Enantioselective Copper-Catalysed Azide-Alkyne Cycloaddition Reactions.

James Patrick Martin.

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I Abstract.

Key Words: Click chemistry, Enantioselective synthesis, Enantioselective desymmetrisation, Kinetic resolution, Copper catalysis, Copper-catalysed azide-alkyne cycloaddition

This thesis describes an investigation into the enantioselective copper-catalysed azide-alkyne cycloaddition reaction as a tool for the synthesis of chiral alkynes and triazoles through the desymmetrisation of prochiral bis(alkynes) and the kinetic resolutions of chiral alkynes.

This thesis will provide an introduction outlining a brief history of the copper-catalysed azide-alkyne cycloaddition reaction followed by an overview of the proposed mechanisms for the reaction. A condensed showcase of the wide range of chemical disciplines the CuAAC reaction has found application in will be provided. Literature examples of enantioenriched chiral triazoles will be discussed across three subchapters, covering synthesis from enantioenriched starting materials, enantioselective desymmetrisations of prochiral triazoles, and finally, the focus of this thesis, synthesis by enantioselective CuAAC reactions.

The research discussed in this thesis is split into four chapters:

The first chapter examines the initial development of an asymmetric screening reaction and details substrate synthesis, solvent screening, and copper(I) source screening.

The second chapter details the screening of chiral ligands, and is further divided into discussion of oxazoline ligands, phosphine ligands, and *N*-hetrocyclic carbene ligands.

The third chapter discusses the use of ferrocenyl ligands and examines the effect of temperature and *in situ* kinetic resolutions on the observed enantioselectivity of the asymmetric CuAAC reaction

The fourth chapter describes the scope of substrates investigated.

II Acknowledgements.

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My family, Patrick, Jane, Billy, Ben, and Lucy.

James, Amanda, Jeremy. Good friends.

Sarah and Olly, sorely missed.

Thu.

III Abbreviations.

Equiv.	equivalent
min	minutes
Ph-	Phenyl
L/ Ln/ L*	Ligand/ $Ligand_n$/ Ligand*
CuAAC	Copper(I)-catalysed Azide-Alkyne Cycloaddition
CuSO4	Copper sulfate
CuI	Copper(I) iodide
Dipp-	2,6-Diisopropylphenyl
LiAlH4	Lithium aluminium hydride
tBuOH	*tert*-Butanol
MeOH	Methanol
BnCl	Benzyl chloride
NaH	Sodium hydride
TBAI	Tetrabutylammonium iodide
TBDMSiCl	*tert*-Butyldimethylsilyl chloride
KOH	Potassium hydroxide
PPh3	Triphenylphosphine
CuOTf	Copper (II) triflate
CH2Cl2	Dichloromethane
^{i}PrNEt2	Diethylisopropylamine
(-)-NORPHOS	(1R,2S,3S,4S)-Bicyclo[2.2.1]hept-5-ene-2,3-diylbis(diphenylphosphine)
CuF2	Copper(II) fluoride
RN3	Azide
(EtO)3P	Triethyl phosphite
DIPEA	N,N-Diisopropylethylamine
EtOH	Ethanol
K2CO3	Potassium carbonate
K3PO4	Potassium phosphate
[Pd2(dba)3]	Tris(dibenzylideneacetone)dipalladium(0)

NaAsc	Sodium ascorbate
HOMO	highest occupied molecular orbital
LUMO	lowest unoccupied molecular orbital
TAAC	thermal azide-alkyne 1,3-dipolar ‘Huisgen’ cycloaddition
TBTA	tris-(benzyltriazolylmethyl)amine
TCEP	tris(2-carboxyethyl)phosphine
DMF	Dimethylformamide
MW	Micro wave
DFT	Density functional theory
SPOS	synthesis solid phase organic synthesis
THF	Tetrahydrofuran
DMAP	4-Dimethylaminopyridine
DCM	Dichloromethane
TBDMSiCl	*tert*-Butyldimethylsilyl chloride
BINOL	1,1′-Bi-2-naphthol
TMEDA	N, N, N', N'-Tetramethylethylenediamine
DIAD	Diisopropyl azodicarboxylate
RT	Room temperature
mCPBA	*meta*-Chloroperoxybenzoic acid
CalB	Candida antarctica lipase B
MS	Molecular sieve
TMSCl	Trimethylsilyl chloride
nBuLi	^{n}Butyllithium
TBAF	Tetrabutylammonium fluoride
TLC	Thin layer chromatography
HFIP	Hexafluoroisopropanol
Me-	methyl
Bn-	Benzyl
DCE	1,2-dichloroethane
CuOTf	Copper(I) trifluoromethanesulfonate
Ph-PyBox	2,6-Bis(4,5-dihydro-4-phenyl-2-oxazolyl)pyridine
Ph-SpiroBox	2,2'-(2,2',3,3'-Tetrahydro-1,1'-spirobi[indene]-7,7'-diyl)bis(4-phenyl-4,5-dihydro-1,3-oxazole)
PyOx ligands	pyridine-oxazoline ligands
TrisOx	Trisoxazolines

BPE	bis(2,5-dimethylphospholane)
DuPhos	(-)-1,2-Bis[(2R,5R)-phospholano]benzene
TIPS	Triisopropylsilyl ether
DIPAMP	1,2-Bis[(2-methoxyphenyl)(phenylphosphino)]ethane
HBpin	4,4,5,5-Tetramethyl-1,3,2-dioxaborolane
DuanPhos	2,2′-Di-*tert*-butyl-2,3,2′,3′-tetrahydro-1H,1′H-(1,1′)biisophosphindolyl
QuinaPhos	3,4-a']dinaphthalen-4-yl]-1,2-dihydroquinoline
(*R*,*R*)-Chiraphite	(+)-6,6'-{[(1R,3R)-1,3-Dimethyl-1,3-propanediyl]bis(oxy)}bis[4,8-bis(*t*butyl)-2,10-dimethoxy-bibenzo[d,f][1,3,2]dioxaphosphepin]
(*S*)-QUINAP	(*S*)-(−)-1-(2-Diphenylphosphino-1-naphthyl)isoquinoline
(*R*)-xylyl-PhanePhos	(*R*)-(–)-4,12-Bis[di(3,5-xylyl)phosphino]-[2.2]-paracyclophane
CuTC	Copper(I) thiophene-2-carboxylate
ht	head-to-tail

IV Table of Contents.

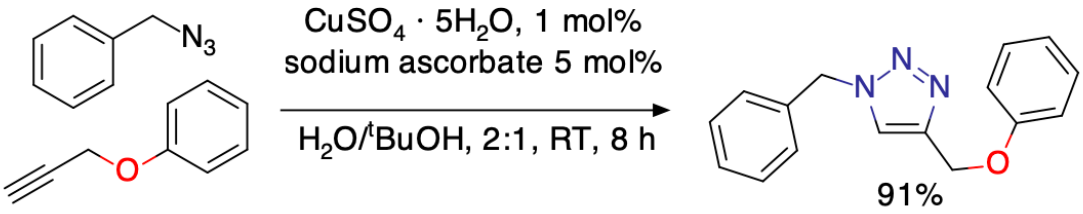
Table of Contents

Introduction.

1.1 The History of the CuAAC Reaction.

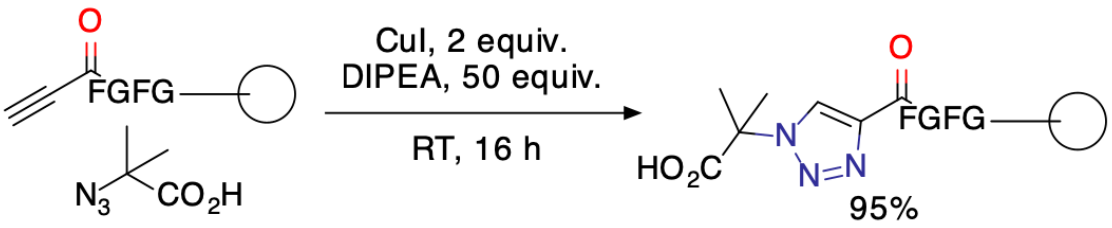
In 2001 Barry Sharpless outlined a concept for grouping organic chemical reactions he dubbed 'click' chemistry.[1] Membership for this group was based on properties chemists have long admired, the cleanness and efficiency of the reaction. Such a reaction should be atom efficient, avoid the use of toxic reagents and solvents, be selective, have little to no by-products, and provide a product which should be isolable with little downstream processing. Among the 'click' reactions are the catalytic Diels-Alder reactions, Sharpless' own asymmetric epoxidation[2] and dihyrdroxylation,[3] Michael additions, and, perhaps most famously, the copper-catalysed azide-alkyne cycloaddition reaction, which would become the type reaction for 'click' chemistry.

The use of copper as a catalyst for the reaction of azides with alkynes to form triazoles was independently reported by the groups of Sharpless[4] and Meldal[5] in 2002. Sharpless' report[4] (scheme 1) was a thorough investigation of the pure methodology, looking at the reaction between azides and alkynes with a broad substrate scope.



Scheme 1: Sharpless' CuAAC

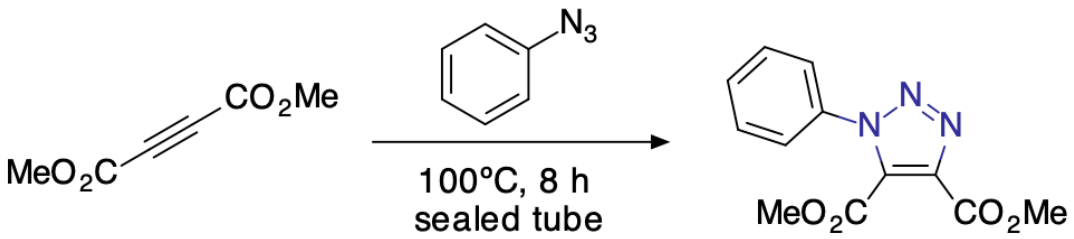
The reported conditions are air and moisture insensitive, utilising a pre-catalyst system of copper(II) sulfate and sodium ascorbate at the respectively low loading of one and five mole percent, respectively. The sodium ascorbate both generates the active copper(I) catalyst and reduces any copper(II) that may be formed during the reaction through oxidation with air. The solvent system of *tert*-butanol/water allowed for homogeneous catalysis, dissolving the catalytic system and the majority of substrates screened, and would often yield the triazole by precipitation from the reaction mixture.



Scheme 2: Meldal's CuAAC

Meldal's report[5] had a focus on the biochemical applications of the reaction (scheme 2) utilising copper(I) chloride in stoichiometric excess they were able to quickly and cleanly couple resin-bound peptide chains modified with alkyne handles to organic azide partners.

Between them these two papers have garnered over 11,000 citations, split roughly 7.1:4.9 in favour of Sharpless' report in the 15 years since their publications, representing a huge surge of interest in the azide-alkyne cycloaddition; a reaction which has been known for more than a hundred years. First reported by Michael in 1893[6] (scheme 3) the 1,3-dipolar cycloaddition between azides and alkynes found little attention.



Scheme 3: Michael's azide-alkyne cycloaddition.

