme 4: *Desymmetrization of prochiral bis(azides)*

The two remaining known examples concern the desymmetrization of bis-alkynes. Zhou and co-workers reported the reaction of bis-alkyne derivatives of *N*-protected oxindoles with various azides (scheme 5) in the presence of (*R*)-phenyl-pybox ligands, yielding chiral 1,2,3-triazoles with enantiomeric excess of up to 98%.[15] The reaction is substrate, solvent, and ligand dependant. Oxindole derivatives with electron-withdrawing *N*-acyl substituents exhibited lower ee% than the more electron rich *N*-alkyl substituents. The azide also affected the yield and the enantioselectivity of the reaction, with the best results coming from the use of 2-azidophenol. However, neither *N*-substituent or azide identity affected the yield and enantiomeric excess as much as the solvent choice. Interestingly, while DCM gave somewhat respectable results, hexane-2,5-dione was required to reach the high yields and enantioselectivity quoted in their title reaction. While the authors do not comment on the role of hexane-2,5-dione in their report, the ketone functionality seems to be particularly important as acetone, butanone, 2-pentanone, and 3-pentanone all gave 75% ee or greater.



Scheme 5: *Desymmetrisation of prochiral bis(alkynes) with pybox-copper complexes.*

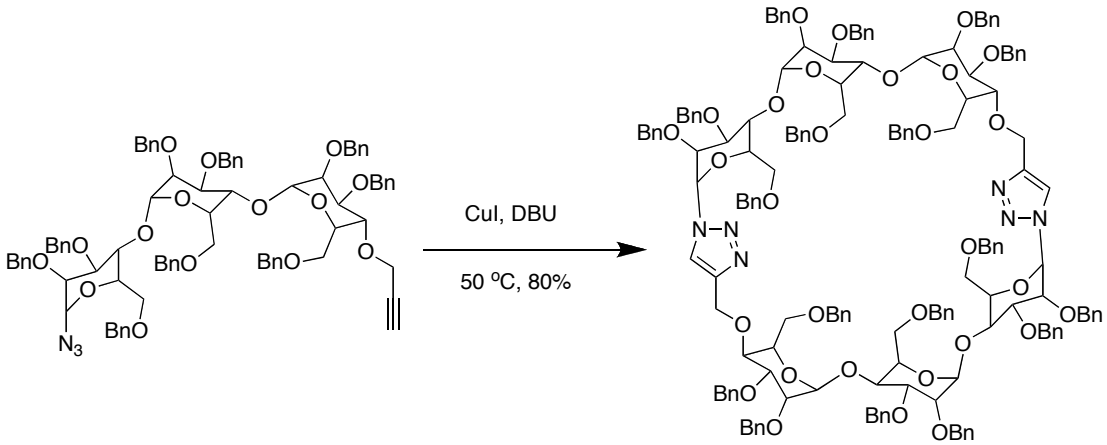
Our group has also provided examples the desymmetrization of bis-alkyne functionality using the CuAAC reaction in the presence of chiral bidentate phosphine ligands (scheme 6).[16]



Scheme 6: *Desymmetrisation of prochiral bis(alkynes) with phosphine-copper complexes.*

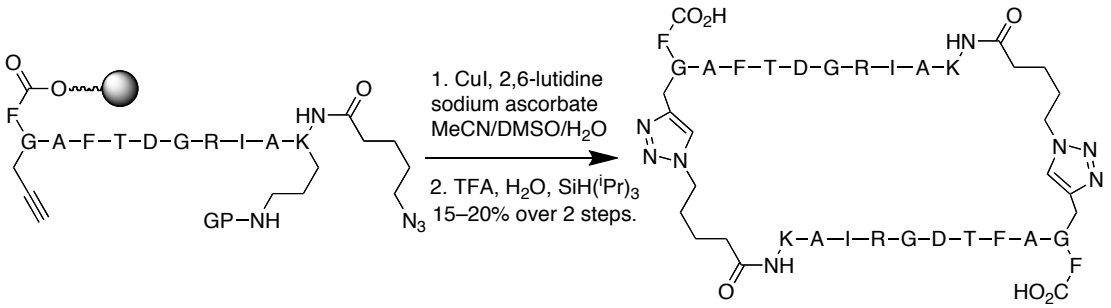
1.5 CuAAC in the synthesis of macrocycles

In 2005 Gin, at the University of Illinois, utilised a CuAAC in the heat-to-tail cyclodimerization of a trisaccharide.[17] The trisaccharide, consisting of 1,4-linked mannose featuring units featuring azide and propargyl ether functionalities, was found to undergo cyclodimerization when heated in toluene, however the reaction was sluggish and produced a mixture of products. Heating the trisaccharide in toluene at 50°C in the presence of CuI and DBU gave the desired dimeric macrocycle in 80% yield, as well as the corresponding trimer in 15% yield (scheme 7.)



Scheme 7: *Macrocyclic trisaccharide dimer.*

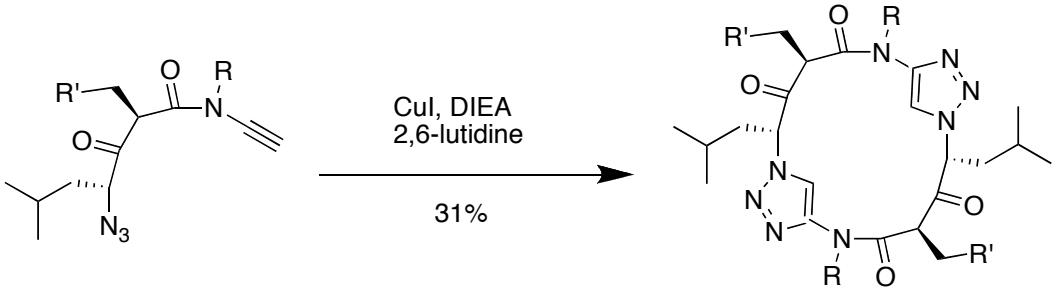
In the same year, Finn, at The Scripps Research institute, employed CuAAC in the head-to-tail cyclodimerization[18] of resin-bound peptides, at room temperature in the presence of CuI, 2,6-lutidine and sodium ascorbate (scheme 8.)



Scheme 8: *Marcocyclic polypeptide dimer.*

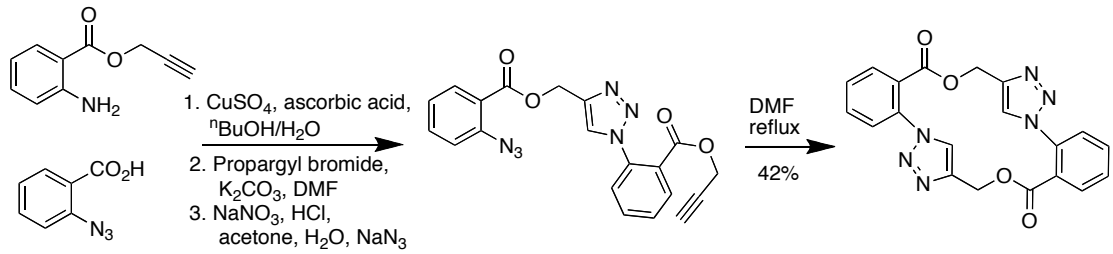
Ghadiri, also at Scripps, employed CuAAC for the cyclodimerization of various dipeptides,[19] again using CuI as the Cu^{I} source, in DIEA and 2,6-lutidine, with

yields ranging from 70% to 80% (scheme 9.) The group also utilized $Cu(OAc)_2/Cu$ as the Cu^I source, in the presence of tris(benzyltriazolyl)methyl amine in 69% yield. As well as the C_2-symmetric dimeric macrocycles, a non-symmetric macrocyclic peptide was synthesised, by reaction between two dipeptides, giving a 1:1 mixture of homo- and hetero-dimeric products, from which the desired non-symmetric macrocycle was isolated in 31% yield.



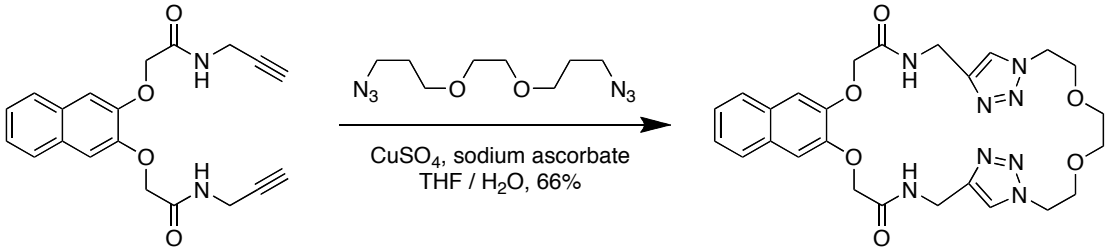
Scheme 9: *Macrocyclic dipeptide dimer.*

Hradil and co-workers reported a stepwise synthesis of macrocyclic dimers, utilising both the CuAAC reaction and the catalyst-free thermal Huisgen azide-alkyne cycloaddition reaction.[20] After a room temperature copper(II) sulfate/ascorbic acid mediated CuAAC reaction between propargyl anthranilate and the propargyl ester derived form the 2-azidobenzoic acid, the remaining carboxylic acid and amine functionalities were converted to a propargyl ester and azide, respectively, in good yields. Refluxing in DMF resulted in the azide-alkyne cycloaddition, affording the desired macrocycle (scheme 10.) Using the same process, the group was also able to synthesise the corresponding trimeric and tetrameric macrocycles.



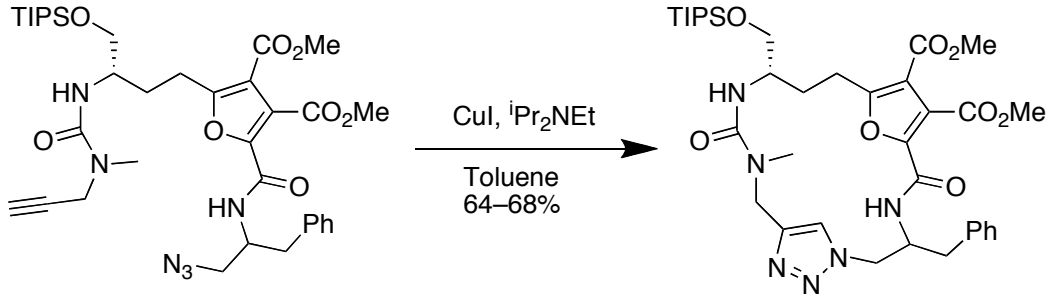
Scheme 10: *The CuAAC dimerisation to 16-membered macrocycles.*

In 2007,[21] non-dimeric C_2-symmetric 1,2,3-triazole containing macrocycles were synthesised by the copper sulfate/sodium ascorbate catalysed azide-alkyne cycloaddition between C_2-symmetric diacetylenes and diazides (scheme 11.)



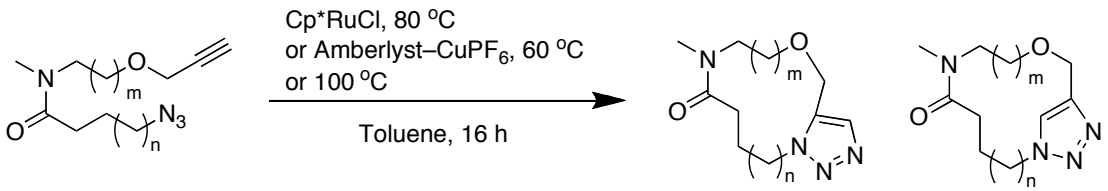
Scheme 11: *Non-dimeric 2-componant macrocycle synthesis*

As an example of non-symmetric 1,2,3-triazole containing macrocycles, Schreiber and co-workers reported the use of a CuAAC reaction in the ring-closing macrocyclization reaction of molecules exhibiting alkyne and azide functionality at opposite termini[22] (scheme 12.) The reported macrocyclic molecules also contain functionality often found in macrocyclic marine natural products, with the furan and urea being of particular note.



Scheme 12: *Highly functionalised 1,2,3-triazole containing macrocycle.*

In 2009, Marcaurelle and co-workers reported an investigation into the use of azide-alkyne cycloadditions mediated thermally, as well as by copper and ruthenium catalysis, in the synthesis of macrocycles from substrates of varying lengths[23] (scheme 13.)

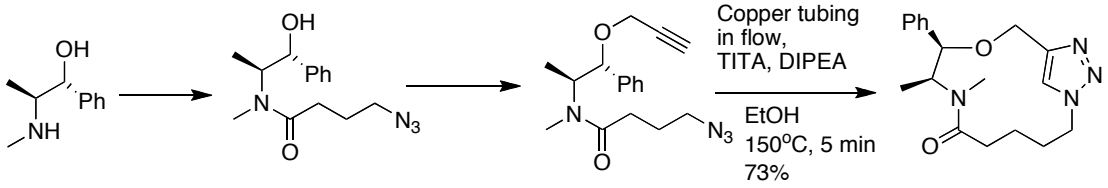


chain length	catalyst	% yield	ratio (1,5:1,4)
n, m = 1, 1	Ru	60	100:0
n, m = 1, 1	Cu	37	0:100
n, m = 1, 1	Thermal	–	80:20
n, m = 1, 2	Ru	61	100:0
n, m = 1, 2	Cu	48	0:100
n, m = 1, 2	Thermal	–	75:25
n, m = 2, 1	Ru	54	100:0
n, m = 2, 1	Cu	40	0:100
n, m = 2, 1	Thermal	–	80:20

Scheme 13: *Macrocycle synthesis by ruthenium catalysed, copper catalysed, and thermal azide-alkyne cycloadditions.*

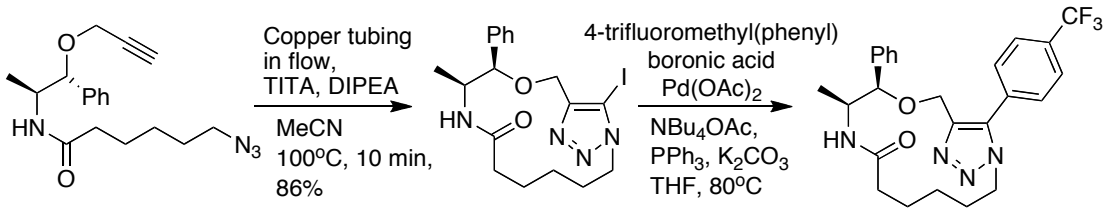
While the thermal Huisgen azide-alkyne cycloaddition gave the less constrained 1,5-substituted triazole as the major product, with the 1,5-subsituted to 1,4-substituted product ratio decreasing as the carbon chain length in the substrate increased, the ruthenium catalysed cycloaddition gave only the 1,5-substituted triazole and the copper catalysed cycloaddition gave, unsurprisingly, only the more constrained 1,4-substituted triazole containing macrocycles, though in lower yields than the corresponding macrocycles accessed via ruthenium catalysis.

James reported, in 2010, efficient access to a variety of 1,4-substituted-1,2,3-triazole-containing macrocycles by intramolecular CuAAC flow chemistry, utilising the copper tubing of the flow reactor as the copper source[8] (scheme 14). Such application of flow chemistry to perform intramolecular CuAAC reactions avoids the problems inherit with the high dilution conditions commonly employed in macrocyclizations, such as high solvent volume and long reaction times. Simple syntheses from a variety of chiral-pool starting materials gave quick access to precursors with both alkyne and azide functionality on which intramolecular CuAAC reactions could be performed.