The catalyst-free (thermal) azide-alkyne 1,3-dipolar cycloaddition is a concerted 6-electron [3+2] pericyclic process requiring an orbital symmetry conserving π4s + π2s frontier molecular orbital overlap as per the Woodward-Hoffmann rules. Orbital overlap of the HOMO of the azide and LUMO of the alkyne, or the LUMO of the azide and the HOMO of the alkyne (figure 1), satisfiy these rules.

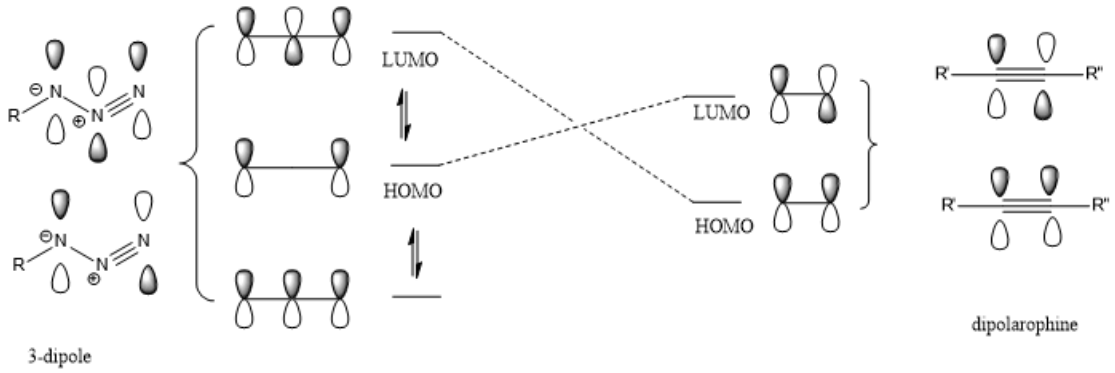
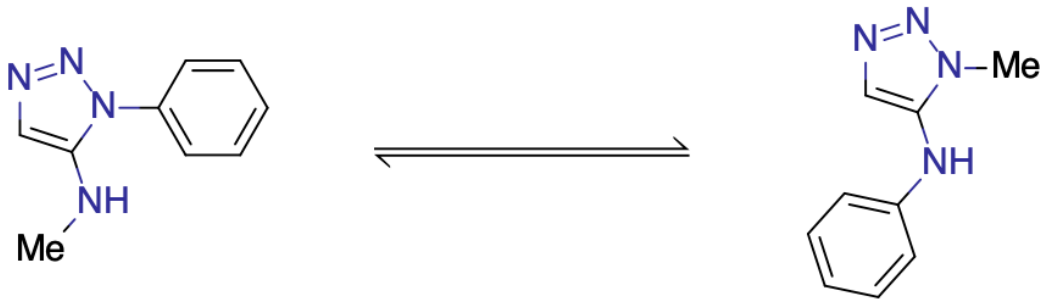


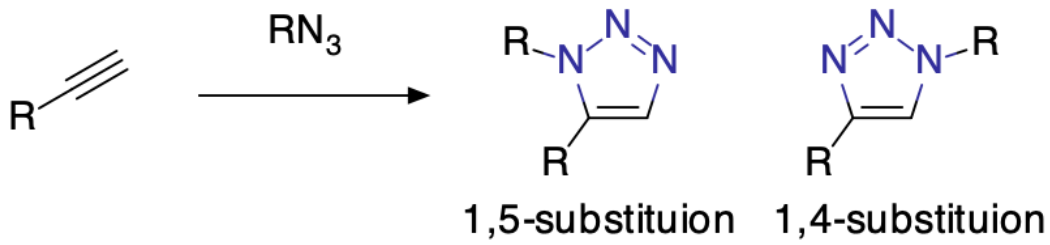
Figure 1: Representation of the azide and alkyne FMOs

Despite its use by Dimroth to prepare substrates for his work on the reaction now known as the Dimroth rearrangement[7] (scheme 4) the reaction had sparse mention in the chemical literature. It was Huisgen's seminal work on 1,3-dipolar cycloadditions[8] that brought the reaction to wider attention.



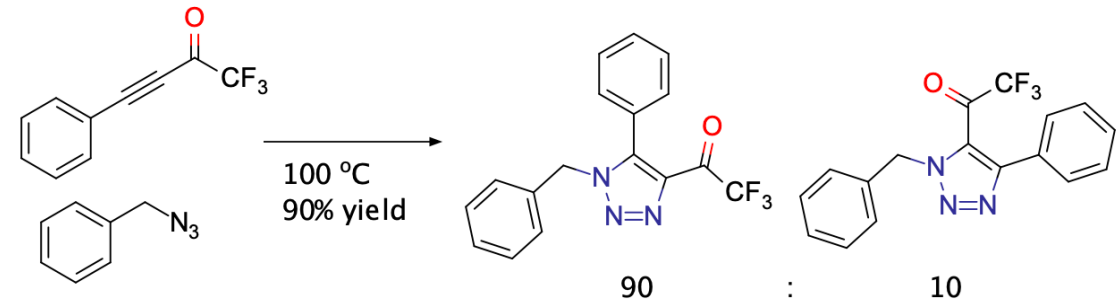
Scheme 4: The Dimroth rearrangement.

Despite its newfound attention, the reaction remained severely limited as a synthetic tool. Harsh reaction conditions and poor control and degree of regioselectivity (scheme 5) restricted both substrate scope and product yield, together with the identity of the 1,2,3-triazole as a non-natural motif and the lack of further chemical transformations, kept the cycloaddition from seeing popular use. The reaction can, however, be tuned through reaction conditions and substituent sterics and electronics to provide regioselectivity.



Scheme 5: 1,2,3-Triazole regioisomers

In 2018, Fan-Hong Wu and coworkers obtained a regioselectivity of 90:10 at 90% yield while investigating catalyst-free azide-alkyne cycloaddition reactions between trifluoroacetyl alkynes and benzylic azides (scheme 6).[9] The regioselectivity in this case could be influenced by possible aryl-aryl π-orbital interactions. Alkyl azides do not have a uniform charge distribution across the nitrogen atoms, with the alkyl-substituted nitrogen tending to have a more negative partial charge.[10] It is possible that this electronic bias of the azide coupled with the partial positive charge on the beta carbon of the trifluoroacetyl alkyne is responsible for the observed high regioselectivity.



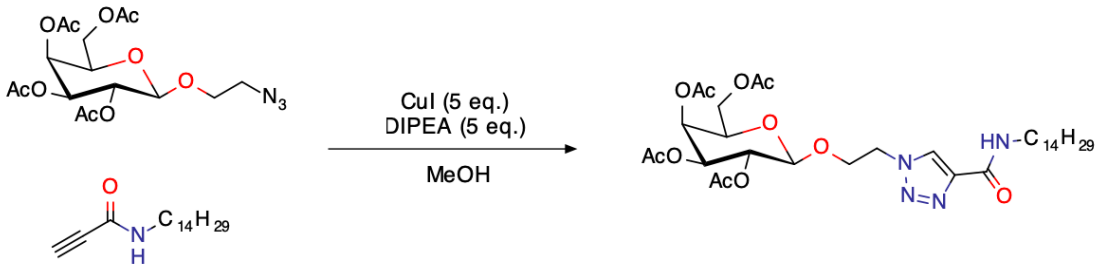
Scheme 6: Regioselective catalyst-free alkyne-azide cycloaddition.

The high temperatures and dependence on electronic properties of the substrates significantly reduce functional group tolerance.

The copper-catalysed azide-alkyne cycloaddition, herein referred to as CuAAC, reaction showed a vast improvement over the catalyst-free thermal azide-alkyne 1,3-dipolar 'Huisgen' cycloaddition (TAAC) reaction first reported by Michael. Where the CuAAC reaction shows complete regioselectivity, the much slower thermal variant gives a mixture of the 1,4- and 1,5-regioisomers where a non-symmetric alkyne is used (scheme 5).

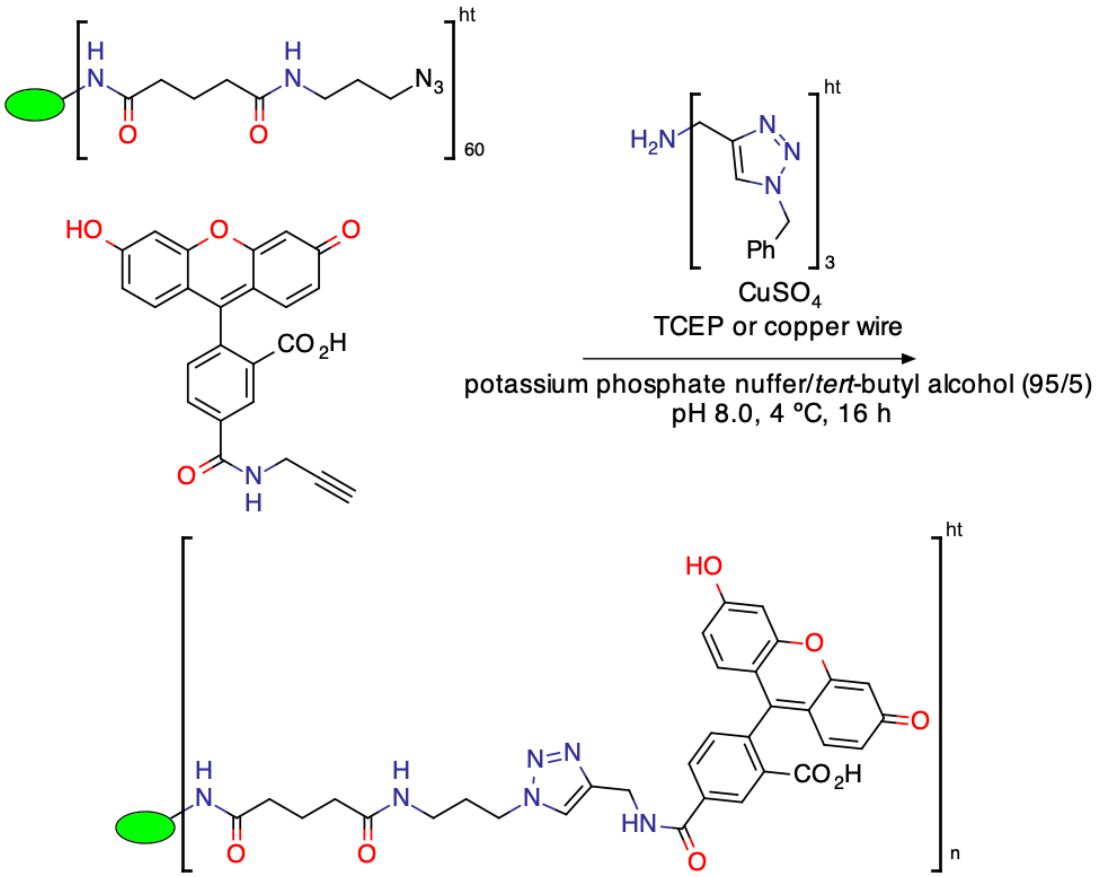
It would take another four decades and the work coming form the laboratories of Meldal and Sharpless for the reaction to become the staple tool of organic chemistry it is today. With its speed, simplicity, broad functional group tolerance, and complete regioselectivity the CuAAC reaction has found use in almost every branch of synthetic chemistry.

The copper-catalysed azide-alkyne cycloaddition reaction was quickly picked up by Wong[11] and coworkers at The Scripps Research Institute who applied the method utilising copper(I) iodide and DIPEA laid out by the laboratory of Meldal to couple a propiolamide derivative bound to polystyrene microtiter plates with a variety of saccharides and oligosaccharides modified to feature azides (scheme 7), demonstrating the utility of the reaction as a high throughput means to swiftly build arrays for biological screening (scheme 7).



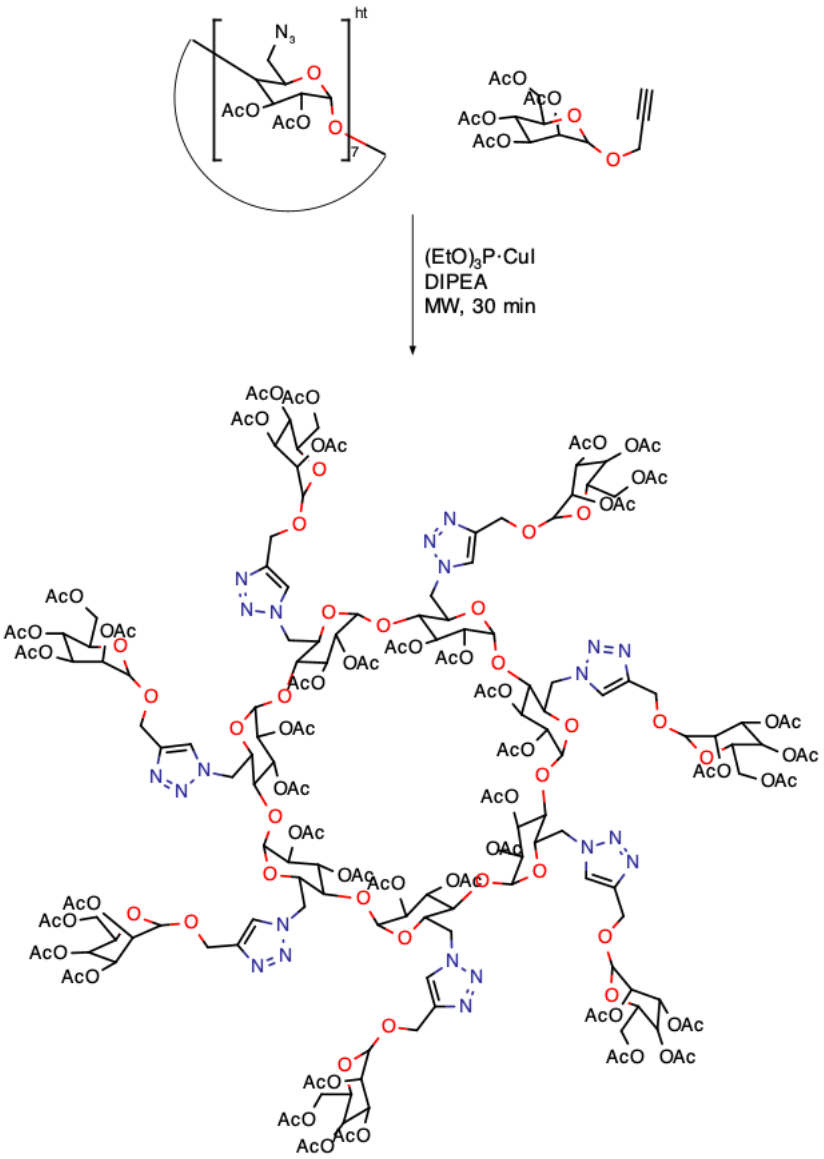
Scheme 7: CuAAC on microtiter plate-bound saccharide derivatives.

In 2003 Finn, Fokin, Sharpless,[12] and coworkers published a paper in which they outlined the application of a variation of the CuAAC procedure they reported in 2002 paper to the bioconjugation of dyes to viruses (scheme 8).
The methodology included the use of either TCEP or copper wire in place of sodium ascorbate as the reducing agent. The use of a tridentate triazole ligand (TBTA) was found to significantly increase the rate of reaction. First mentioned in the footnotes of the aforementioned paper, the preparation and use of the ligand was described in 2004 by Fokin and coworkers who noted that the accelerating effects of the ligand were bought to their attention during its synthesis.[13]



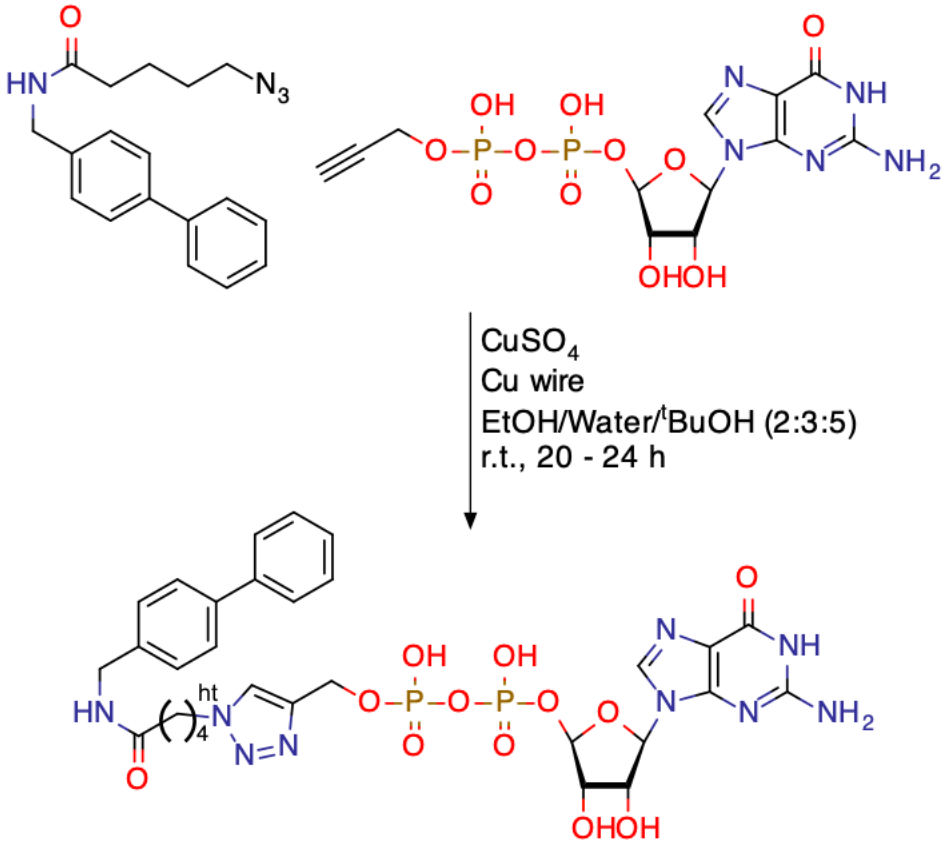
Scheme 8: CuAAC as a tool for viral bioconjugation

Santoyo-González and coworkers[14] used the CuAAC reaction to produce divalent and multivalent neoglycoconjugates, including branched cyclodextrins (scheme 9). Coupling sugars together with a triazole linker or furnishing a multivalent-azide core with sugars was achieved by the use of a phosphine-ligated copper(I) iodide catalyst and took advantage of microwave irradiation to achieve short reaction times.

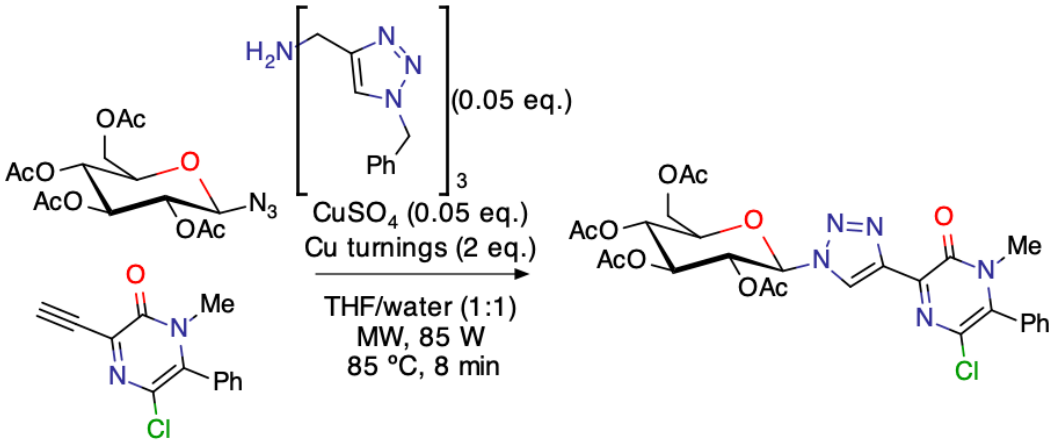


Scheme 9: CuAAC synthesis of branched cyclodextrins

Wong,[15] along with Sharpless, Fokin, and coworkers also applied the high throughput microtiter plate synthesis and screening of triazoles to the development of an α-1,3-fucosyltransferase inhibitor (scheme 10). The triazole features in scheme 10 emerged as a selective inhibitor of human α-1,3-fucosyltransferase IV during the screening of 85 GDP-triazoles.



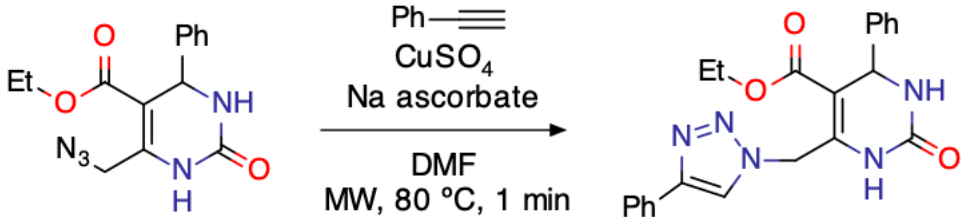
Scheme 10: CuAAC synthesis of a human α-1,3-fucosyltransferase IV inhibitor å



Scheme 11: CuAAC coupling of saccharides with pyrazinones

The laboratory of Van der Eycken reported[16] the coupling of saccharides to pyrazinones using the accelerating tris(triazolyl) ligand TBTA with copper(II) sulphate/copper turnings as the catalyst under microwave conditions (scheme 11).

Kappe and coworkers used copper(II) sulphate along with sodium ascorbate as the reducing agent to synthesis dihyrdopyrimidone libraries,[17] utilising microwave irradiation to achieve high yielding CuAAC reactions with reaction times of only one minute (scheme 12), demonstrating the rapidity of the CuAAC reaction.