Scheme 14: *CuAAC in the synthesis of macrocycles containing 1,4-disubstituted-1,2,3-triazoles under flow conditions..*

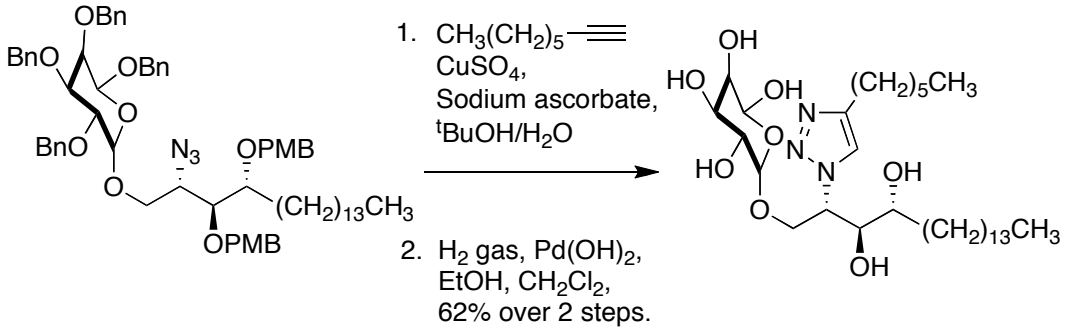
Building on this work, they later reported the synthesis of 1,4,5-trisubstituted-1,2,3-triazole-containing macrocycles under flow conditions.[24] The synthesis was achieved by the use of 1-iodoalkynes, in place of terminal alkynes (scheme 15), in the CuAAC reactions, followed by palladium catalysed coupling of the 5-iodo-1,2,3-triazole. In both these applications of flow CuAAC reactions, a ligand additive, (1-*tert*-butyl-1H-1,2,3-triazolyl)methyl amine, TTTA, member of the previously mentioned tris(triazolyl) ligand class, was employed and found to be essential to obtaining high yields.



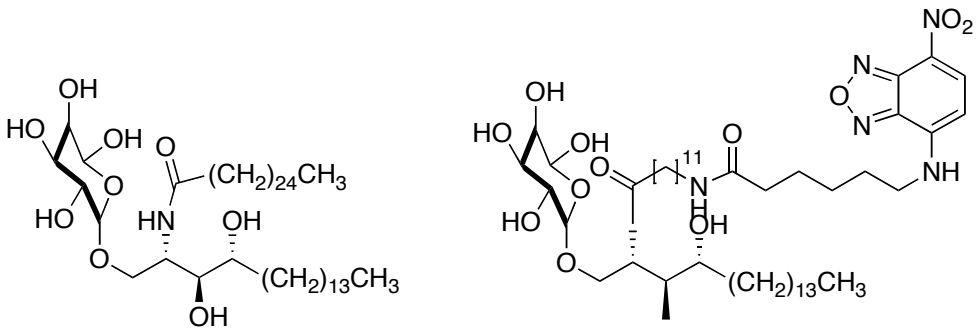
Scheme 15: *CuAAC in the synthesis of macrocycles containing 1,4,5-trisubstituted-1,2,3-triazoles.*

1.6 CuAAC in the synthesis of natural product analogues

Due to it's modular nature, and functional group tolerance, the CuAAC reaction is well suited to drug discovery, as a result, it has been used in the synthesis of biologically active natural product analogues. In 2007, Kim and co-workers[25] used copper catalysed azide-alkyne cycloadditions to synthesise analogues (scheme 16) of α-GalCer **10**, a potent agonistic antigen of αβ T cell receptors and analogue of the marine natural product α-galactosylceramide **11** (figure 2), replacing the amide functionality with triazoles.



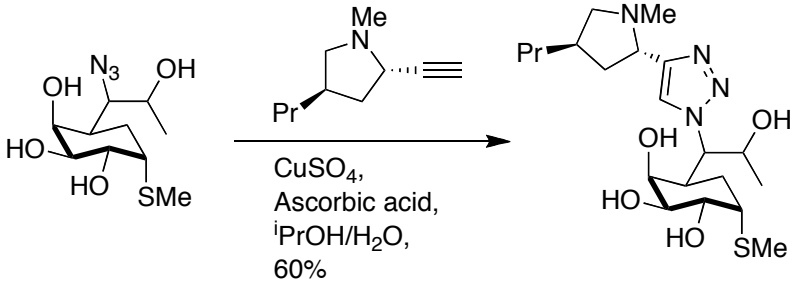
Scheme 16: *The CuAAC synthesis of α-GalCer analogues.*



10 **11**

Figure 2: *α-GalCer and α-galactosylceramide*

Another example of amide linkers being mimicked by 1,4-substituted 1,2,3-triazoles in analogue synthesis is that reported in 2008 by Vasella and co-workers,[26] who reported the use of the CuAAC in the synthesis of lincomycin analogues (scheme 17), a broad-spectrum antibiotic isolated from the bacterium *Streptomyces lincolnensis*.



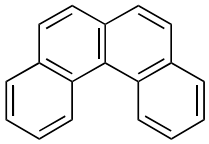
Scheme 17: *The CuAAC synthesis of lincomycin analogues.*

1.7 Carbohelicenes

Helicenes are polycyclic aromatic compounds exhibiting helical chirality due to the 'screw' shape, arising from steric interaction as the ortho-fused rings curl in on themselves. When the helical structure consists solely of carbon it is known as a carbohelicene, or simply helicenes. The standard nomenclature of carbohelicenes, avoiding complex IUPAC nomenclature, involves prefixing 'helicene' with the number of fused aromatic cycles it contains either using the number in brackets or the Greek prefix, for example in the case of the carbohelicene consisting of six ortho-fused benzene rings, [6]helicene, or hexahelicene.

1.8 Carbohelicene syntheses

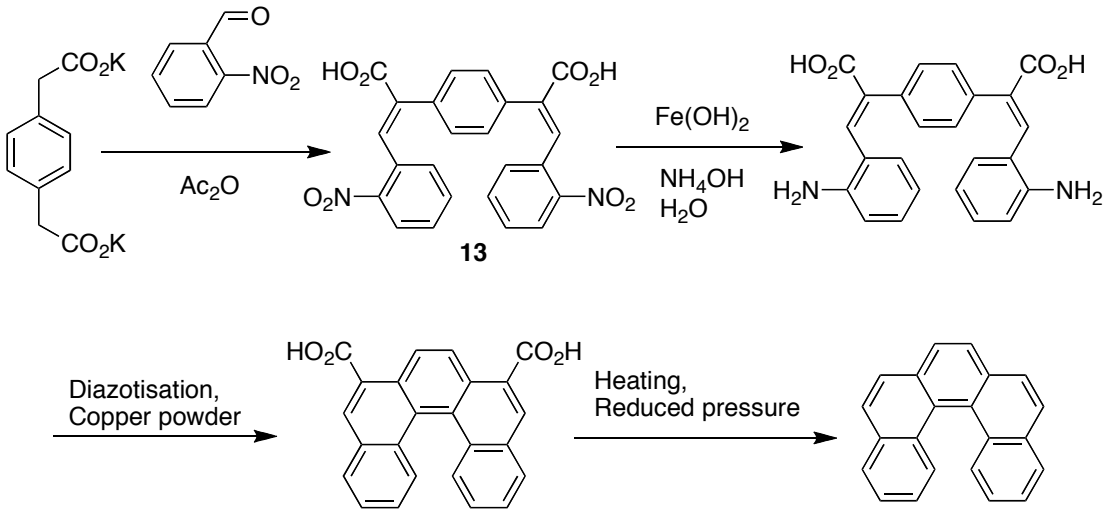
The smallest helicene which exhibits distortion of the π-system is [4]helicene **12**, first synthesised a hundred years ago in 1912.[27]



12

Figure 3: *[4]helicene*

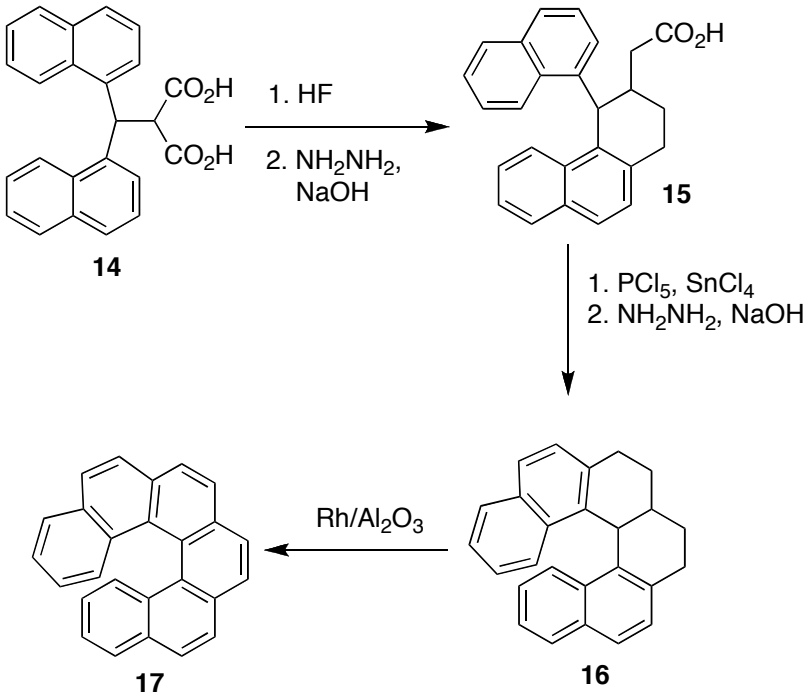
This was followed by the synthesis of [5]helicene, published in 1918 by Weitzenböck and Klingler.[28] Potassium 1,4-phenylenediacetate was heated with 2-nitrobenzaldehyde in acetic acid to give the stilbene **13**. Reduction by iron (II) hydroxide in aqueous ammonium hydroxide, followed by aromatic coupling via the diazonium salts in a Pschorr reaction, and decarboxylation yielded the [5]helicene and the linear regioisomer. The two regioisomers were separated and purified by recrystallization (scheme 18).



Scheme 18: *The first published synthesis of [5]helicene.*

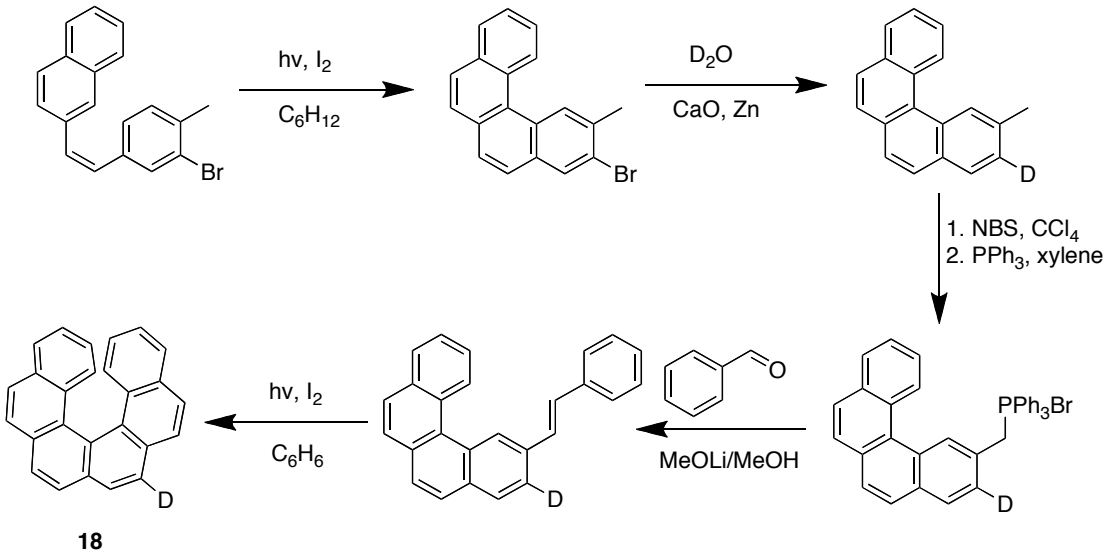
The synthesis of [6]helicene (scheme 19) was then published in 1956 by Newman,[29] though they had reported that they had achieved the synthesis and resolution of the molecule in a communication the previous year.[30] Bis(naphthalene) **14** was synthesised in five steps from 1-naphthaldehyde, a

subsequent hydrogen fluoride mediated ring closure followed by Wolff-Kishner reduction gave the tricycle **15** . A second ring closure, mediated by phosphorous pentachloride and stannic chloride, followed by another Wolff-Kishner reduction gave the fused hexacyclic helical molecule **16** . Oxidation by rhodium on alumina furnished the fully aromatic [6]helicene **17** .



Scheme 19: *The first published synthesis of [6]helicene.*

In 1967 two reports of photochemical helicene syntheses emerged, Scholz's synthesis of [5]helicene,[31] and Flammang-Barbieux's synthesis of [7]helicene.[32] Both syntheses employ a photochemically-induced intramolecular coupling of stilbenes. These reports were quickly followed up by the photochemical syntheses of [6]helicene, [8]helicene, and [9]helicene.[33] The next year a photochemical synthesis of deuterated [6]helicene (scheme 20) was devised.[34] The position of the deuterium label was chosen so that it would be retained in the helicene product, but would be lost in the alternative regioisomer (see Figure 4). With this labeled substrate, mass spectrometry could be used to differentiate between the desired helicene **18** and the corresponding deuterium-free linear isomer **19**.



Scheme 20:

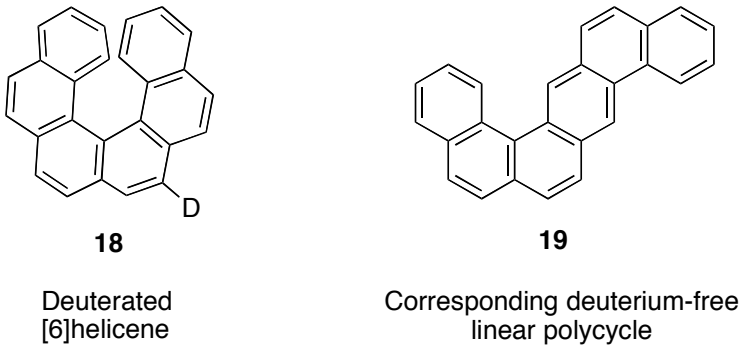


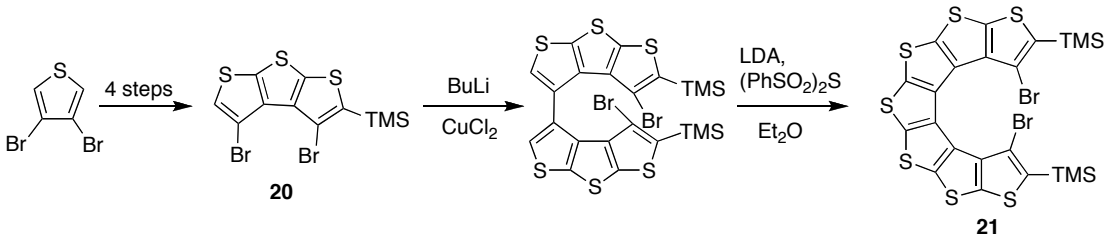
Figure 4: *Isomeric helical and linear fused aromatic systems.*

These were shortly followed by the photochemical syntheses of [11]helicene, [12]helicene, and [14]helicene.[35]

1.8 Heterohelicene syntheses

Related to the carbohelicenes are heterohelicenes, helicenes consisting of, or containing, fused aromatic heterocycles. An elegant example of this class of helicene is the synthesis of a heterohelicene consisting of seven fused thiophenes (scheme 21).[36]

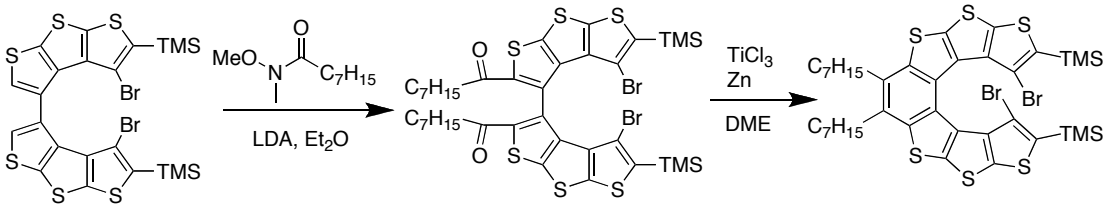
.



Scheme 21: *Synthesis of heptathiophene.*

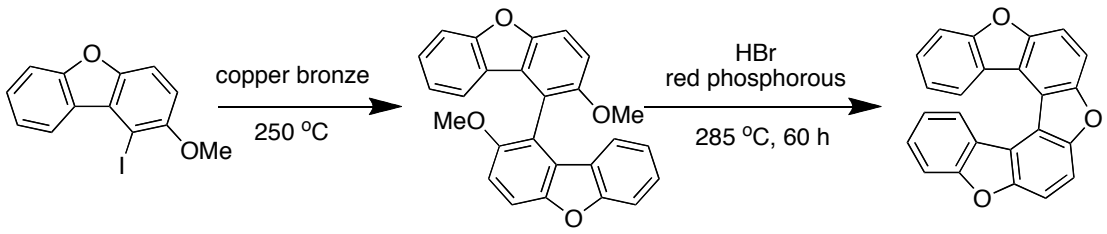
Starting from 3,4-dibromothiophene, the fused tricycle **20** was synthesised in four steps. After lithium-halogen exchange followed by $CuCl_2$-mediated coupling, deprotonation and subsequent attack onto an electrophilic source of sulfur furnished the heterohelicene **21**.

Another thiophene-based heterohelicene synthesis was published by the same group,[37] this time using the fused tricyclic thiophene ketone and utilising a McMurry reaction to close the final ring, producing the helicene **(Scheme 22)**.



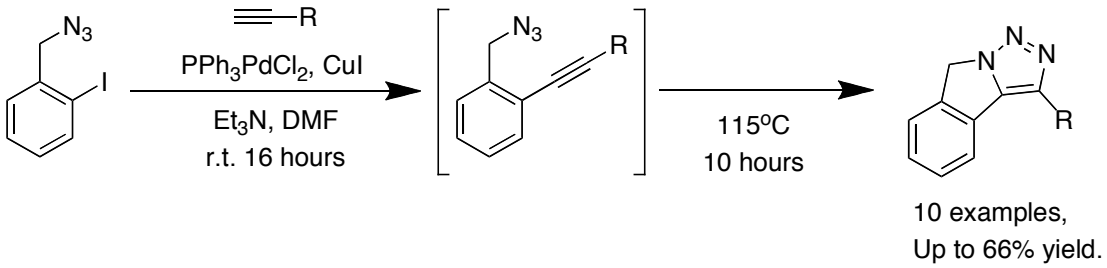
Scheme 22: *The utilisation of the McMurry reaction as the final step in a heterohelicene synthesis.*

Previous to these syntheses, and very much in the same vein, was the 1973 synthesis of furan-based heterohelicenes reported by Högberg.[38] In which a copper-mediated coupling of the fused tricycle was followed by alcohol deprotection and ring closure to give the heterohelicene (scheme 23.)



Scheme 23: *The synthesis of a heterohelicene exhibiting fused furans.*

In 2005, Chowdhury and coworkers published a copper- and palladium-mediated annulation of 2-iodobenzyl azide with various terminal alkynes, yielding fused tricyclic triazoles[39] (scheme 24). The reaction proceeds over 26 hours, with the first 16 hours being the ambient temperature Sonogashira coupling of the alkyne to the aryl iodide. The temperature of the one-pot reaction is then increased to 115°C for 10 hours to perform the copper mediated azide-alkyne cycloaddition. The group later published findings that showed the reaction is improved by heating at 115°C for a short period of time.



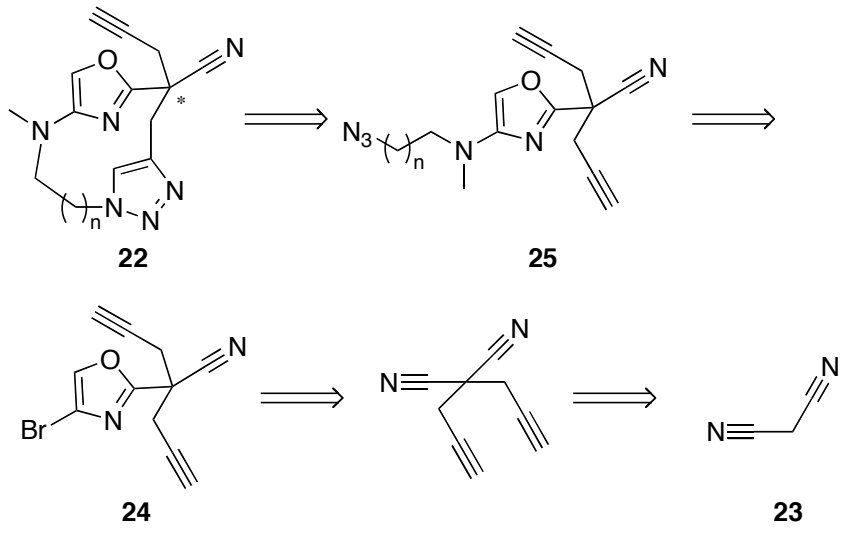
Scheme 24: *Tandem Sonogashira/cycloaddition synthesis of fused tricycles.*

The mechanism of this cycloaddition reaction differs from the conventional CuAAC reactions of terminal alkynes. Computational studies predict that the transition states of the pi-Lewis acid copper-mediated cycloaddition of azides to terminal alkynes are higher than the traditional catalyst-free Huisgen 1,3-dipolar cycloaddition. However, previous work in our group[39] has shown that the intramolecular cyclization of the azide with the alkyne in this reaction only proceeds in the presence of copper.

2.0 Results and Discussion

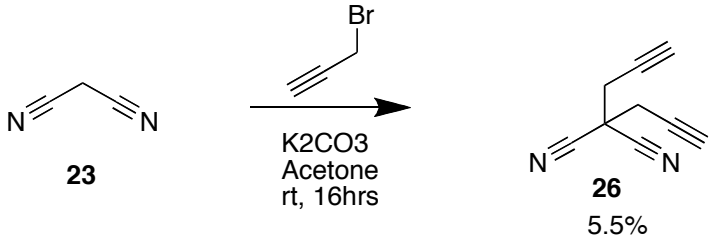
2.1 Studies towards the asymmetric CuAAC reaction synthesis of macrocycles.

The aim of this project was to apply the asymmetric CuAAC reaction intramolecularly as the ring-closing step in the synthesis of enantioenriched 1,2,3-triazole-containing macrocycles. As we wished to demonstrate that this methodology could be applied to the synthesis of natural product analogues, the envisioned target **22** would exhibit an oxazole, due to their appearance in many macrocyclic marine natural products. Our retrosynthetic analysis (scheme 25) led us to malonitrile **23**, a cheap and commercially available starting point. Malonitrile contains two acidic protons alpha to electron-withdrawing groups, allowing the installation of the 1,6-diyne motif, as well functionality that may be converted to an oxazoline, which may then by oxidized to the 2-alkyl-4-bromooxazole **24** by *N*-bromosuccinimide. A long carbon chain terminating in an azide could then be incorporated by a Buchwald-Hartwig coupling reaction. Finally, a CuAAC reaction in the presence of a chiral ligand would result in enantioselective macrocyclization to give **22**.



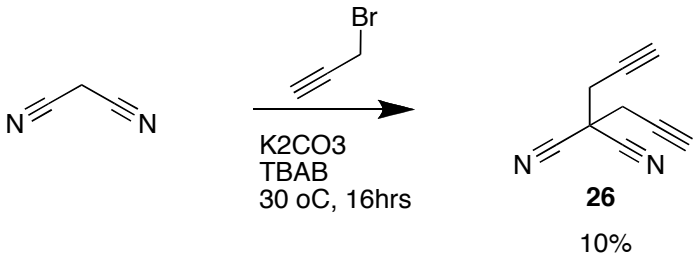
Scheme 25: Retrosynthetic analysis of 1,2,3-triazole-containing macrocycle, **22**.

For our first approach to the desired 2-oxazoline for oxidation to the 4-bromo-2-oxazole we intended to use a zinc-catalysed method to produce non-symmetric bis-oxazoline ligands from disubstituted malononitriles reported by García and Pires[41]. Starting from malononitrile the *bis*-propargyl motif was installed, giving **26** in the poor yield of 5.5%, by the reaction of malononitrile **23** with propargyl bromide and potassium carbonate in acetone (scheme 26).



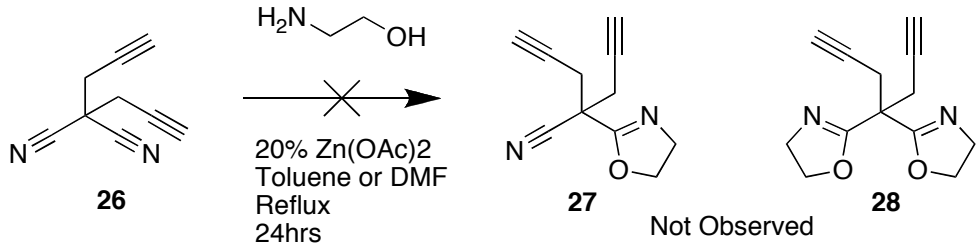
Scheme 26

Carrying out this reaction at a higher temperature, in the absence of solvent and the presence of tetrabutylammonium bromide, as a phase transfer catalyst to transport the carbonate anion into the organic phase[42], increased the yield of **26** to 10% (scheme 27), providing enough material, though the reaction was still low yielding, to proceed with the investigation.



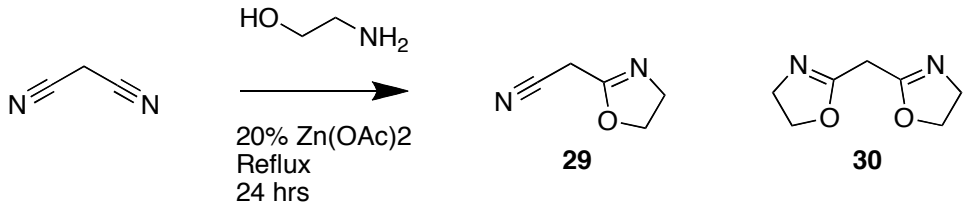
Scheme 27

Reaction of the disubstituted malononitrile **26** with 2-ethanolamine in the presence of zinc(II) acetate did not yield any of the desired oxazoline **27**, nor the corresponding *bis*-oxazoline **28** (scheme 28). This is likely to be a result of the zinc(II) salt coordinating preferentially to the alkynes.



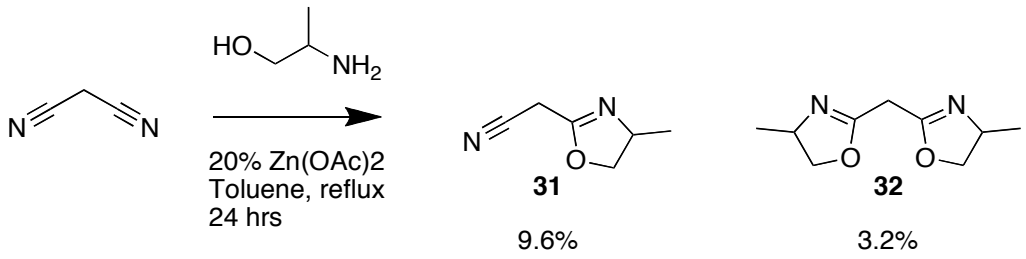
Scheme 28

To avoid the problem discussed above, it was decided that modification of the nitrile functionality to the oxazoline should be performed first (scheme 29), installing the *bis*-propargyl later in the synthesis. The reaction yielded none of the desired oxazoline **29**, and trace amounts of the undesired *bis*(oxazoline) **30**, as determined by the characteristic peaks of two triplets at 4.24 ppm and 3.70 ppm, each integrating as 4H, and a singlet at 4.04 ppm integrating as 2H in the ^{1}H NMR spectrum.



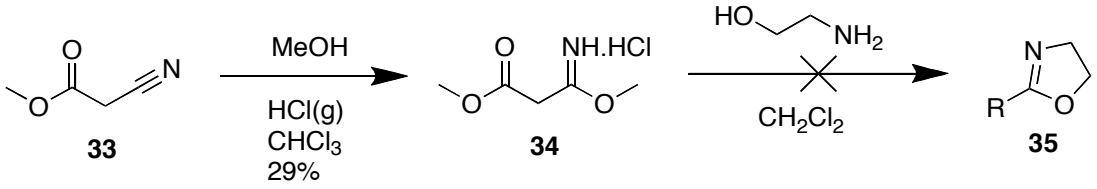
Scheme 29

It was reasoned that the lack of reaction was a result of the low solubility of 2-ethanolamine in toluene. To test this theory the condensation was attempted with the more toluene soluble substituted alcohol amine, 2-aminopropanol (scheme 30). While this reaction produced the *mono*-oxazoline **31**, the yield remained unsatisfactory, and the product was unsuitable for oxidation to the desired 4-bromooxazole.



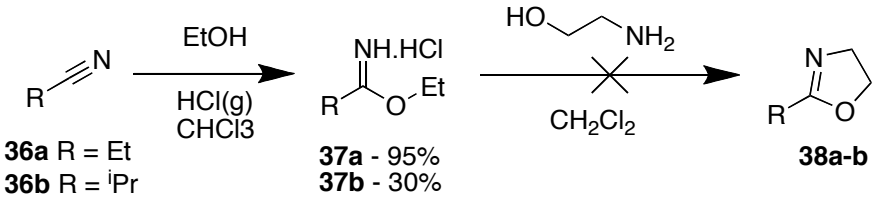
Scheme 30

An alternative route to prepare oxazolines from nitriles proceeds *via* imidate esters (scheme 31). The nitrile chosen for this preparation was methyl cyanoacetate **33** as the acidic protons alpha to the carbonyl should facilitate the introduction of the *bis*-propargyl motif later in the synthesis. Reaction between methyl cyanoacetate **33** and methanol in the presence of dry hydrogen chloride yielded the hydrochloride salt of the desired imidate ester **34**. However, the attempted condensation with 2-ethanolamine did not yield the desired 2-oxazoline **35**.