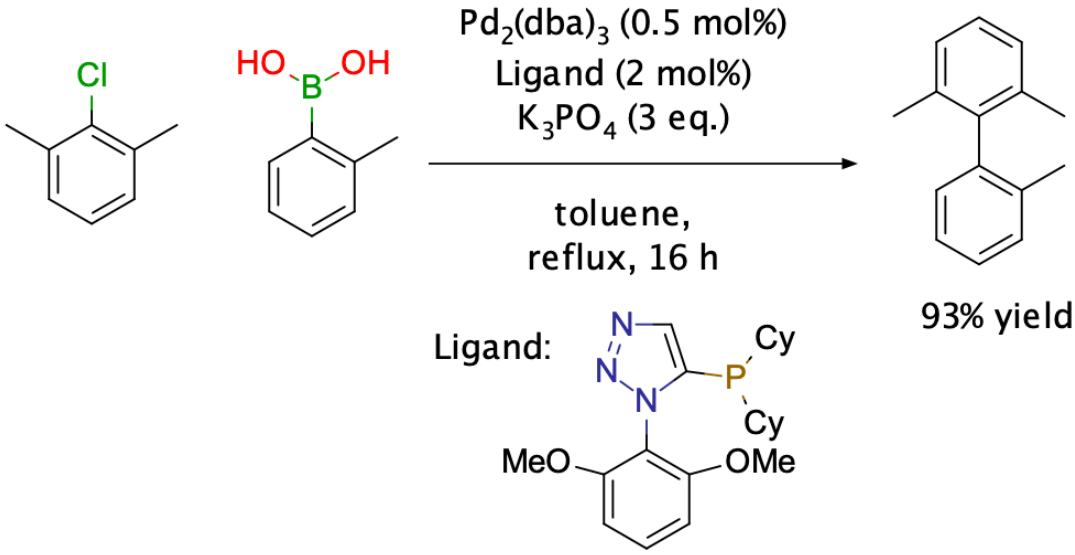
Scheme 12: Rapid CuAAC by microwave irradiation

Fossey, Buckley and coworkers[18] applied a class of phosphino-triazoles previously reported by the laboratories of Choubey[19] and Glover[20] and structurally similar, though regio-isomerically distinct, to the phosphino-triazoles reported in 2005 by the laboratory of Zhang[21] as ligands for palladium-catalysed cross-coupling reactions.

Scheme 13: Synthesis of phosphino-triazoles

The ligand was synthesised over two steps by first reacting trimethylethynylsilane, acting as masked ethyne, with an aryl azide in the presence of copper(II) sulphate and sodium ascorbate to provide the mono-

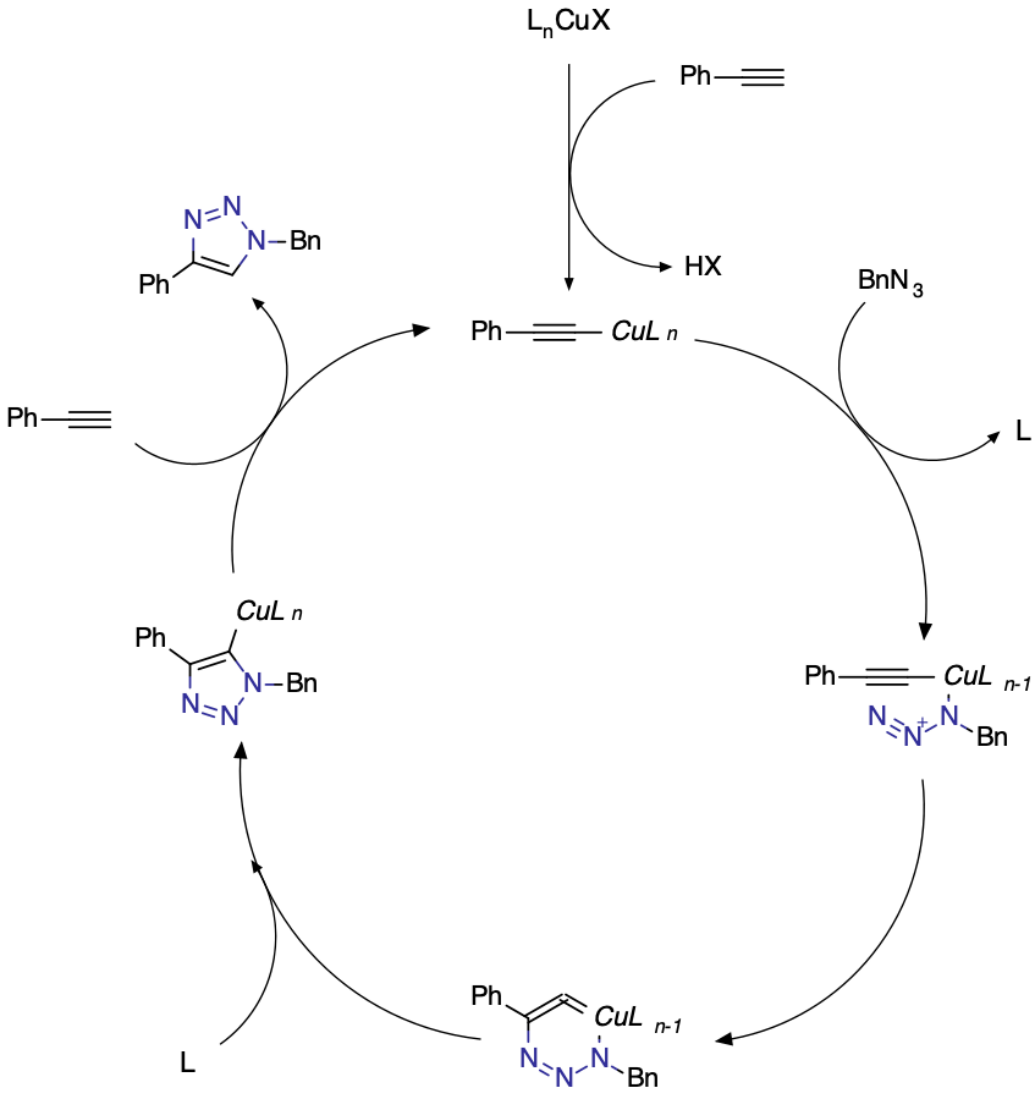
substituted triazole in 72% yield. Selective deprotonation with ^{n}BuLi followed by a dicyclohexylphosphorous chloride quench yielded the desired 1,5-phosphino-triazole ligand (scheme 13). Application of this triazole as a ligand in palladium-catalysed cross coupling reactions lead to biaryls in high yields (scheme 14).



Scheme 14: Phosphine-triazoles as ligands for palladium-catalysed cross-coupling reactions

1.2 CuAAC Mechanism.

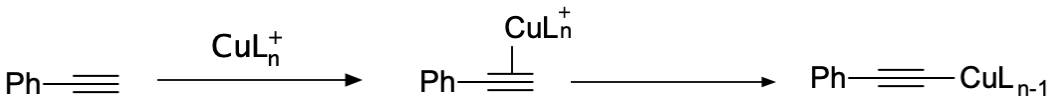
Despite the name, copper-catalysed azide-alkyne cycloaddition reactions do not proceed by a concerted cycloaddition process. The stepwise mechanism proposed by Sharpless and Fokin (scheme 15) first features C-H insertion of copper(I) to produce a copper(I) acetylide, to which the azide then ligates. Cyclisation to an unusual six-membered cyclic copper carbene which then undergoes a ring contraction to provide a triazolyl cuprate. Proto-demetalation yields the 1,4-triazole and regenerates the active catalytic species.



Scheme 15: Stepwise CuAAC mechanism.

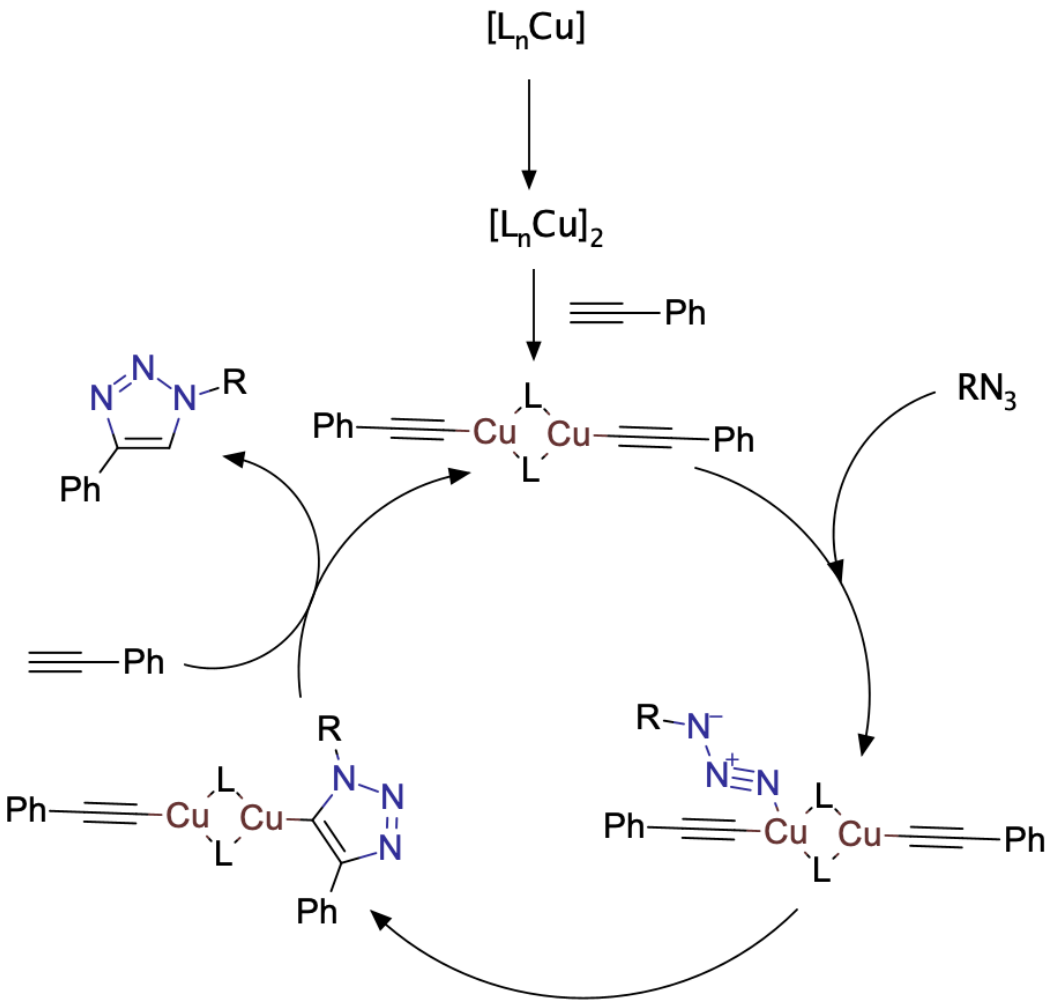
It was later proposed that the reaction requires two copper(I) species to proceed at the high rates observed, one to form the alkynyl cuprate and the other to act as a π-Lewis acid. Computational studies showed that π-coordination of copper(I) to the alkyne increases the energy barrier for azide-alkyne cycloaddition, however, as described above, the reaction is not thought to proceed by a concerted cycloaddition pathway.

DFT studies performed by the laboratories of Fokin and Sharpless[22] published in 2005 suggest that the copper(I) ion initially ligates to the alkynyl π-system (scheme 16). This coordination significantly lowers the pK_a of the alkynyl proton by up to 9.8, facilitating the formation of the copper acetylide.



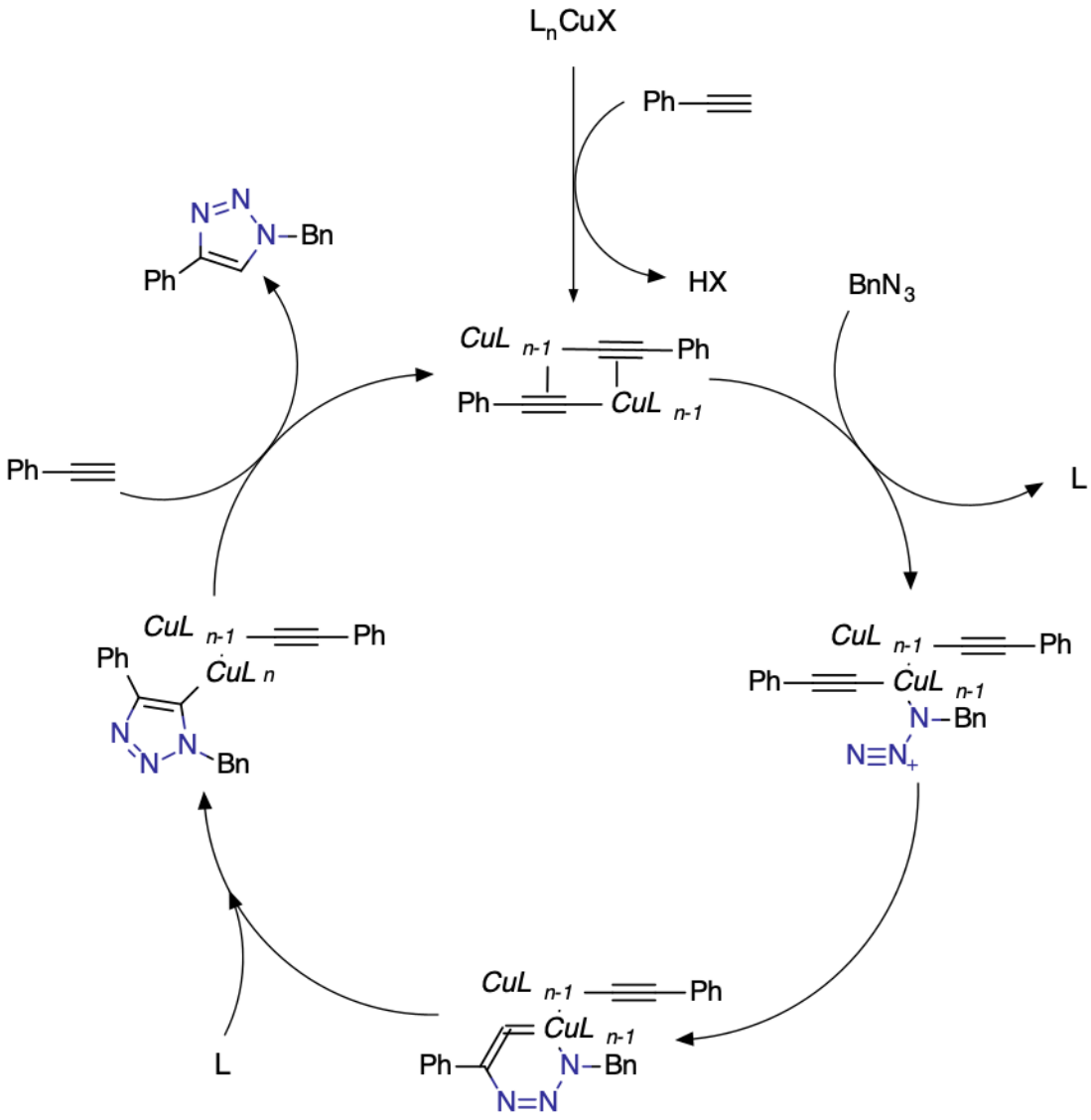
Scheme 16: C-H Insertion facilitated by π-coordination.

Later in the same year of 2005 Rodionov, Finn, and Fokin[23] published kinetic studies on the CuAAC reaction. They had found that the reaction is second order in copper and proposed an updated mechanism exhibiting a dinuclear copper species as the catalytic species (scheme 17). Fokin and coworkers also noted that CuAAC reactions of bis(azides) resulted in bis(triazoles) being isolated as the major product, even when a large excess of the bis(azide) was used, in comparison when azides reacted with bis(alkynes) statistical mixtures of bis- and monotriazoles were isolated. This observation was put forward as evidence for the presence of a second copper acetylide in the catalytic cycle.[24]



Scheme 17: Dinuclear CuAAC mechanism.

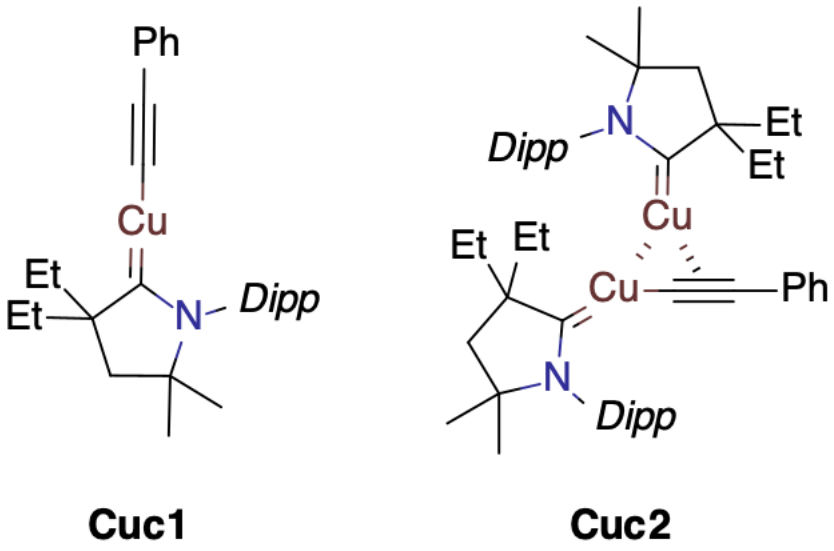
An expansion of the dinuclear-copper mechanism (scheme 18) was published by Heaney and coworkers in 2010, providing computational and experimental evidence for dimeric alkynyl cuprate ladderanes as the active catalytic species.[25]



Scheme 18: CuAAC ladderanes

2015 saw the publication of a landmark investigation into the active catalytic species of the CuAAC reaction, in which the stability of copper(I) *N*-heterocyclic carbenes was capitalised upon to isolate copper acetylides.[26] Bertrand and coworkers[1] prepared both mononuclear and dinuclear copper acetylides. (scheme 19) Bertrand and coworkers demonstrated through kinetic studies that the dinuclear species **Cuc2** was an extremely active catalyst when compared to

the relatively sluggish **Cuc1**, reporting a difference in observed rate of two orders of magnitude.



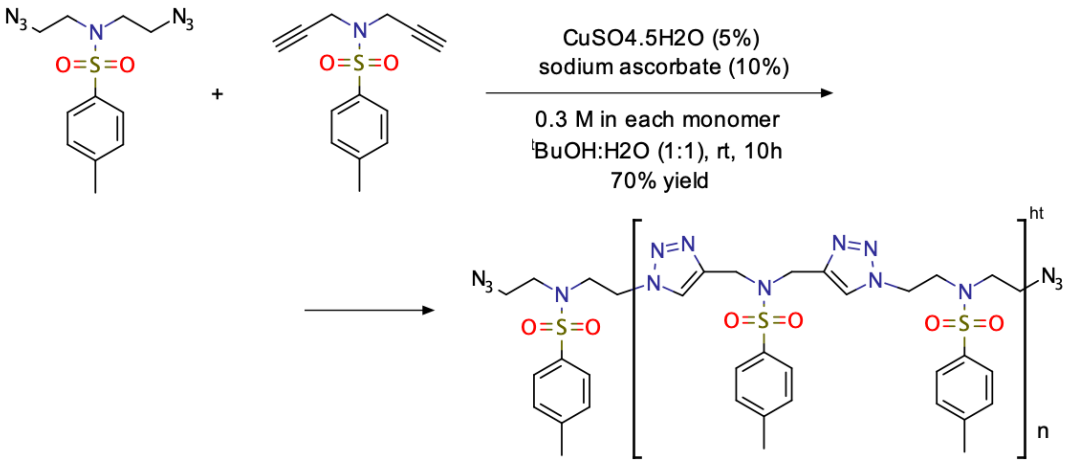
Cuc1 **Cuc2**

Scheme 19: Isolated copper acetylides.

1.3 Applications of the CuAAC Reaction.

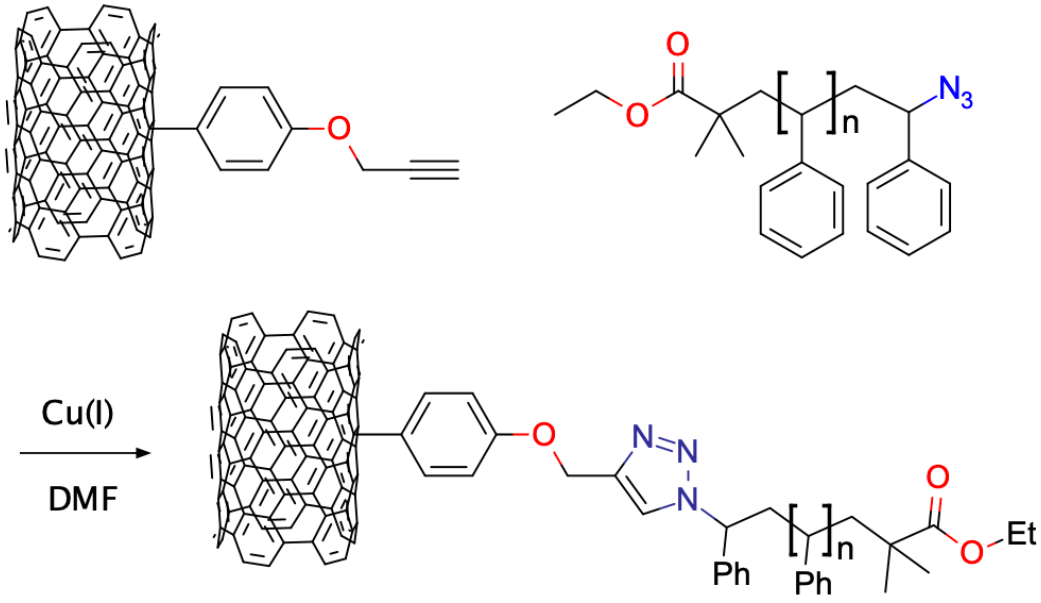
Since its discovery in 2001, the CuAAC reaction has found use in a variety of applications, ranging from materials and polymer science[76] to drug discovery[77] to bioorthogonal chemistry.[78]

Finn and coworkers applied the CuAAC reaction to polymerization in 2004[79]. A catalytic system of copper(ii) sulphate with sodium ascorbate in ^{t}butanol/water effected the copolymerization of a diyne and diazide, both derived from *p*-toluenesulfonamide, in 70% yield (scheme 20).



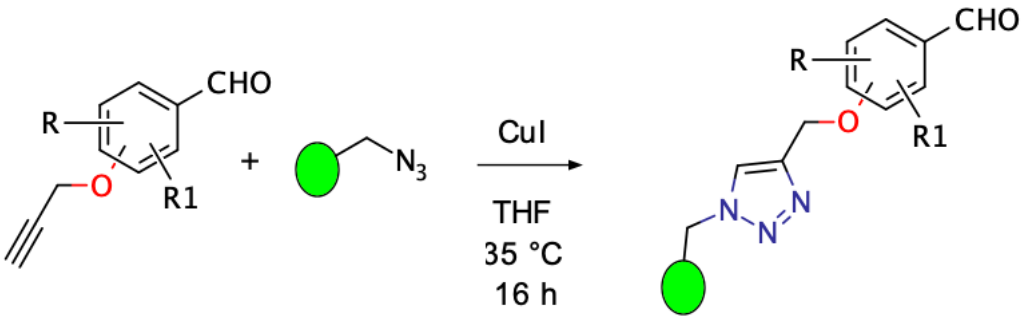
Scheme 20: CuAAC Mediated Polymerisation

In 2005 Ardronov[80] and colleagues demonstrated the application of the CuAAC reaction to the functionalisation of single-walled carbon nanotubes with polystyrene (scheme 21), using a catalytic system of copper(i) bromide in the presence of 2,2′-Bipyridine.