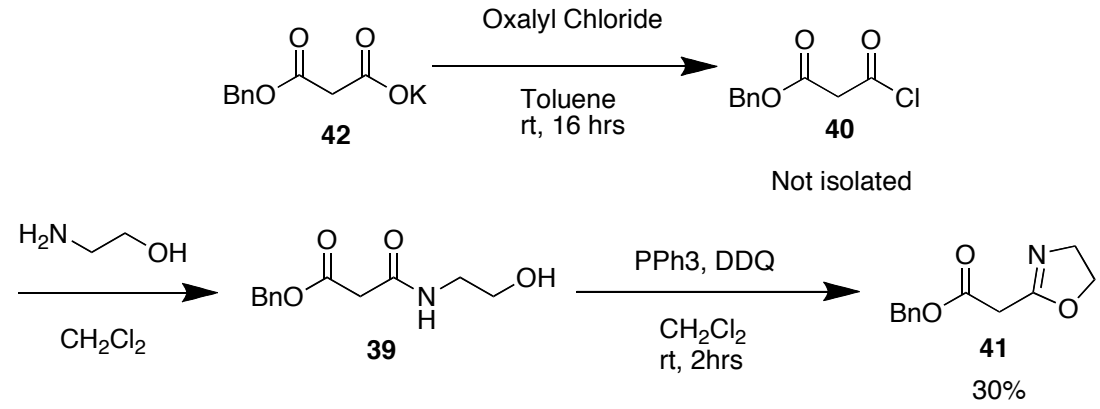
Scheme 31

The use of alternative nitriles, ethyl nitrile **36a** and isopropyl nitrile **36b** similarly yielded the respective hydrochloride salts of the imidate esters **37a-b**, but subsequent reaction of either with 2-ethanolamine did not yield the desired 2-oxazolines **38a** and **38b** (scheme 32).



Scheme 32

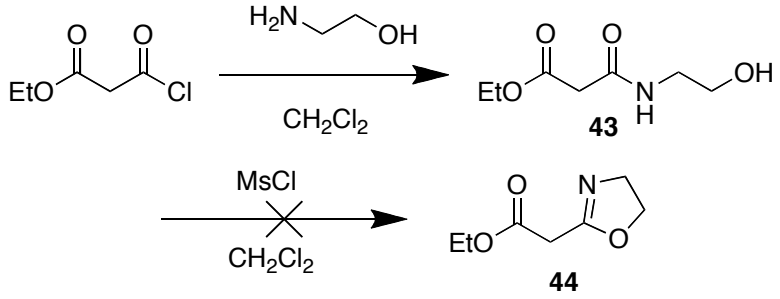
And alternate route to oxazolines proceeds via a cyclization of the N-(2-hydroxyethane) amide **39**, synthesized by the attack of ethanolamine to the acyl chloride **40**. A dehydrative cyclization employing DDQ and TPP yielded the desired oxazoline **41** in 30% yield from the potassium salt of the benzyl malonic half-ester **42** (scheme 33). The reaction likely proceeds via the nucleophilic attack of TPP to the quinone to give the phenoxide zwitterion, activating the phosphine towards nucleophilic attack. Displacement of the phenoxide by the N-ethan-2-ol amide activated the amide for base mediated cyclization.



Scheme 33

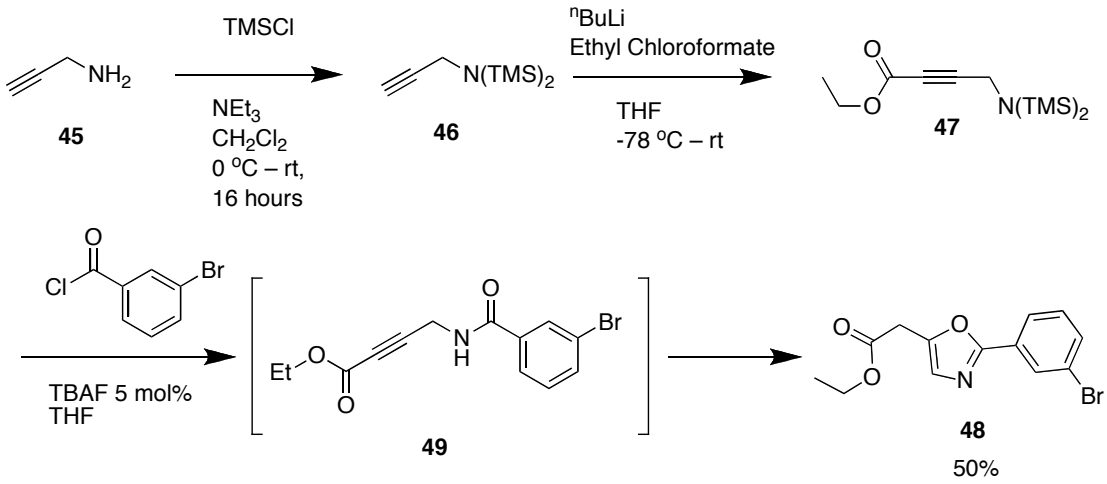
However, the unpleasant nature of the workup, requiring repeated washing to remove the unreacted DDQ and TPP led us to seek an alternate cyclization method.

A simple procedure involving the methylsulfonylation of **43** allows the cyclization to the oxazoline **44** to occur at ambient temperatures in the presence of triethylamine. However, when attempted with the ethyl malonate derived amide, the reaction was unsuccessful (scheme 34).



Scheme 34

Oxazoles may be synthesized directly by Lewis acid mediated cyclizations of propargyl amides, utilizing transition metal catalysis or silica gel. By this method, we could rapidly construct the desired heterocycle, with desirable functionality for the introduction of both the bis-alkynes and the long carbon chain terminating in the azide (scheme 35). Starting with propargylamine **45**, protection of the nitrogen with trimethylsilyl chloride to give **46** allowed the formation of an alkynyl ester, **47**. Surprisingly, a one pot deprotection and amidation, in the presence of catalytic TBAF, yielded the desired oxazole, **48** after column chromatography, and not the propargyl amide, **49**.

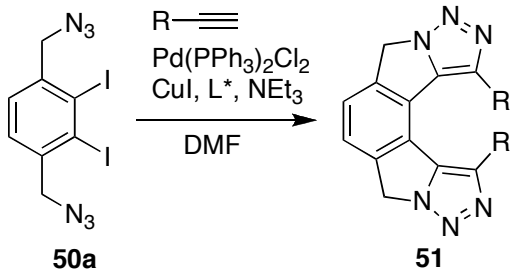


Scheme 35

Overnight reaction in the presence of silica gel or triflic acid resulted in no reaction. A D_2O shake also resulted in no significant change to peak intensity in ^1H NMR, as would be expected in the case of the propargyl amide. Possible explanations for this may be the acidic nature of the TMSCl formed in the reaction, or trace water hydrolysing the acid chloride to give benzoic acid. However it is more likely that the cyclization occurred during purification by column chromatography. The crude product was dry loaded onto silica gel, a process involving the removal of solvent, in this case dichloromethane, from a solution of the crude mixture in the presence of silica gel by rotary evaporation. Heating the alkyne **49** in the presence of Lewis acidic silica gel in this way may have resulted in the rearrangement.

2.2 Studies towards the asymmetric CuAAC reaction synthesis of heterohelicenes.

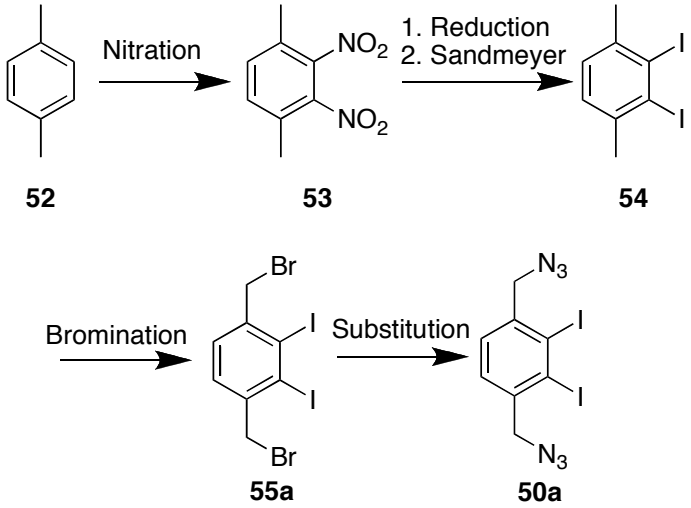
Expanding upon the work of Chowdhury[39] (scheme 24), it was rationalized that applying this methodology to the corresponding symmetric dibenzyl azide, **50a**, would produce fused-pentacyclic compounds exhibiting helical chirality **51** (scheme 36).



50a **51**

Scheme 37

Furthermore, it was envisaged that use of a chiral catalyst would result in an enantioselective *intra*molecular azide-alkyne cycloaddition, producing enantioenriched helical molecules. It was planned to access the dibenzyl azide **50a** from *para*-xylene **52** in five steps (scheme 38).

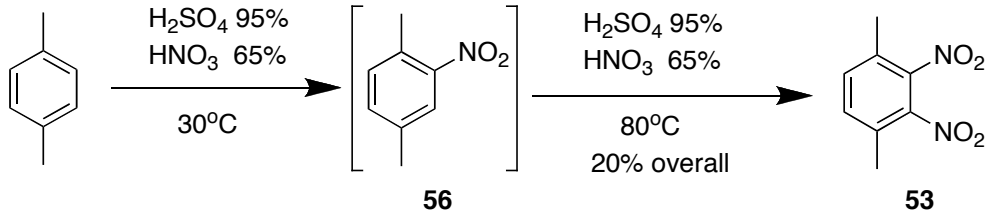


52 **53** **54**

55a **50a**

Scheme 38

In a two-pot procedure, *para*-xylene was nitrated using a nitrating mixture of sulfuric acid (95%) and nitric acid (65%), first at room temperature to produce the *mono*-nitrated product **56**, and then at 80°C, to produce 1,2-dinitro-3,6-dimethylbenzene **53** (scheme 39).



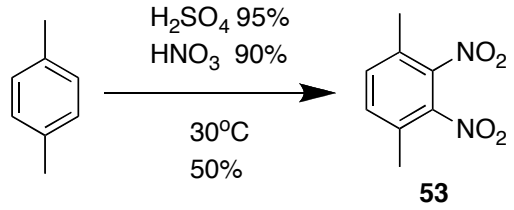
Scheme 39

It has been reported[43] that purification can be achieved by successive recrystallizations from ethanol, removing the less soluble nitroxylene **56** and 1,3-dinitroxyelene products. Our group, without success, previously attempted to purify the 1,2-dinitroarene **53** in this manner. In this work, the process was once more attempted, however, first a recrystallization from hot acetic acid was performed to remove impurities other than the aforementioned nitroxylene and two dinitroxylenes, again without success. A more thorough description of the recrystallization for this synthesis was given by Kobe and Hudsen,[44] who describe the process taking weeks, and requiring the hand picking of desirable crystals.

Purification of this reaction by column chromatography, in which a large solvent gradient must be used, is vastly improved if a recrystallization from hot acetic acid is first performed, allowing a smaller mass/mass ratio of silica gel to be used with a single solvent system, rather than a gradient.

Previous work in the group[40] showed that when more concentrated nitric acid is used for the nitration, yields were somewhat increased, with 70% nitric acid giving 21% yield of the desired dinitro arene **53**. Taking the observed increase in yield with increased nitric acid concentration into consideration, the nitration was performed with fuming 90% nitric acid (scheme 40) resulting in a significantly higher yield. Two other benefits came with the use of fuming nitric

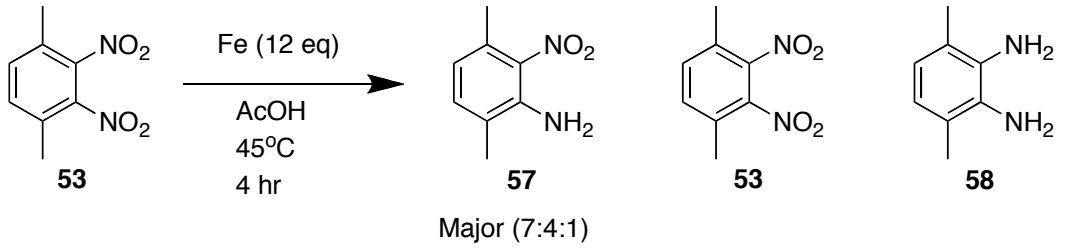
acid, the dinitration of p-xylene could be performed in one step, and the purification was simplified, not requiring large solvent gradients during column chromatography or recrystallization prior to column chromatography. Two equivalents of the nitrating mixture were used at 30°C, producing the desired 1,2-dinitroxylene **53** in 50% yield, and only the trivially removed, by flash chromatography, mononitroxylene and 1,3-dinitroxylene as by-products.



Scheme 40

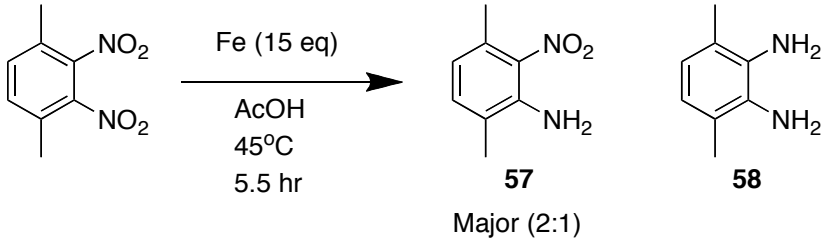
Interestingly, the major product, the 1,2-dinitroxylene **53**, results from the second electrophilic aromatic substitution unexpectedly occurring in both the most sterically-hindered and electron-deficient position.

A clean reduction of the dinitrate to diamine, which didn't require purification after a simple workup, was desired. Iron-mediated reductions of nitro-arenes are well known, often being clean and selective. The initial attempt of iron-mediated reduction to the diamine was unsatisfactory, yielding a mixture of the monoamine **57**, the unreacted dinitroxylene **53**, and, as the minor product, the desired diamine **58** (scheme 41).



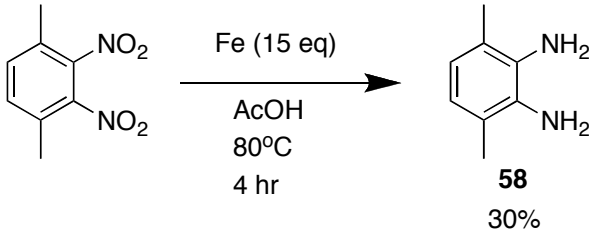
Scheme 41

Increasing the equivalents of iron and reaction time produced better results, yielding only the monoamine **57** and the desired diamine **58** as the major and minor products, respectively (scheme 42).



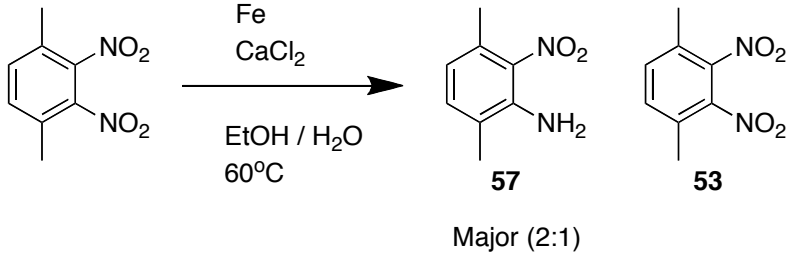
Scheme 42

Increasing the equivalents of iron and the reaction temperature yielded the desired diamine **58** with none of the monoamine **57** or unreacted the dinitro compound **53** (scheme 43). However, many products from side reactions were also seen.



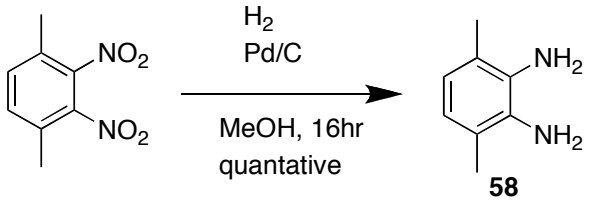
Scheme 43

Another common iron-mediated reduction of aryl nitro functionality uses calcium chloride in water/ethanol in place of acetic acid (scheme 44). While this system avoids the tedious workup associated with the use of acetic acid as solvent, the reaction yielded only the monoamine **57** and the unreacted dinitroxylene **53** as the major and minor products, respectively.