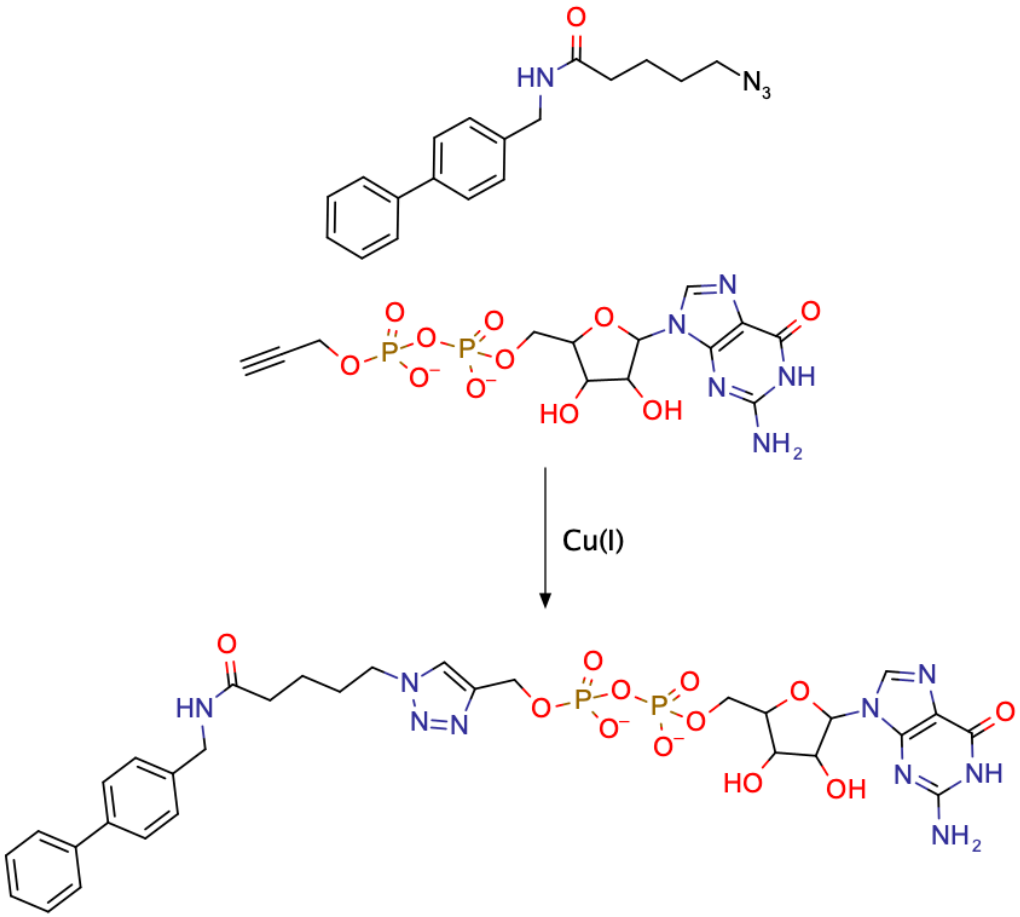
Scheme 21: CuAAC Functionalisation of Carbon Nanotubes.

The CuAAC found applications in drug discovery soon after it was first reported in 2001. Gmeiner and coworkers used CuAAC reactions to synthesis solid phase organic synthesis (SPOS) resins[81]. By converting the chloride functionality on a Merrifield resin to an azide the group were able to construct a modest library SPOS resins through CuAAC reactions with substrates featuring an alkyne handle (scheme 22). The group used these resins to demonstrate the synthesis of dopaminergic compounds.



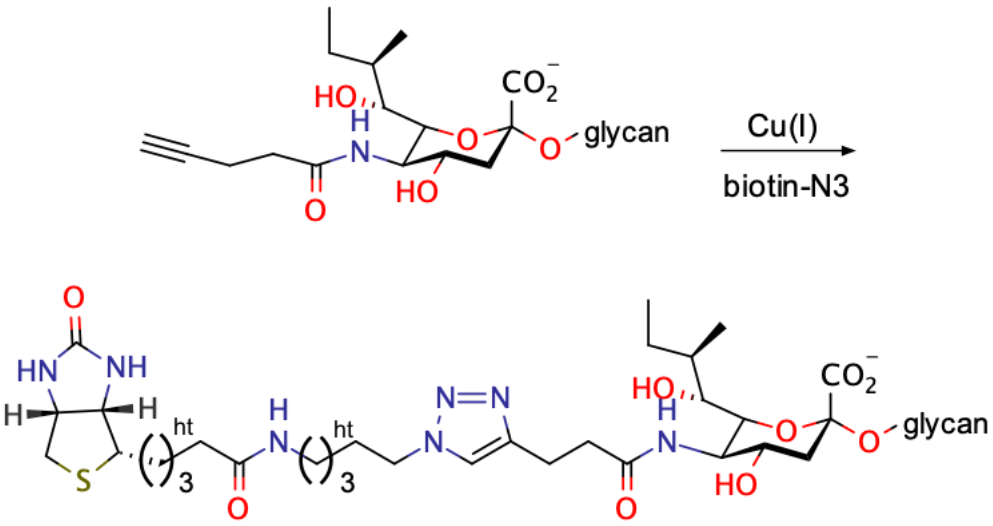
Scheme 22: CuAAC Synthesis of SPOS Resins.

Also in 2003, Fokin, Sharpless, Wong, and coworkers applied the CuAAC reaction in the synthesis of an inhibitor of human r-1,3-fucosyltransferase. The group coupled Guanosine diphosphate, modified with an alkyne handle, with a library of azides (scheme 23). The cleanliness of CuAAC reactions and the lack of need for functional group protection strategy when using these reactions allowed the screening of the library to be performed using the crude reaction mixture, ultimately concluding in the discovery of a highly selective inhibitor.[82]



Scheme 23: CuAAC in the Synthesis of a Selective r-1,3-Fucosyltransferase Inhibitor.

As demonstrated by Fokin and coworkers by their *in situ* CuAAC reaction and screening methodology, the CuAAC reaction is a great candidate for bioorthogonal chemistry. The reaction has seen use in the bioorthogonal labelling of proteins, glycans, lipids, and nucleic acids.[84] Tirrel and coworkers utilised the CuAAC reaction to label newly expressed protein in bacterial[85] and mammalian cells.[86] In 2007, the groups of Cravatt and Wong,[87] in collaboration, used the CuAAC reaction to label glycans with saccharide selective probes (scheme 24).

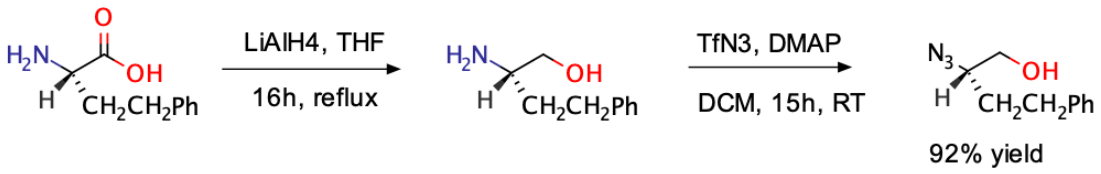


Scheme 24: Bioorthogonal Labelling with CuAAC Reactions.

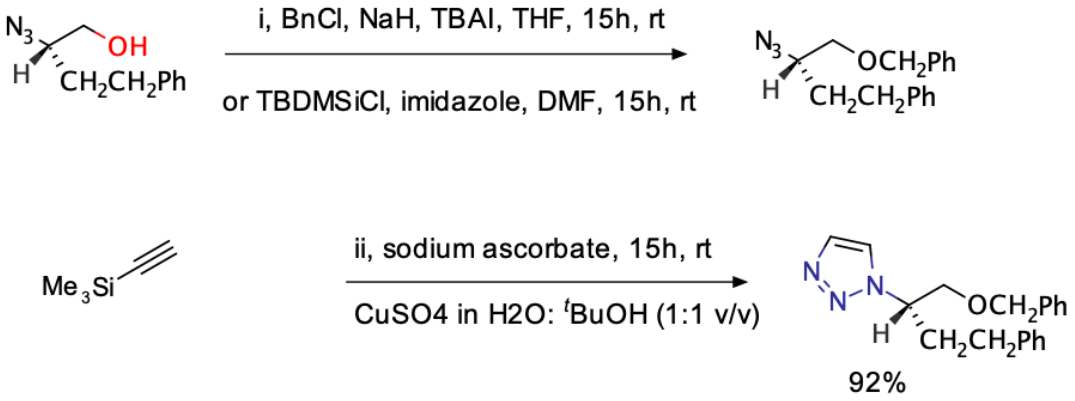
1.4 Enantioenriched Triazole Construction.

1.4.1 CuAAC with Enantioenriched Starting Materials.

Given the vast use 1,2,3-triazole construction has seen in organic synthesis, it is unsurprising that examples of chiral non-racemic triazoles exist. A generally uncomplicated means towards enantioenriched triazoles is the utilisation of enantioenriched starting materials. Primary amine to azide functional group conversion methodologies and availability make amino acids a prime candidate for the role of enantioenriched starting material. Grøtli and coworkers[27] reported the synthesis of chiral triazoles starting with amino acids, which they reduced to the amino alcohol before performing an amine-azide functional group conversion with trifluoromethanesulfonyl azide (scheme 25). Protection of the alcohol followed by reaction with an alkyne under copper(II) sulphate/sodium ascorbate copper-catalysed azide-alkyne cycloaddition reaction conditions yielded enantioenriched 1,4-disubstituted 1,2,3-triazoles (scheme 26).