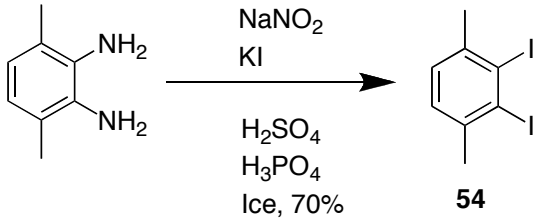
Scheme 44

However, it was found that hydrogenation over palladium on charcoal yielded the desired diamine **58** in quantitative yield after a simple workup (scheme 45).



Scheme 45

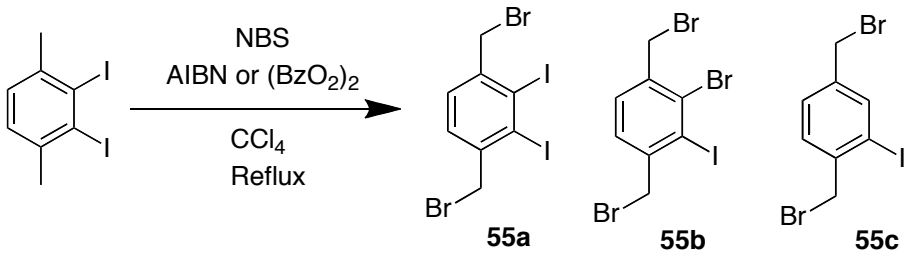
A Sandmeyer reaction, introducing diiodide functionality required for the one-pot Sonogashira coupling and intramolecular cycloaddition reaction, gave **54** in good yield, as previously performed within our group[40] (scheme 46).



Scheme 46

Deviating from the traditional use of copper in the reaction, phosphoric acid was used in order to switch from a radical intermediate to a cationic intermediate in the hope of avoiding side-reactions.

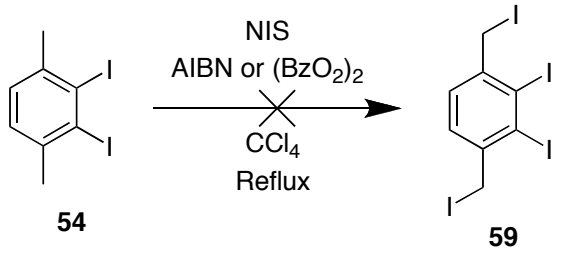
The radical bromination of the two benzylic positions with *N*-bromosuccinimide was problematic, giving low yields and unforeseen products (scheme 47).



Scheme 47

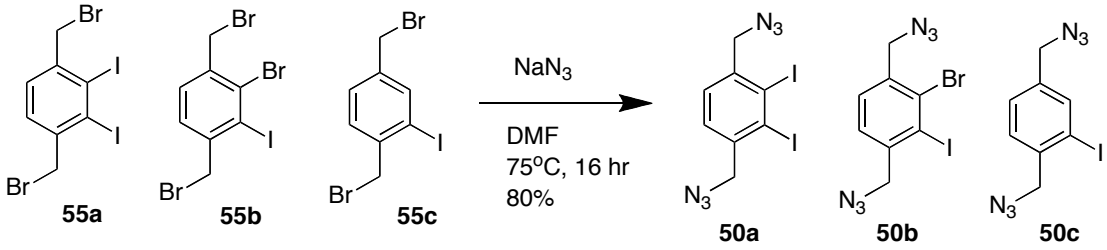
Despite attempted optimization, satisfactory yields could not be achieved. Furthermore, the side products, **55b** and **55c**, presumably formed *via* the aryl radical, were inseparable from the desired product **55a** by column chromatography on silica gel. As the reaction proceeded, a pink colour arose, indicating the presence of iodine.

To avoid the aromatic substitution, a radical benzylic iodination with N-iodosuccinimide to give **59** was attempted (scheme 48). However, no reaction occurred, and the 1,2-diiodo-3,6-dimethylbenzene **54** was recovered quantitatively.



Scheme 48

Using ^1H NMR to determine a weighted average molar mass, the mixture of benzyl bromides **55a-c** was reacted with sodium azide in DMF to give the desired benzyl azides in good yield (scheme 49). Unfortunately it was once more impossible to separate the dibenzyl azides **50a-c** by column chromatography. The reaction was worked up tentatively, extracting into diethyl ether, and washing repeatedly with water to remove residual DMF. Removal of the organic solvent was done without heating, in order to avoid potential explosive decomposition of the low molecular weight *bis*-azide.



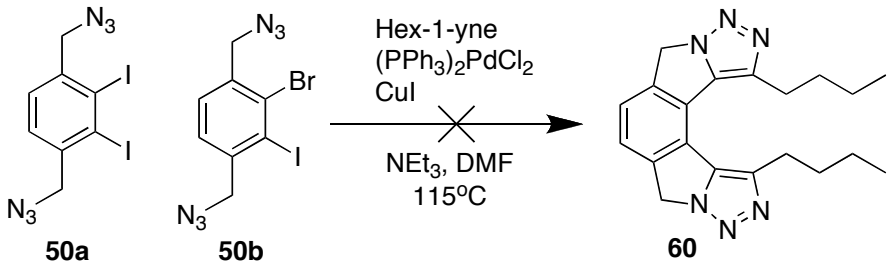
Scheme 49

Although the reaction was left to stir overnight, analysis by thin layer chromatography indicated the reaction had gone to completion within 3 hours.

It was reasoned that, while using the mixture of dibenzyl azides in the annulation reaction would result in a more complex mixture of products, it would be possible to separate the desired helical triazole **60** from the mixture. It was also reasoned that the mixture could be advantageous, as the higher reactivity of aryl

iodides when compared to aryl bromides in Sonogashira coupling reaction would allow the synthesis of non-symmetric helicenal triazoles.

Using the conditions of Chowdhury[39] and coworkers for the annulation reaction of the dibenzyl azide with hex-1-yne resulted in a complex mixture of triazoles **61a-g**, but none of the desired fused cycle **60** (scheme 50).



Scheme 50.

The products **61a-g**, determined by high-resolution mass spectroscopy, suggest the CuAAC reaction occurs with a lower energy barrier than the Sonogashira coupling (figure 5).

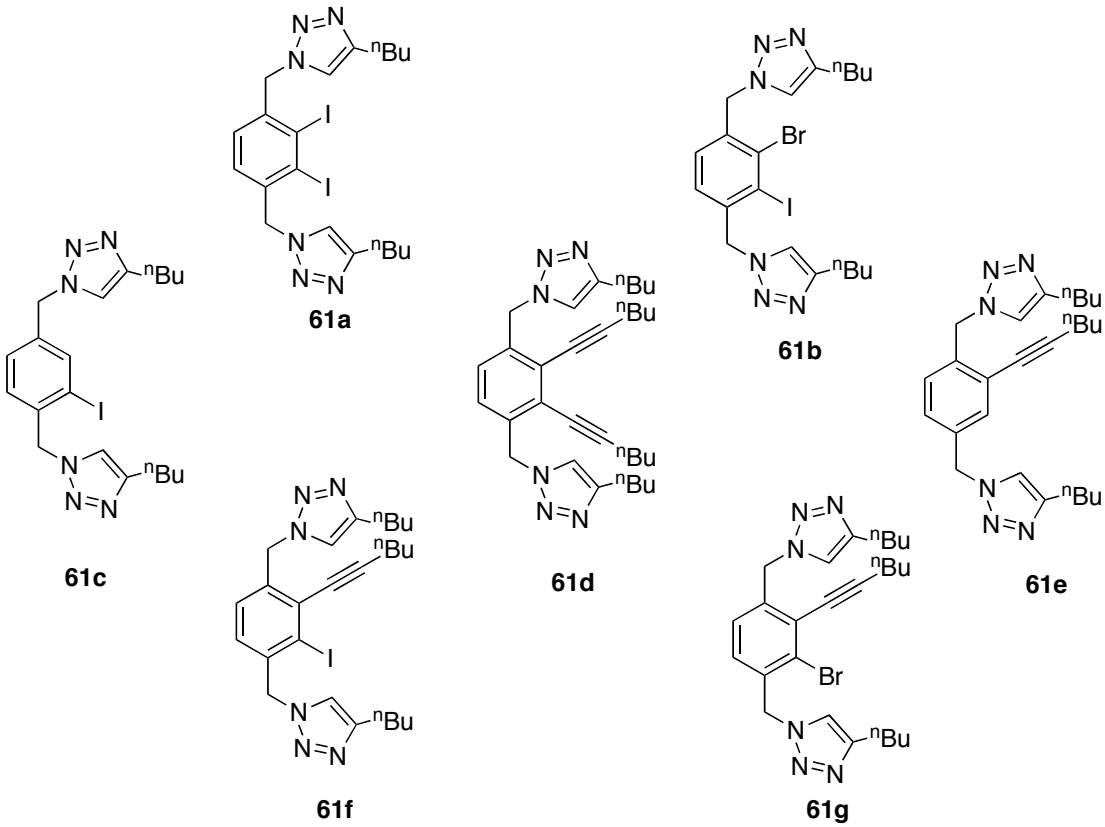


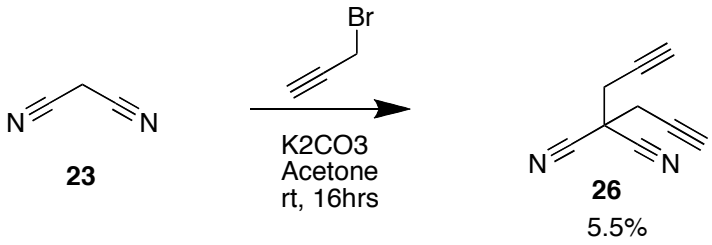
Figure 5.

The annulation reaction of the C_2-symmetric *bis*-azides differs from the annulation reaction of 2-iodobenzyl azide with terminal alkynes, for which only the acyclic products of Sonogashira coupling and the desired fused-tricyclic annulation products were observed. This is possibly due to the increased steric hindrance of the aryl diiodide increasing the energy barrier of the coupling reaction. While the observation of a product containing both triazole and alkyne functionalities indicate that the Sonogashira coupling occurs at the desired position under the annulation conditions, it is only after the azides have been consumed by CuAAC reactions this occurs. If exactly two equivalents of the alkyne were used, one would expect to see no product containing alkyne functionality.

3.0 Experimental.

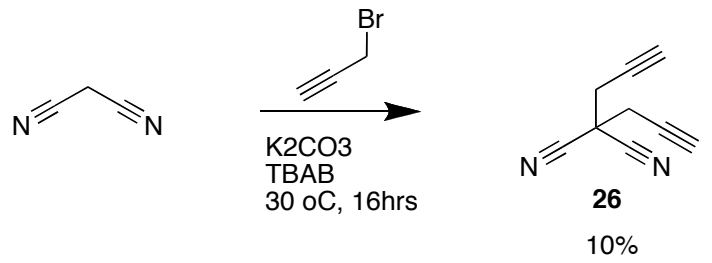
3.1 Experimental procedures in the syntheses towards macrocycles.

2,2-diprop-2-ynyl malononitrile, 26.[45]



A 100-ml rbf was charged with malononitrile (1.1 g, 17 mmol), K_2CO_3 (7.0 g, 50 mmol), propargyl bromide (80%wt in toluene, 4.9ml, 50 mmol), and acetone (50 ml). The mixture was stirred for 16 hrs, after which the solvent was removed in vacuo. The residue taken up in water (200 ml) and extracted with CH_2Cl_2 (3x 200 ml), the combine organic fractions were dried over $MgSO_4$, and the solvent removed in vacuo. Purification by column chromatography (petrol ether/ethyl acetate, 7:1) to yield the bis-alkyne as off-white crystals (0.13 g, 5.5%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) : 3.06 (d, 4H, *J* = 2.5 Hz), 2.42 (t, 2H, *J* = 2.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) : 113.78, 76.11, 74.22, 36.26, 27.64. IR (cm^{-1}) : 3305 (C-H stretch, alkyne), 2967, 2957, 2932 (C-H stretch, alkane), 2255 (C-N stretch, nitrile), 2130 (C-C stretch, alkyne).

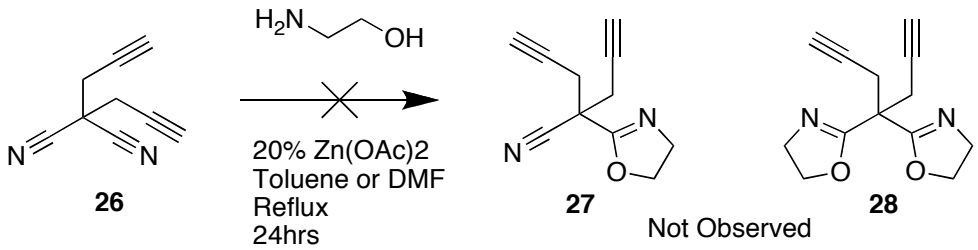
2,2-diprop-2-ynyl malononitrile, 26.[42]



A 100-ml rbf was charged with malononitrile (5.1 g, 78 mmol) K_2CO_3 (24 g, 17 mmol) and TBAB (1.0 g, 3.1 mmol) and propargyl bromide (80%wt in toluene,

19 ml, 21 mmol). The mixture was stirred at 40°C for 30 minutes, allowed to cool and stirred for a further 14 hours. The mixture was then stirred at 35°C for 21 hours, diluted in CH_2Cl_2 and filtered through a pad of Celite®. The solvent was removed in vacuo, and the residue purified by column chromatography (CH_2Cl_2) to yield the product as off-white crystals (1.0 g, 10%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) : 3.06 (d, 4H, *J* = 2.5Hz), 2.42 (t, 2H, *J* = 2.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) : 113.78, 76.11, 74.22, 36.26, 27.64. IR (cm^{-1}) : 3305 (C-H stretch, alkyne), 2967, 2957, 2932 (C-H stretch, alkane), 2255 (C-N stretch, nitrile), 2130 (C-C stretch, alkyne).

Oxazoline, 27, synthesis from 2,2-diprop-2-ynyl malononitrile, 26, in toluene.



26 **27** Not Observed **28**

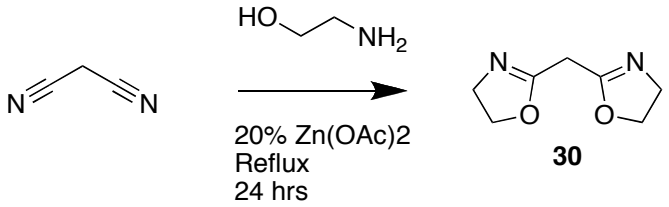
A 50-ml rbf was charged with 2,2-diprop-2-ynyl malononitrile (0.49 g, 3.5 mmol), zinc(II) acetate (0.13 g, 0.72 mmol), and toluene (15 ml). The mixture was stirred for 10 minutes, 2-aminoethanol (0.21 ml, 3.5 mmol) was added, and the mixture brought to reflux for 48 hrs. The mixture was allowed to cool, washed with brine (3x 20 ml) and saturated $NaHCO_3$ solution (2x 20 ml). The solvent was removed in vacuo, and the residue analysed by ^{1}H NMR.

Bis(oxazoline), 27, synthesis from 2,2-diprop-2-ynyl malononitrile, 26, in DMF.