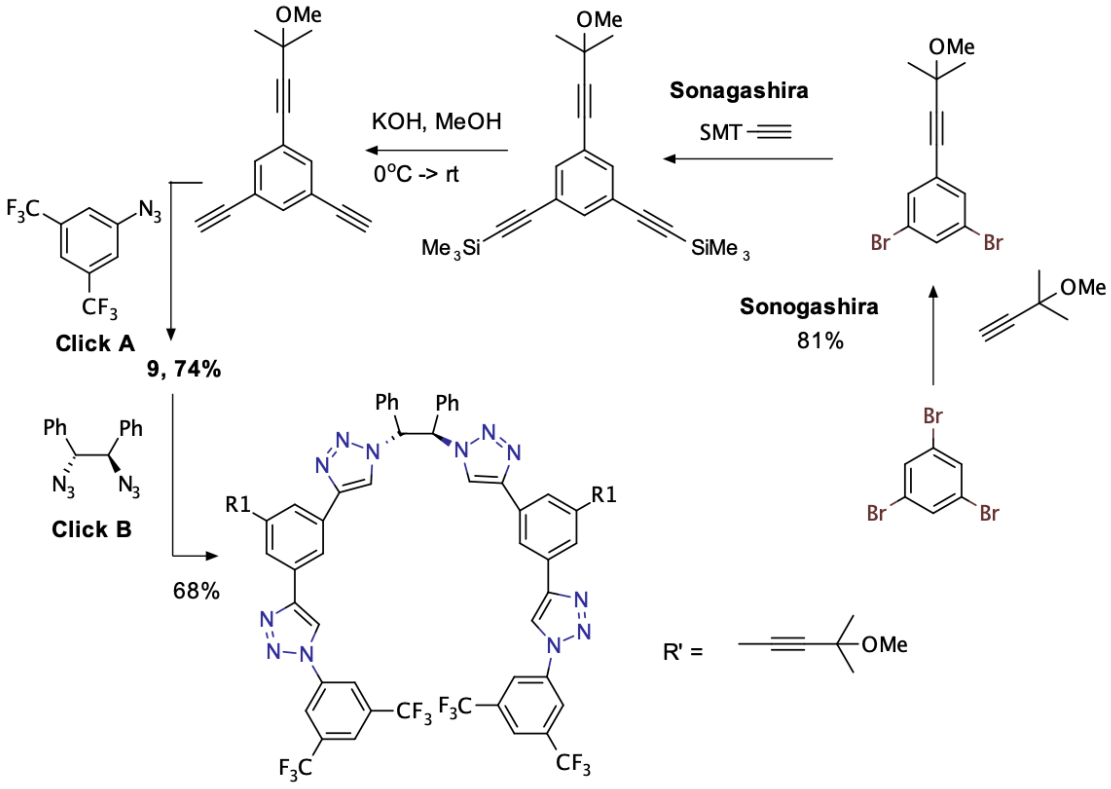


Scheme 25: Amine to azide functional group conversion



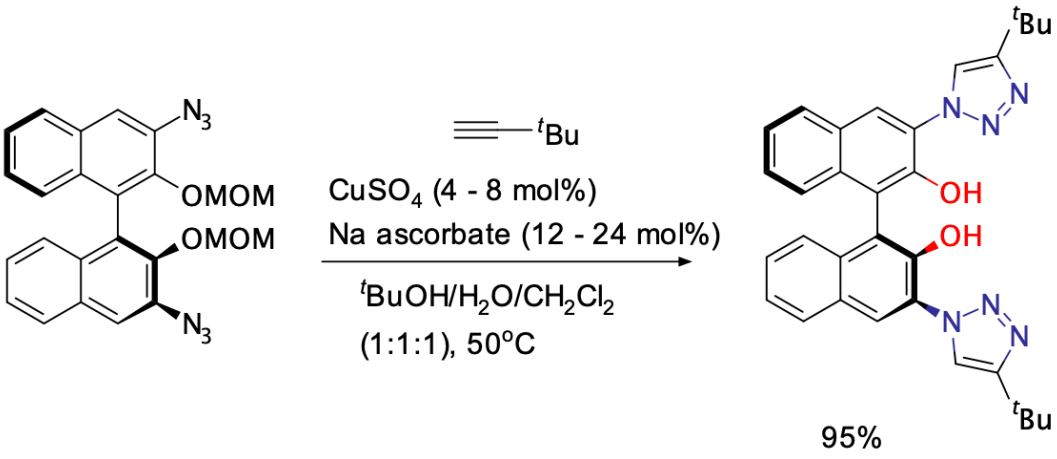
Scheme 26: Amino acid-derived enantioenriched triazoles

Mancheño and coworkers also utilised amine-azide functional group conversion to access enantioenriched azides for the CuAAC synthesis of enantioenriched triazoles.[28] Conversion of 1,2-diamines to to 1,2-diazides followed by CuAAC reactions delivered a library of C_2-symmetric ligands, which they applied to the enantioselective Reissert-like dearomatisation of isoquinoline (scheme 27).



Scheme 27: Synthesis of chiral triazoles from enantioenriched 1,2-diamines

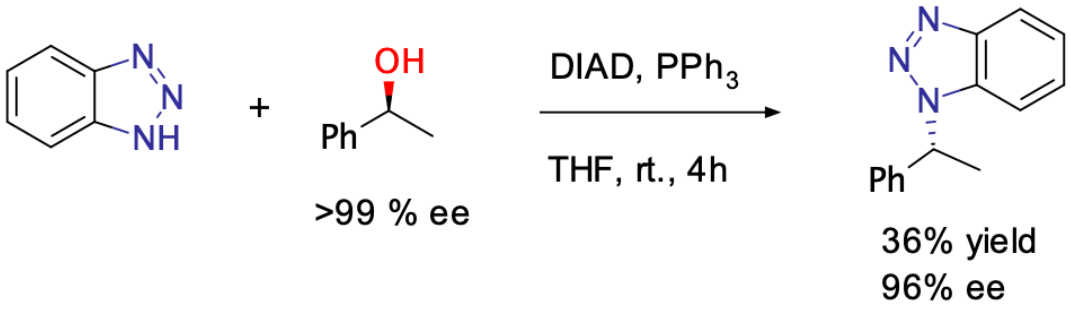
The laboratory of Mañcheno also reported the use of BINOL as an chiral starting material for the synthesis of chiral 1,2-disubstituted 1,2,3-triazoles.[29] Masking of the hydroxyls with the *ortho*-directing methoxymethyl group following by *ortho*-lithiation with ^{n}BuLi and TMEDA at 0 °C followed by a 4-toluenesulfonyl azide quench delivered a C_2-symmetric bis(azide) with a binaphthyl backbone. Reaction with alkynes under copper(II) sulphate/sodium ascorbate CuAAC reaction conditions yielded bis(triazoles) (scheme 28), which they then utilised as ligands in asymmetric titanium-catalysed reductions of aldehydes.



Scheme 28: Synthesis of chiral triazoles from enantioenriched BINOL

1.4.2 Synthesis of Enantioenriched Triazoles Without CuAAC Reactions.

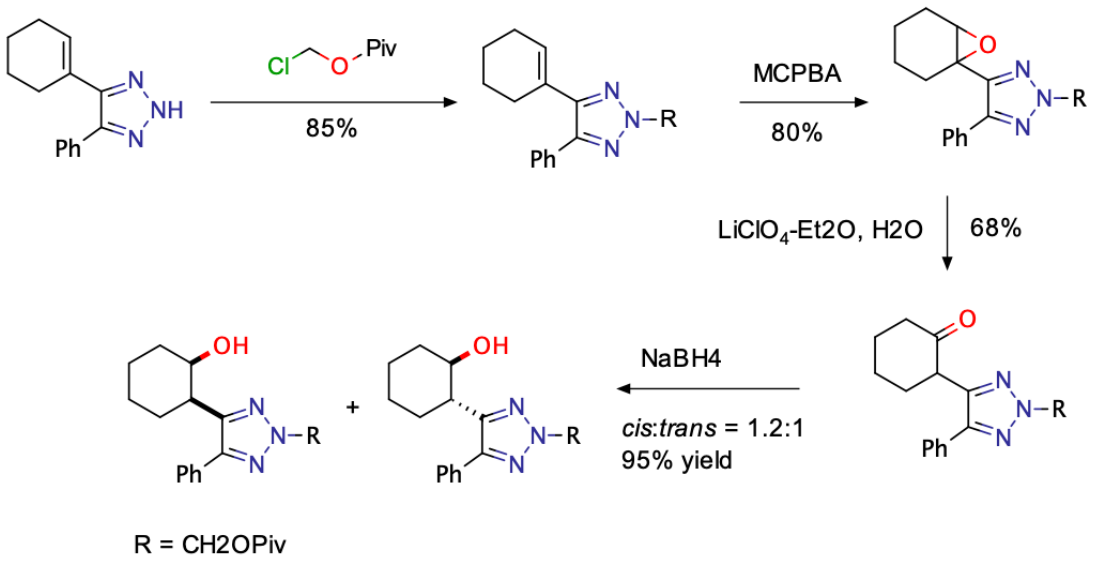
As a means to enantioenriched triazoles, achiral triazoles may first be constructed with the intent to desymmetrise the triazole, for example through *N*-functionalisation with an enantioenriched reaction partner or through desymmetrisation of a functional group adjacent to the triazole.



Scheme 29: Synthesis of an enenatioenriched benzotriazole through reaction with enantioenriched alcohols

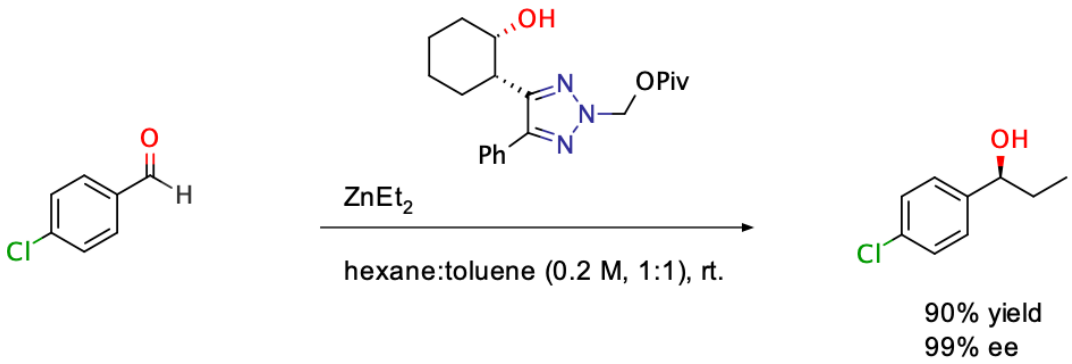
The laboratory of Shi reported the diisopropyl azodicarboxylate/triphenyl phosphine mediated reaction of benzotriazole with (*S*)-(–)-1-Phenylethanol to produce an enantioenriched benzotriazole derivative (scheme 29).[30]

Chiral triazoles may also be obtained by the separation of enantiomers.[31] Starting with an achiral 1,2,3-triazole featuring a cyclohexene handle, Shi and coworkers obtained enantioenriched triazoles by first epoxidising the cyclohexene moiety with *m*CPBA, which they converted to the ketone with a Meinwald rearrangement. Reduction of the ketone yielded a pair of separable diastereomers (scheme 30). The separated diastereomers were subjected to kinetic resolution by acetylation with Candida antarctica lipase B (CalB) to yield the enantioenriched triazoles.



Scheme 30: Conversion of racemic triazoles to diastereomers for CalB kinetic resolution

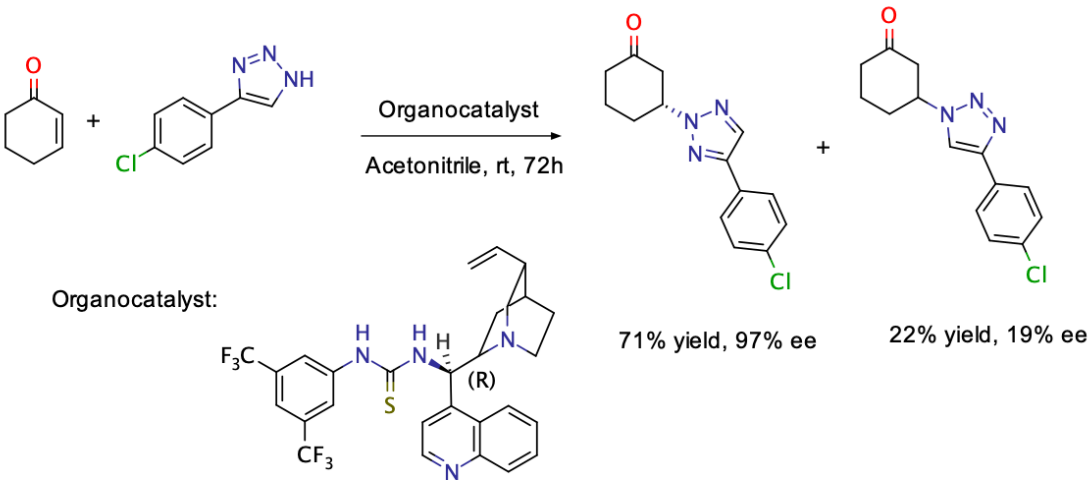
Shi and coworkers demonstrated application of the resulting chiral triazoles as mediators for the enantioselective addition of diethyl zinc to aldehydes (scheme 31).