A 100-ml rbf was charged with 2,2-diprop-2-ynyl malononitrile (0.37 g, 2.6 mmol), zinc(II) acetate (0.10 g, 0.56 mmol), and DMF (50 ml). The mixture was stirred for 10 minutes, and 2-aminoethanol (0.16 ml, 2.6 mmol) was added. The mixture stirred at reflux overnight. The solvent was removed in vacuo, the

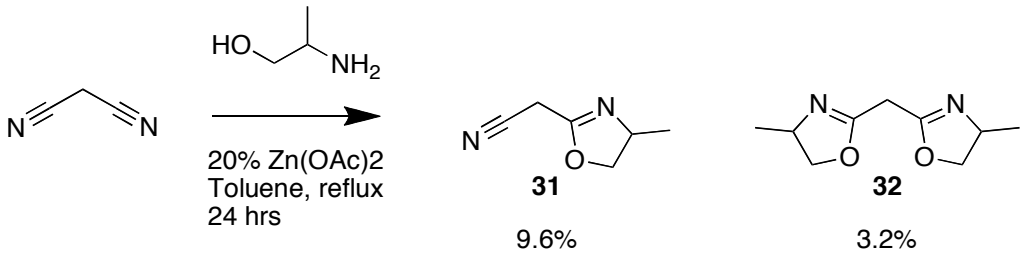
residue taken up in ethyl acetate (15 ml), washed with brine (3x 20 ml) and saturated $NaHCO_3$ solution (2x 20 ml). The solvent was removed in vacuo, and the residue analysed by ^1H NMR.

2,2'-Methylenebis[2-oxazoline] 30.[46]



A 50-ml rbf was charged with malononitrile (1.0 g, 16 mmol), zinc(II) acetate (0.56 g, 3.0 mmol), 2-aminoethanol (0.94 ml, 16 mmol), and toluene (25 ml). The mixture was stirred at reflux for 24 hrs, after which it was allowed to cool, and washed with brine (2x 50 ml) and saturated $NaHCO_3$ solution (2x 50 ml). The solvent was removed in vacuo, and the residue analysed by ^1H NMR. ^1H NMR (500 MHz) δ (ppm) : 4.24 (t, 4H, *J* = 8.5 Hz), 4.04 (s, 2H), 3.70 (t, 4H, *J* = 8.5 Hz).

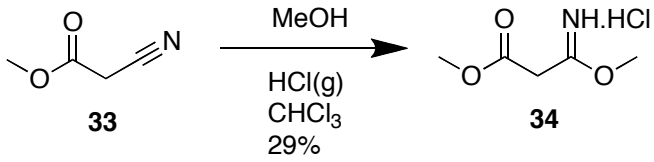
2-Cyano-2'-[4-methyl-2-oxazoline]methylene 31 and 2,2'-Methylenebis[4-methyl-2-oxazoline] 32.[47]



A 250-ml rbf was purged with nitrogen and charged with malononitrile (0.96 g, 14 mmol), zinc(II) acetate (0.52 g, 2.8 mmol), and toluene (150 ml) under an atmosphere of argon. The mixture was stirred for 10 minutes, 2-aminopropanol (1.1 ml, 14 mmol) was added, and the mixture was stirred at reflux for 24 hrs. The mixture was washed with brine (2x 100 ml) and saturated $NaHCO_3$ solution, and dried over $MgSO_4$. The solvent was removed in vacuo, and the solid residue

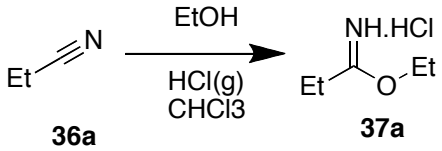
purified by recrystallization from hot ethanol to yield a mixture of the mono- and bis-oxazolines. ^{1}H NMR (500 MHz) δ (ppm) : 4.38 (t, 1H, *J* = 7.8 Hz), 4.16 (m, 1H, *J* = 8.5 Hz), 3.81 (t, 1H, *J* = 7.8 Hz), 3.36 (s, 2H), 3.19 (d, 3H, *J* = 8.5 Hz).

Methyl propanoate imidate methyl ester hydrochloride, 34.[48]



A 250-ml 3-necked flask was purged with nitrogen and charged with methyl cyanoacetate (10 ml, 110 mmol), methanol (5.5 ml, 140 mmol) and chloroform (100 ml). The mixture was cooled in a salt-ice bath and HCl gas was bubbled through the mixture for 1 hour. The mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed in vacuo, and the resulting clumpy white solid dried in a vacuum oven at 60°C overnight, to give a colourless liquid, which solidified when left to stand. The white solid was washed with Et_2O to yield the imidate hydrochloride salt (5.5 g, 29%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) : 7.10 (s broad, 1H), 6.36 (s broad, 1H), 3.73 (s, 3H), 3.72 (s, 2H), 3.32 (s, 3H). IR (cm^{-1}) : 3430, 3350, 3198 (N-H stretch, imidate salt), 1737 (C-O stretch, ester), 1674 (C-N stretch, imidate salt).

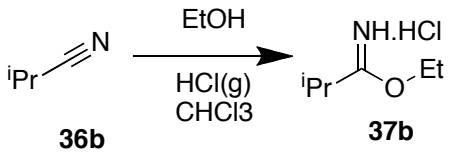
Ethyl propanimidoate hydrochloride, 37a.[49]



A 100-ml 3-necked flask was purged with nitrogen and charged with propionitrile (6.0 ml, 84 mmol), ethanol (5.4 ml, 92 mmol), and chloroform (50 ml). The mixture was cooled in a salt-ice bath and HCl gas was passed through the mixture for 1 hour. The mixture was allowed to warm to room temperature and stirred for 4 hours. The mixture was again cooled in a salt-ice bath, and HCl gas was passed through the mixture for a further hour. The mixture was allowed

to warm, and stirred overnight. The mixture was cooled in a salt-ice bath and HCl gas was passed through the mixture for an hour. The mixture was allowed to warm, and stirred for three days. The solvent was removed in vacuo, and the residue washed with Et_2O to yield a white solid (12 g, 95%). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) : 12.29 (s broad, 2H), 11.44 (s broad, 1H), 4.62 (q, 2H, *J* = 7.0 Hz), 2.76 (q, 2H, *J* = 7.6 Hz), 1.47 (t, 2H, *J* = 7.0 Hz), 1.28 (t, 2H, *J* = 7.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) : 180.34, 71.00, 27.20, 13.91, 10.18. IR (cm^{-1}) : 3329, 3164, 2991 (N-H stretch, imidate salt), 1659 (C-N stretch, imidate salt), 1471, 1412 (C-H bending, alkane), 1108 (C-O stretch, imidate ester).

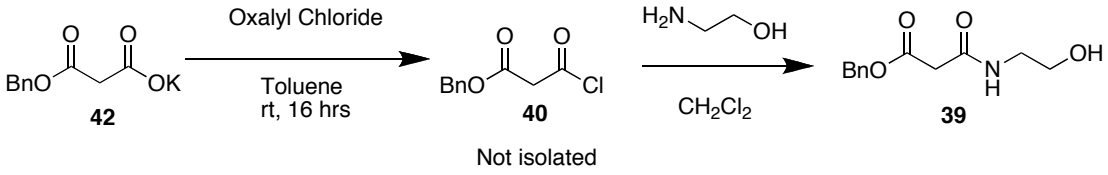
Ethyl 2-methylpropanimidoate hydrochloride.[50]



36b **37b**

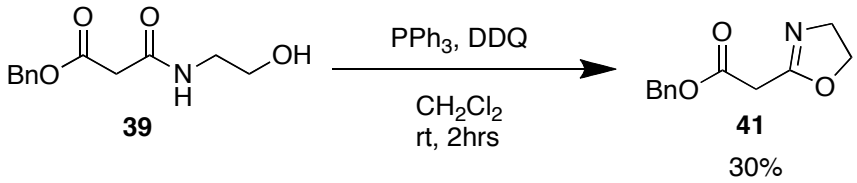
A 100-ml 3-necked flask was purged with nitrogen and charged with isobutyronitrile (6.0 ml, 67mmol), ethanol (6.0 ml, 74 mmol), and chloroform (50ml). The mixture was cooled in a salt-ice bath and HCl gas was passed through the mixture for 1 hour. The mixture was allowed to warm to room temperature and stirred for 4 hours. The mixture was again cooled in a salt-ice bath, and HCl gas was passed through the mixture for a further hour. The mixture was allowed to warm, and stirred overnight. The mixture was cooled in a salt-ice bath and HCl gas was passed through the mixture for an hour. The mixture was allowed to warm, and stirred for three days. The solvent was removed in vacuo, and the residue washed with Et_2O to yield a white solid (3.0 g, 30%). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) : 4.64 (q, 2H, *J* = 7.0 Hz), 2.43 (m, 1H, *J* = 6.9 Hz), 1.48 (t, 3H, J = 7.0 Hz), 1.29 (d, 6H, *J* = 6.9 Hz). IR (cm^{-1}) : 3350, 3164 (N-H stretch, imidate ester salt), 2967 (C-H stretch, alkane), 1652 (C-N stretch, imidate ester salt), 1408, 1290 (C-H bend, alkane), 1106 (C-O stretch, imidate ester salt).

***N*-(2-hydroxyethane) malonic acid monoamide benzyl ester, 39.**



A 50-ml rbf was purged with nitrogen and charged with potassium benzyloxycarbonyl acetate (2.0 g, 8.9 mmol) and toluene (29 ml). Oxalyl chloride (2.5 ml, 29 mmol) was added to the suspension, and the mixture was stirred at 35°C for 24 hours. The volatiles were removed under vacuo. The residue was taken up in CH_2Cl_2 (10 ml) and added in small portions to an ice-bath cooled solution of 2-aminoethanol (1.1 ml, 18 mmol) in CH_2Cl_2 (25 ml). The mixture was allowed to warm, and stirred for 4 hours. The mixture was washed with 5% HCl (2x 10 ml), water (2x 10 ml), dried over $MgSO_4$, and the solvent removed in vacuo. The residue was purified by column chromatography (petrol ether/ethyl acetate, 1:1) to yield the amide **39** as a yellow oil (1.4 g, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) : 7.36 (aromatic multiplet, 5H), 5.18 (s, 2H), 3.73 (t, 2H, *J* = 5.3 Hz), 3.46 (q, 2H, *J* = 5.3 Hz), 3.39 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) : 182.76, 70.54, 34.93, 33.33, 13.53.

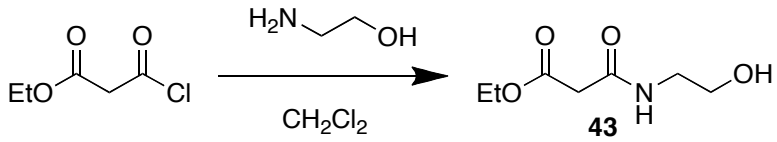
Oxazoline, 41.



A 50-ml 3-necked flask was purged with nitrogen and charged with triphenyl phosphine (2.4 g, 9.0 mmol), DDQ (2.0 g, 9.0 mmol), and CH_2Cl_2 (30 ml). After the mixture was stirred for several minutes, *N*-(2-hydroxyethane) malonic acid monoamide benzyl ester (1.4 g, 6.0 mmol) was added, and the mixture was stirred for a further 30 minutes. The mixture was poured into 10% NaOH (250 ml), and extracted with DCM (4x 90 ml). The combined organic was washed with brine. The solvent was removed in vacuo, and the residue taken up in Et_2O,

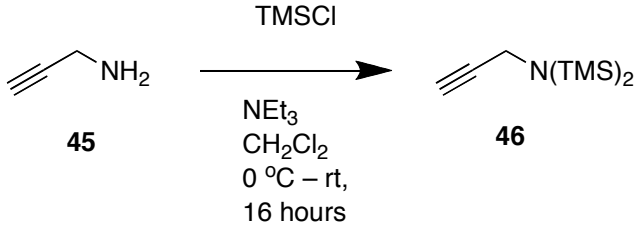
filtered through sintered glass to remove undissolved solid, and the Et_2O was removed in vacuo to yield the oxazoline as an oil (0.53 g, 41%). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) : 7.36 (Aromatic), 5.19 (s, 2H), 4.30 (t, 2H, *J* = 9.5 Hz), 3.89 (t, 2H, *J* = 9.5 Hz), 3.42 (s, 2H).

N-(2-hydroxyethane) malonic acid monoamide ethyl ester, 43.[51]



To a salt-ice bath 100-ml rbf charged with 2-aminoethanol (0.80 ml, 13 mmol) and DCM (30 ml) was added a solution of ethyl 3-chloro-3-oxopropanoate (1.0 g, 6.7 mmol) in DCM (10 ml) dropwise. The reaction mixture allowed to warm to room temperature, and stirred for a further 4 hours. The mixture was filtered through sintered glass and the solvent removed in vacuo to yield the amide (0.90 g, 5.2mmol), which was used without further purification. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) : 4.21 (q, 2H, *J* = 71 Hz), 3.75 (t, 2H, *J* = 5.4 Hz), 3.48 (q, 2H, *J* = 5.4 Hz), 3.34 (s, 2H), 1.30 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) : 169.95, 166.69, 62.65, 42.88, 41.26, 14.38. IR (cm^{-1}) : 3307 (O-H stretch, alcohol), 3093 (N-H stretch, amide), 2983, 2941 (C-H stretch, alkane), 1738 (C-O stretch, ester), 1660 (C-O stretch, amide).

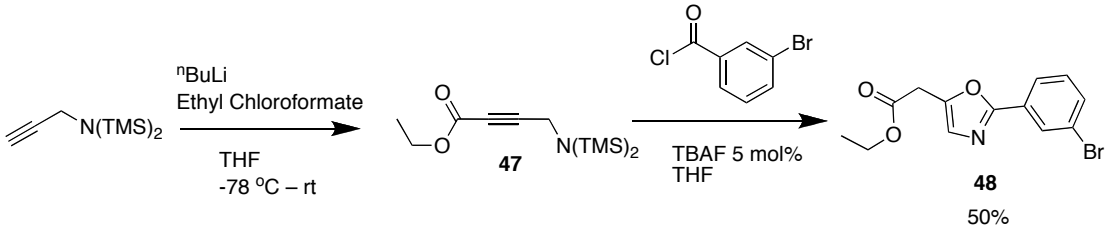
***N*-trimethylsilyl protection of propargyl amine, 46.**[52]



A 50-ml rbf was charged with propargyl amine (0.56 ml, 8.7 mmol) and DCM (15 ml) and cooled in an ice bath. TMSCl (2.3 ml, 18 mmol) was added dropwise, followed by NEt_3 (3.7 ml, 26 mmol). The reaction mixture was allowed to warm

and stirred overnight. The mixture was diluted with DCM (20 ml), washed with brine (3x 20 ml), and dried over $MgSO_4$. The solvent was removed by rotary evaporation to give the silyl-protected amine in quantitative yield, which was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) : 5.29 (d, 2H, J = 2Hz), 3.23 (t, 1H, J = 2Hz), 0.15 (s, 12H).

Oxazole, 48.[52]



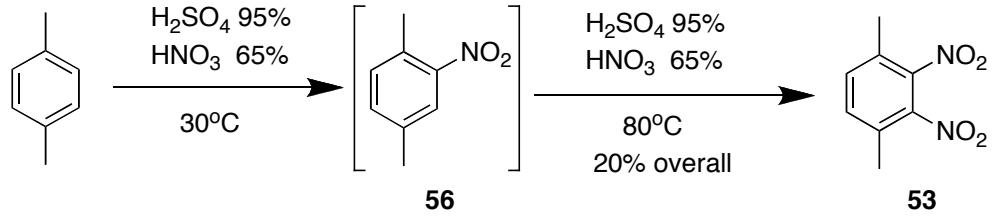
A 100-ml rbf was charged with propargyl-*N*-bis(timethylsilyl)amine (1.6 g, 8.2 mmol) and THF (10 ml). The mixture was cooled to -78°C and BuLi, 2.5 M in hexane (3.6 ml, 9.0 mmol) was added dropwise and the mixture was allowed to stir for 15 minutes. Ethyl chloroformate (0.86 ml, 9.0 mmol) was added dropwise. The mixture was allowed to warm slowly, and stirred for a total of 2 hours. The mixture was quenched with brine (30 ml) and extracted with ethyl acetate (2x 30 ml). The combined organic layers were washed with brine (50 ml), dried over $MgSO_4$, and the solvent removed in vacuo.

To the crude product from the previous step in a 100-ml rbf was added 3-bromobenzoyl chloride (1.2 ml, 9.1 mmol), and TBAF (0.41 ml, 0.41 mmol). The mixture was stirred overnight, and quenched with 1M HCl (40 ml), extracted with ethyl acetate (2x 30 ml). The combined organic layers were washed with brine (40 ml) and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue purified by column chromatography on silica gel (petrol ether/ethyl acetate, 1:1) to yield the oxazole (0.99 g, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) : 8.17 (t, 1H, *J* = 1.7 Hz), 7.95 (ddd, 1H, *J* = 7.8, 1.5, 1.1 Hz), 7.56 (ddd, 1H, *J* = 8.0, 2.0, 1.0 Hz), 7.32 (t, 1H, *J = 7.9* Hz), 7.10 (t, 1H, *J* = 0.9 Hz), 4.23 (q, 2H, *J* =

7.1 Hz), 3.79 (d, 2H, *J* = 0.9 Hz), 1.30 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) : 168.34, 160.16, 145.67, 133.26, 130.42, 129.34, 129.26, 126.79, 124.84, 122.94, 61.72, 32.00, 14.24. ^{13}C DEPT NMR (126 MHz, $CDCl_3$) δ (ppm) : 133.17 (CH), 130.33 (CH), 129.18 (CH), 126.73 (CH), 124.75 (CH), 61.63 (CH_2), 31.92 (CH_2), 14.15 (CH_3). 2982, 2935 (C-H stretch, alkane), 1740 (C-O stretch, ester).

3.2 Experimental procedures in the syntheses towards heterohelicenes.

Synthesis of 1,2-dinitro-3,6-dimethylbenzene, 53, by stepwise dinitration.[40, 41]



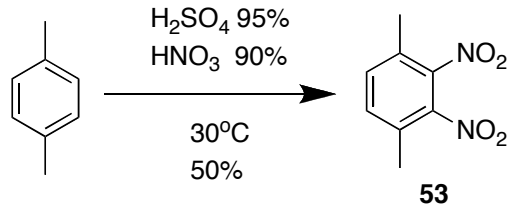
p-Xylene (21 g, 0.20 mol) was added dropwise to a nitrating mixture of nitric acid 65% (1.1 eq) and sulphuric acid 95% (1.1 eq) ensuring the temperature did not exceed 30°C. Upon complete addition the mixture was stirred for a further 10 minutes before being poured onto crushed ice (ca. 350 g) and extracted with EtOAc (3x 200 ml.) Solvent was removed in vacuo and the product, **56**, was used for the second nitration without further purification.

The 2,5-dimethylnitrobenzene, **56**, was heated to 70°C and a nitrating mixture of nitric acid 65% (1 eq) and sulphuric acid 95% (1 eq) was added dropwise ensuring the temperature did not exceed 80°C. Upon complete addition the mixture was stirred for 30 minutes before being poured onto crushed ice. The precipitating clumpy yellow solid was collected by filtration.

Purification by column chromatography (gradient of Pentane/EtOAc) yields the desired product. (20%)

A column of significantly smaller size with pentane/EtOAc (4:1) as the eluent may be used if the crude product is first recrystallized from hot acetic acid yielding the desired product (20%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) : 7.39 (s, 2H), 2.43 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) : 113.9, 130.6, 17.88.

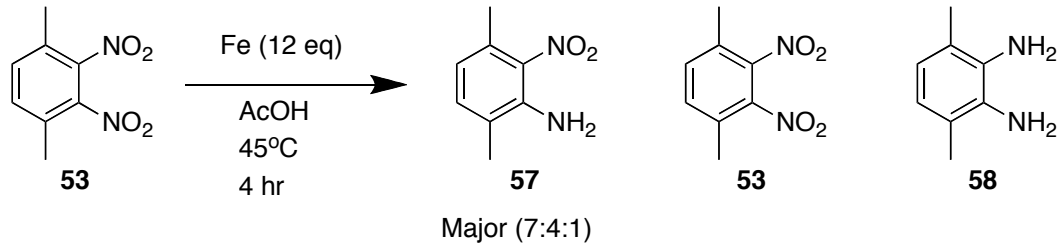
Synthesis of 1,2-dinitro-3,6-dimethylbenzene, 53. [40, 41]



53

To an ice-bath cooled mixture of sulphuric acid 95% (4.6 ml, 2 eq) and fuming nitric acid 90% (3.7 ml, 2 eq) was added dropwise p-xylene (5.0 ml, 41 mmol) ensuring the temperature did not exceed 30°C. A solid formed during addition, care was taken to ensure temperature homogeneity. Upon complete addition the mixture was allowed to stir for a further 20 minutes before being poured onto crushed ice (ca. 150 g.) The solid was collected by filtration and purified by column chromatography (pentane/EtOAc, 4:1.) to yield the dinitro arene as an off-white solid (50%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) : 7.39 (s, 2H), 2.43 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) : 113.9, 130.6, 17.88.

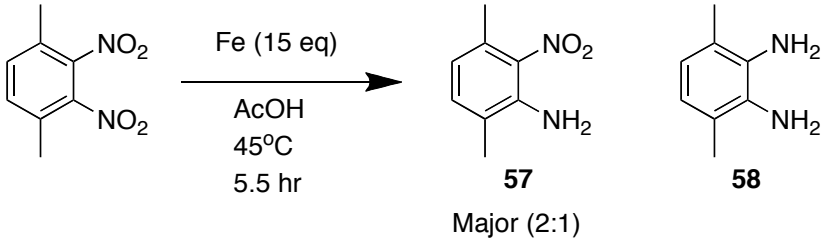
Iron-mediated reduction of 1,2-dinitro-3,6-dimethylbenzene, 53, in acetic acid.[53]



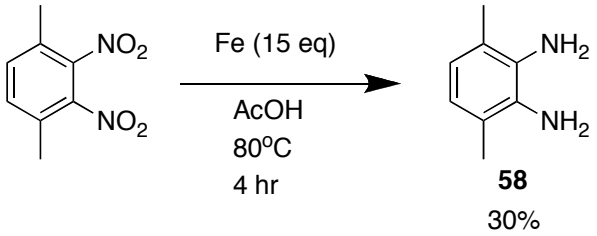
53 **57** **53** **58**

Major (7:4:1)

1,2-Dinitro-3,6-dimethylbenzene (0.53 g, 2.7 mmol) and iron powder (1.8 g, 32 mmol) were stirred in glacial acetic acid (55ml) at 45°C for 4 hours. The mixture was poured into cold aqueous 5% NaOH solution (100ml) and extracted with Et_2O (4x 50 ml.) The combined organic were washed with 5% $NaHCO_3$ (4 x 100ml) dried over $MgSO_4$. Solvent removed in vacuo to yield a mixture of products as a red solid.

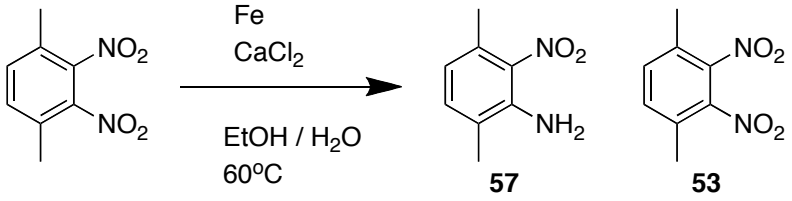


1,2-Dinitro-3,6-dimethylbenzene (0.48 g, 2.5 mmol) and iron powder (2.1 g, 37 mmol) were stirred in glacial acetic acid (50 ml) at 45°C for 5.5 hours. The mixture was poured into cold aqueous 5% NaOH solution (100 ml.) Extraction by Et_2O (4x 50 ml.) The combined organic were washed with 5% $NaHCO_3$ (4x 100 ml) dried over $MgSO_4$. Solvent removed in vacuo to yield a mixture of products as a red-yellow oil (0.34 g).



1,2-Dinitro-3,6-dimethylbenzene (0.34 g, 2.0 mmol) and iron powder (1.7 g, 30 mmol) were stirred in glacial acetic acid (40 ml) at 80°C for 4 hours. The mixture was poured into cold aqueous 5% NaOH solution (100 ml.) Extraction by Et_2O (4x 50 ml.) The combined organic were washed with 5% $NaHCO_3$ (4x 100 ml) dried over $MgSO_4$. Solvent removed in vacuo to yield the diamine **58** and unidentified impurities as a red solid (0.11 g). No starting material **53** or product from the mono-reduction **57** were observed.

Iron/calcium chloride mediated reduction of 1,2-dinitro-3,6-dimethylbenzene.[53]

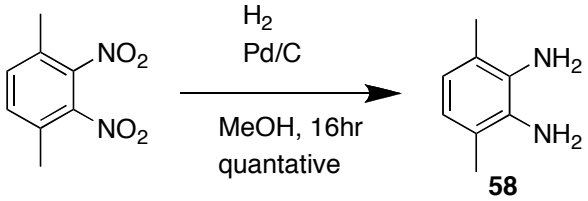


57 **53**

Major (2:1)

1,2-Dinitro-3,6-dimethylbenzene (0.32 g, 1.6 mmol), $CaCl_2$ (0.37 g, 3.3 mmol), iron powder (0.59 g, 11 mmol) and water (0.2 ml) were stirred in ethanol (2 ml) at 60°C overnight. The mixture was washed through Celite and with EtOAc (30 ml), and washed with water (3x 10 ml). Solvent was removed in vacuo to yield a mixture of starting material **53** and the product from mono-reduction **57** as a red oil (0.1741 g.)

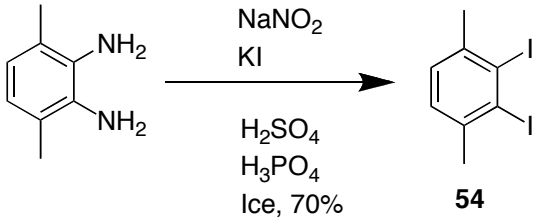
Palladium catalysed hydrogenation of 1,2-dinitro-3,6-dimethylbenzene 53 to 1,2-diamino-3,6-dimethylbenzene 58.[53]



58

1,2-Dinitro-3,6-dimethylbenzene (0.49 g, 2.5 mmol) and Pd/C 5%wt (0.048 g, 10% of substrate weight) were stirred in methanol (45 ml) under an atmosphere of hydrogen overnight. The mixture was filtered through Celite and the solvent removed in vacuo to yield 0.36g (100%) of the diamine as a brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) : 6.58 (s, 2H), 2.19 (s, 6H).

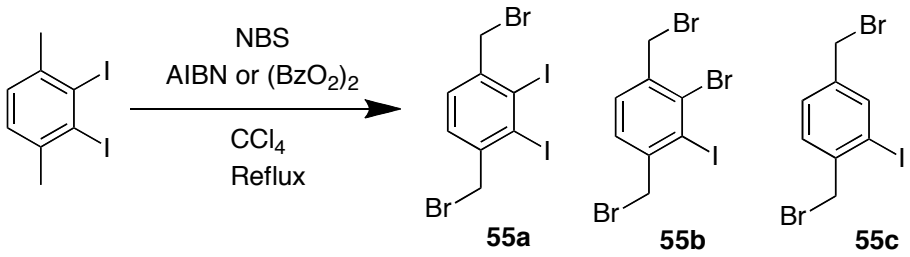
1,2-diiodo-3,6-dimethylbenzene 54.[53]



54

1,2-Diamino-3,6-dimethylbenzene (1.8 g, 13 mmol) in sulphuric acid 95% (33 ml) was slowly added to sodium nitrite (2.7 g, 39 mmol) in sulphuric acid 95% (27 ml), ensuring the temperature did not exceed 5^{0}C. Phosphoric acid 85% (27 ml) was slowly added, ensuring the temperature did not exceed 10^{0}C. The mixture was poured onto a stirred mixture of crushed ice (ca. 270 g) and KI (11 g, 67 mmol) and stirred overnight. The mixture was extracted with DCM (3 x 200ml) and the combine organic washed with saturated sodium thiosulphate (1x 200 ml) and water (2x 200 ml). The solution was dried over magnesium sulphate and the solvent removed in vacuo to yield 2.9 g (62%) of the 1,2-diiodo-3,6-dimethylbezene **54** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) : 7.11 (s, 2H), 2.56 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) : 128.8, 116.2, 32.7.

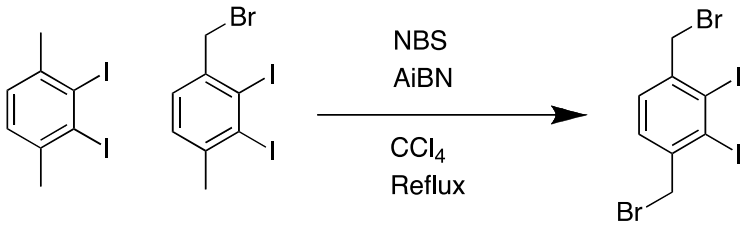
1,2-dimethyl-3,6-di(methylbromo)benzene, 55a.[53]



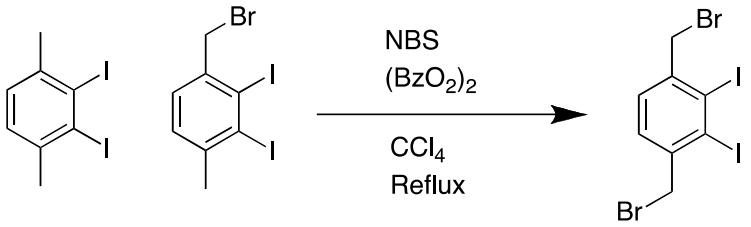
55a **55b** **55c**

1,2-diiodo-3,6-dimethylbezene (0.60 g, 1.7mmol), NBS (0.60g, 3.4mmol), and AIBN (0.048g, 0.29mmol) were refluxed in CCl_4 under an atmosphere of nitrogen for 4 hours. The mixture was left to stand overnight, followed by continued refluxing. The mixture was once more left to stand overnight before being refluxed for 6 hours. The mixture was diluted in pentane/EtOAc (100 ml, 9:1) and filtered through a pad of silica. Purification by column chromatography yielded the desired product in 2% yield. **55a** ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) :

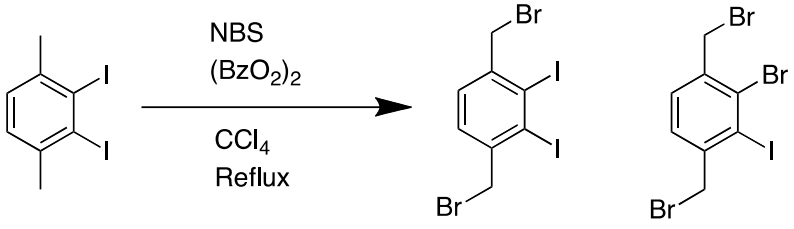
7.47 (s, 2H), 4.75 (s, 4H). **55b** ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) : 7.43 (s, 2H), 4.70 (s, 2H), 4.68 (s, 2H). **55c** ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) : 7.50 (s, 1H), 7.37 (d, 1H, *J* = 1.7 Hz), 7.35 (d, 1H, *J* = 1.7 Hz), 4.64 (s, 2H), 4.57 (s, 2H).



A mixture of diiodoxylenes (0.51 g, 1.3 mmol - weighted average) recovered from the previous bromination, NBS (0.38 g, 2.1 mmol), AIBN (0.035 g, 0.23 mmol) were refluxed in CCl_4 under an atmosphere of nitrogen for 18 hours. Purification by coloumn chromatography (cyclohexane) yielded 0.12 g (18%) of the desired product as a white solid.



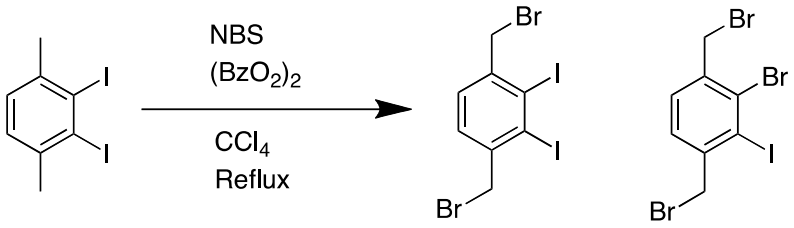
1,2-diiodo-3,6-dimethylbezene (0.45 g, 1.3 mmol), NBS (0.50 g, 2.8 mmol), and $(BzO_2)_2$ (0.064 g, 0.26 mmol) were refluxed in CCl_4 under an atmosphere of nitrogen for a total of 36 hours. After 12 hours $(BzO_2)_2$ (0.057 g, 0.24 mmol) was added. After 21 hours NBS (0.19 g, 1.1 mmol), and $(BzO_2)_2$ (0.020 g, 0.12 mmol) were added. Purification by column chromatography (cyclohexane) yielded the desired product in 8% yield.



1,2-diiodo-3,6-dimethylbezene (0.45 g, 1.2 mmol) was refluxed in CCl_4 with NBS (1.1 g, 6.3440 mmol) and $(BzO_2)_2$ (0.18 g, 0.74 mmol) added in portions (table 1) over 40 hours. Purification by column chromatography yielded the desired product and an analogous product in which an iodide had been replaced by a bromide as a white solid (0.13 g, 20%)

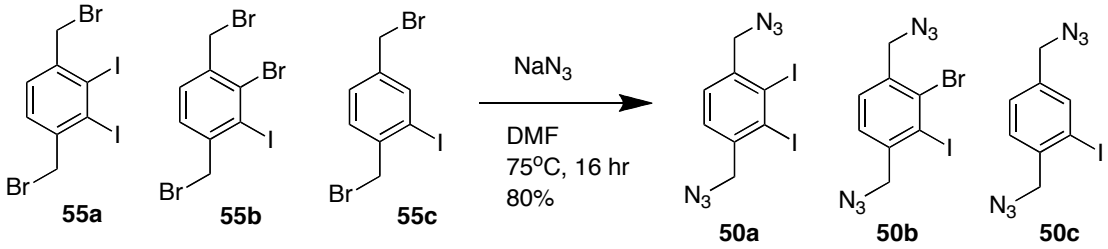
Time / hr	NBS mass / g	Initiator mass / g
0	0.1775	0.0249
1	0.1779	0.0232
2	0.1972	0.0531
17	0.2073	0.0253
21	0.1871	0.0226
26	0.1821	0.0308

Table 1.



1,2-diiodo-3,6-dimethylbezene (2.5 g, 7.1 mmol), NBS (3.2 g, 18 mmol), and AIBN (0.23 g, 1.4 mmol) were refluxed in CCl_4 under an atmosphere of nitrogen for 16 hours. Filtration through a pad of silica (Pentance/EtOAc, 9:1) yielded starting material and the product of monobromination. This was further brominated without further purification with NBS (3.0 g, 17 mmol) and $(BzO_2)_2$ (0.32 g, 1.3 mmol) in CCl_4 for 16 hours. Purification by column chromatography yielded the desired product and an analogous product in which an iodide had been replaced by a bromide as a white solid (0.41 g, 12%.)

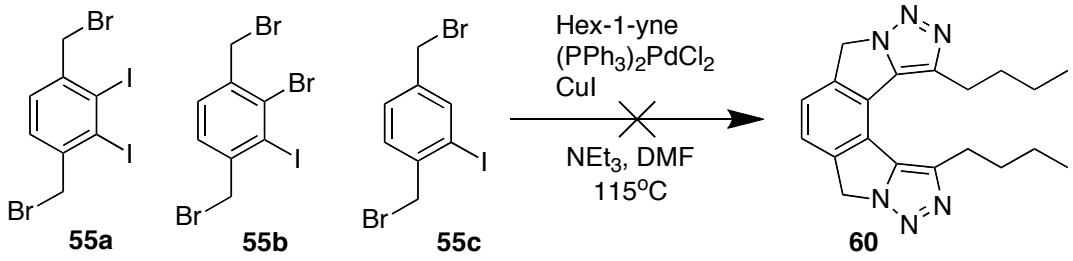
1,2-diiodo-3,6-di(methylazide)benzene, 50a



A mixture of dibezyl bromides **55a-c** (0.31 g, 0.62 mmol weighted average) and sodium azide (0.089 g, 1.353 mmol) were stirred in dry DMF (4 ml) under nitrogen overnight. The mixture was diluted with water (10 ml) and extracted with diethylether (3x 10 ml). The combined organic layers were washed with water (3x 10 ml), dried over magnesium sulphate and the solvent removed in vacuo to yield 0.23 g (80%) of the desired azides **50a-c**, which were used in the next step without further purification.

TLC shows the reaction has gone to completion after 3 hours.

Helical fused-pentacycle 60 synthesis by one-pot Sonogashira/cycloaddition



A mixture of benzyl azides **50a-c** (0.22 g, 0.51 mmol), $(PPh_3)_2PdCl_2$ (0.025 g, 7 mol%), CuI (0.014 g, 14 mol%), and triethylamine (0.86 ml, 6.2 mmol) were stirred in DMF (3 ml) under nitrogen for 1 hour. Hex-1-yne (0.11 g, 1.3 mmol) was added and the mixture was stirred for 17 hours. The mixture was then stirred at 110°C for 11 hours. The mixture was diluted with water (10 ml) and extracted with EtOAc (3 x 10 ml). The combined organic layers were washed with water (3 x 10 ml), dried over magnesium sulphate and the solvent removed in vacuo to yield brown oil.

Attempted purification by column chromatography (Pentane/EtOAc, 1:1) yielded five distinct fractions, each containing a mixture of products (see figure 5). **61a**: m/z (ES+) 605.2645 – $C_{20}H_{26}I_2N_6$ $[M-H]^+$ requires 605.2775. **61b**: m/z (ES+) 557.2616 – $C_{20}H_{26}BrIN_6$ $[M-H]^+$ requires 557.0525. **61c**: m/z (ES+) 479.1743 – $C_{20}H_{27}IN_6$ $[M-H]^+$ requires 479.3810. **61d**: m/z (ES+) 513.3974 – $C_{32}H_{44}N_6$ $[M-H]^+$ requires 513.3706. **61e**: m/z (ES+) 433.4589 – $C_{26}H_{35}N_6$ $[M-H]^+$ requires 433.3080. **61f**: m/z (ES+) 559.2436 – $C_{20}H_{26}I_2N_6$ $[M-H]^+$ requires 559.2046. **61g**: m/z (ES+) 511.1002 $C_{26}H_{35}BrN_6$ $[M-H]^+$ requires 511.2107.

REFERENCES

1. Michael, A., *J. Prakt. Chem.*, 1893, 94.
2. Huisgen, R., *Proc. Chem. Soc.*, 1961, 357.
3. Rostovtsev, V. V., Green, L. G., Fokin, V. V., Sharpless, K. B., *Angew. Chem. Int. Ed.*, 2002, *41*, 2596.
4. Tornøe, C. W., Chrisensen, C., Meldal, M., *J. Org. Chem.*, 2002, *67*, 3057.
5. Sharpless, K. B., Finn, M. G., Kolb, H. C., *Angew. Chem. Int. Ed.*, 2001, *40*, 2004.
6. Himo, F., Lovell, T., Hilgraf, R., Rostovstev, V. V., Noodleman, L., Sharpless, K. B., Fokin, V. V., *J. Am. Chem. Soc.*, 2005, *127*, 210.
7. Buckley, B. R., Dann, S. E., Heaney, H., *Chem. Eur. J.*, 2010, *16*, 6278.
8. Bogdan, A. R., James, K., *Chem. Eur. J.*, 2010, *16*, 14506.
9. Hein, J. E., Fokin, V. V., *Chem. Soc. Rev.*, 2010, *39*, 1302.
10. Chan, T. R., Hilgraf, R., Sharpless, K. B., Fokin, V. V., *Org. Lett.*, 2004, *6*, 2853.
11. Özçubukçu, S., Ozkal, E., Jimeno, C., Pericàs, A., *Org. Lett.*, 2009, *11*, 4680.
12. Hong, V., Presolski, S. I., Ma, C., Finn, M. G., *Angew. Chem. Int. Ed.*, 2009, *48*, 9879.
13. Pérez-Balderas, F., Ortega-Muñoz, M., Morales-Sanfrutos, J., Hernández-Mateo, F., Calvo-Flores, F. G., Calvo-Asin, J. A., Isac-García, J., Santoyo-González, F., *Org Lett.*, 2003, *5*, 1951.
14. Meng, J., Fokin, V. V., Finn, M. G., *Tetrahedron Lett.*, 2005, *46*, 4543.
15. Zhou, F., Tan, C., Tang, J., Zhang, J., Zhang, Y.-Y., Gao, W.-M., Wu, H.-H., Yu, Y.-H., Zhou, J., *J. Am. Chem. Soc.*, 2013, 135, 10994.
16. Bulman Page, P., Stephenson, G. R., *Synlett*, 2013, *24*, 2723.
17. Bodine, K. D., Gin, D. Y., Gin, M. S., *J. Am. Chem. Soc.*, 2004, *126*, 1638.
18. Punna, S., Kuzelka, J., Wang, Q., Finn, M. G., *Angew. Chem. Int. Ed.*, 2005, *44*, 2215.
19. van Maarseveen, J. H., Horne, W. S., Ghadiri, M., R., *Org. Lett.*, 2005, *7*, 4503.
20. Hradilová, L., Grepl, M., Hlaváč. J., Lyč ka, A., Hradil, P., *Synthesis*, 2012, 44, 1398.
21. Liu, Y., Zhang, X., Klivansky, L. M., Koshkakaryan, G., *Chem. Commun.,* 2007, 4773

22. Looper, R. E., Pizzirani, D., Schreiber, S. L., *Org. Lett.*, 2006, *8*, 2063.
23. Kelly, A. R., Jingqiang, W., Kesavan, S., Marié, J.-C., Windmon, N., Young, D. W., Marcaurelle, L. A., *Org. Lett.*, 2009, *11*, 2257.
24. Bogdan, A. R., James, K., *Org Lett.*, 2011, *13*, 4060.
25. Taeho, L., Minjae, C., Sung-Youl, K., Hyun-Jun, Y., Dong, J. B., Won-Jae, C., Chang-Yuil, K., Sanghee, K., *J. Med. Chem.*, 2007, *50*, 585.
26. Collin, M.-P., Hobbie, S. N., Böttgerm E. C., Vasella, A., *Helv. Chim. Acta*, 2008, *81*, 1838.
27. Weitzenböck, R., Lieb, H., *Monatsh. Chem.*, 1912, 549.
28. Weitzenöck, R., Klingler, A., *J. Chem. Soc.*, 1918, *114*, 494.
29. Newman, M. S., Lednicer, D., *J. Am. Chem. Soc*., 1956, *78*, 4765.
30. Newman, M. S., Lutz, W. B., Lednicer, D., *J. Am. Chem. Soc.*, 1955, *77*, 3420.
31. Schölz, M., Mülstaed, M., Dietz, F., *Tetrahedron Lett.*, 1967, *8*, 665.
32. Flammang-Barbieux. M., Nasielski, J., Martin, R. H., *Tetrahedron Lett.*, 1967, *8*, 743.
33. Martin, R. H., Flammang-Barbieux, M., Cosyn, J. P., Gelbcke, M., *Tetrahedron Lett.*, 1968, *9*, 3507.
34. Martin, R. H., Morren, G., Schurter, J. J., *Tetrahedron Lett.*, 1969, *10*, 3679.
35. Martin, R. H., Baes, M., *Tetrahedron*, 1975, *31*, 2135.
36. Rajca, A., Wang, H., Pink, M., Rajca, S., *Angew. Chem. Int. Ed.*, 2000, *39*, 4481.
37. Miyasaka, M., Rajca, A., Pink, M., Rajca, S., *Chem. Eur. J.*, 2004, 6531.
38. Högberg, H.-E., *Acta Chim. Scand.*, 1973, *27*, 2591.
39. Chowdhury, C., Mandal, S. B., Achari, B., *Tetrahedron Lett.*, 2005, *46*, 8531.
40. Aubertin, J.-N., Master's Thesis, The Univerity of East Anglia, Norwich, 2012
41. García, J. I., Mayoral, J. A., Pires, E., Villalba, I., *Tetrahedron. Asym.*, 2006, *17*, 2270
42. Díez-Barra, E., del la Hoz, A., Moreno, A., Sánchez-Verdú, P., J. Chem. Soc. 1991, 1991, 1, 2589
43. Yan-Hong, L., Tong-Lai, Z., Jian-Guo, Z., Jin-Yu, G., Kai-Bei, Y., *Molcules,* 2005, *10*, 978.
44. Kobe, K. A., Hudson, T. B., Ind. Eng. Chem, 1950, 42, 356.
45. Haeffner, T., Hashmi, A., Stephen, K., Rominger, F., Rudolph, M., *Chem. Eur. J.,* 2011, *17*, 8195

46. Ilkgul, B., Gunes, D., Sirkecioglu, O., Bicak, N., *Tetrahedron., Lett.,* 2010, *51*, 5313
47. Brown, J. M., Guiry, P. J., Price, D. W., *Tetrahedron Asym.,* 1994, *5*, 561.
48. Ueno, H., Maruyama, A., Miyake, M., Nakao, E., Nakao, K., Umezu, K., Nitta, I., *J. Med. Chem*., 1991, *34*, 2468.
49 Zimmerman, S. C., Cramer, K. D., Galan, A. A., *J. Org. Chem.,* 1989, *54*, 1256
50 McElvain, S. M., Tate, B. E., *J. Am. Chem. Soc.*, 1951, *73*, 2233.
51 Tikhomirov, D. A., Sladenskaya, O. S., Eremeev, A. V., *Khim, Geterotsikl. Soedin.,* 1992, *5*, 684.
52 Wipf, P., Aoyama, Y., Benedum, T. E., *Org. Let.,* 2004, *6*, 3593
53 Thulin, B., Wennerstrom, O., *Acta Chem. Scand.,* 1983, *B37*, 589