Scheme 31: Enantioenriched triazoles as a mediator for the enantioselective alkyl zinc addition to aldehydes.

Bhagat and Peddinti reported[32] the synthesis of enantioenriched triazoles from achiral substrates by the enantioselective organocatalysed desymmetrisation of cyclohexenone. The use of mono-substituted triazoles as a Michael donor,

enantioselectively reacting with cyclohexenone in the presence of an organocatalyst to provide enantioenriched triazoles in up to >99% ee, with the 2,4-disubstituted triazole as the major product (scheme 32).

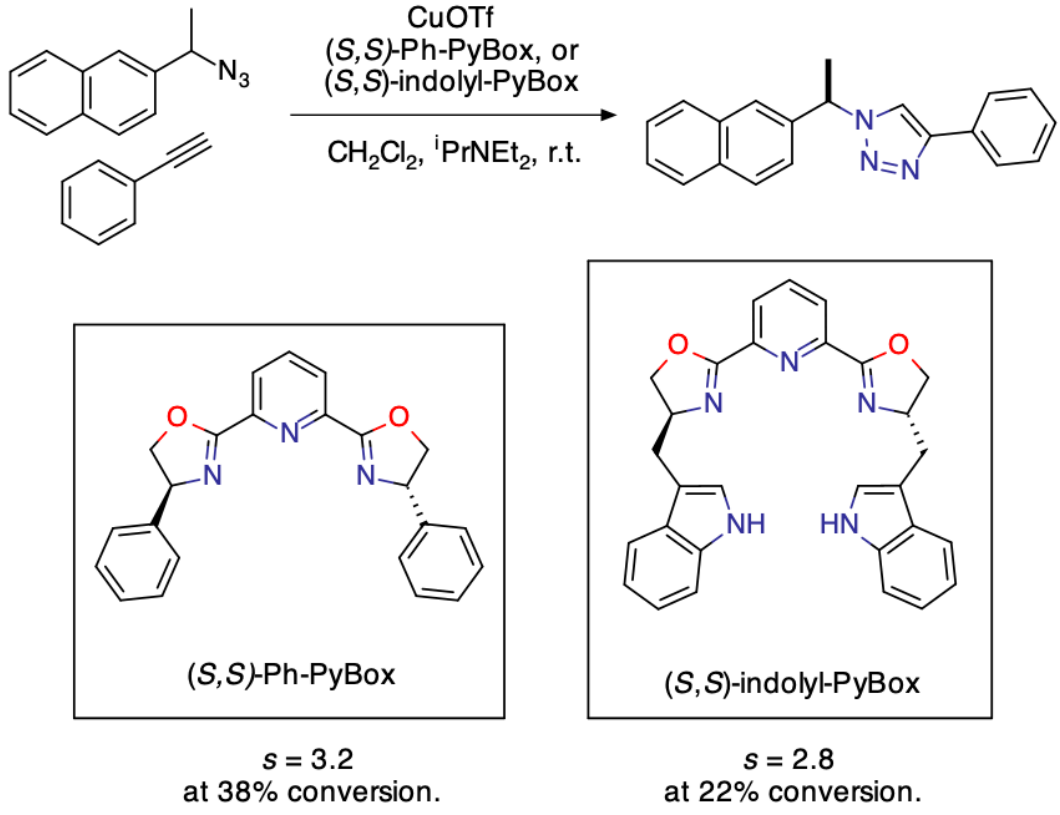


Scheme 32: Organocatalysed enantioselective desymmetrisation of Michael accepters with mono-substituted 1,2,3-triazoles to yield enantioenriched 2,4-disubstituted 1,2,3-triazoles

1.4.3 Asymmetric CuAAC Reactions.

The field of asymmetric 1,3-dipolar cycloaddition reactions has been heavily studied,[33] yet only a handful of examples of asymmetric copper-catalysed azide-alkyne cycloaddition reactions exist in the chemical literature.[34]

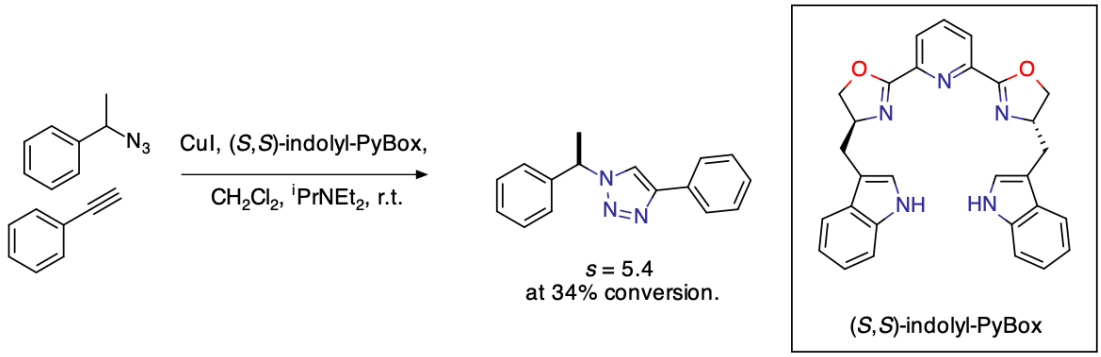
The first report of an enantioselective CuAAC reaction came from the laboratory of Fokin.[35] Ten PyBox ligands were screened for the kinetic resolution of a racemic sample of naphthylethyl azide with phenylacetylene to varying degrees of success. The most promising results came from (*S*,*S*)-Ph-PyBox and (*S*,*S*)-indolyl-PyBox, providing triazoles with *s* = 3.2 at 38% conversion and *s* = 2.8 at 22% conversion, respectively (scheme 33).



Scheme 33: Kinetic resolution of naphthylethyl azide.

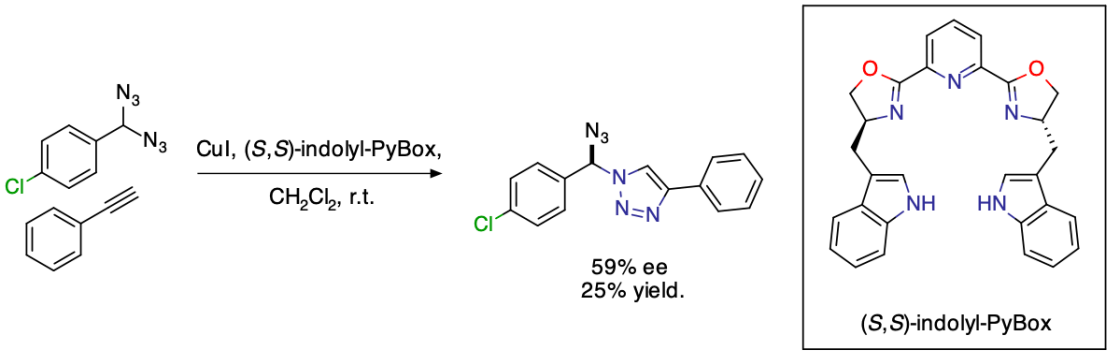
Copper screening and modification of the azide-containing substrate to phenethyl azide lead to an increased selectivity of *s* = 5.9 at 37% conversion with (*S*,*S*)-

indolyl-PyBox (scheme 34). It was found that copper(I) iodide provided the highest selectivity.



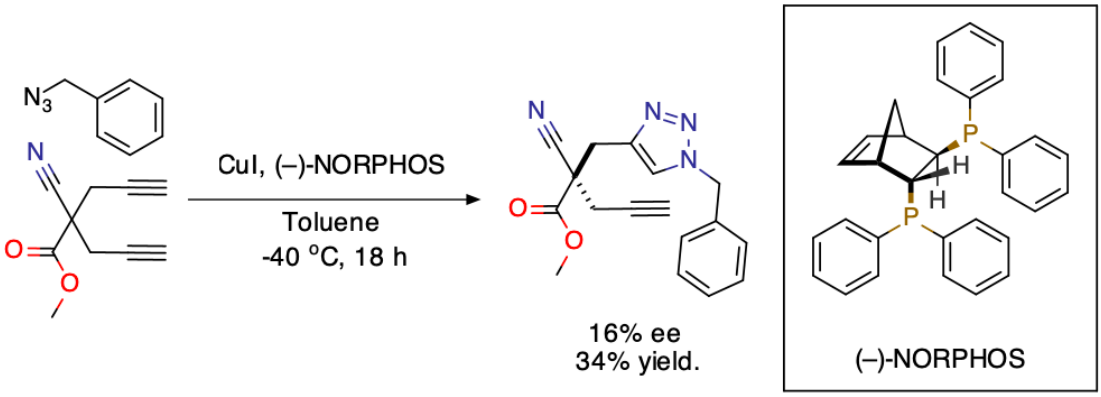
Scheme 34: Kinetic resolution of phenethyl azide.

Desymmetrisations of prochiral geminal diazides (scheme 35) with the optimised conditions from the kinetic resolution above (scheme 34) resulted in the bis(triazole) as the major product in 60% yield, with the chiral monotriazole isolated as the minor product in up to 25% yield and 59% ee. The enantioselectivity of this desymmetrisation appeared to be very substrate dependent. 1-(Diazidomethyl)-2-methylbenzene (not shown) reacted with phenylacetylene to give the corresponding monotriazole in only 16% ee.



Scheme 35: Desymmetrisation of p-chlorophenyl diazide.

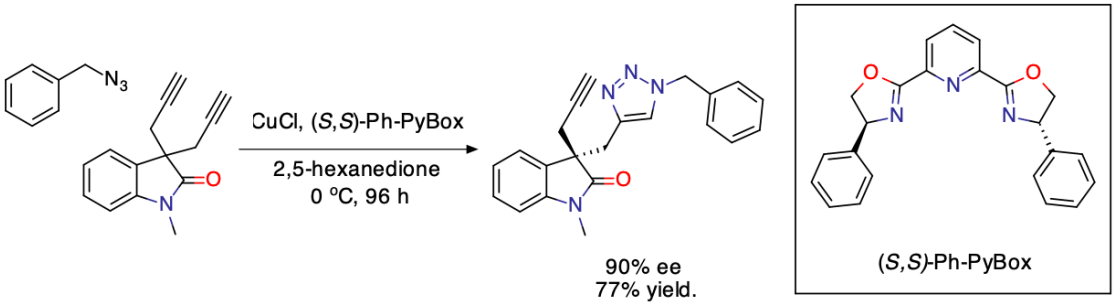
In 2013 the first examples of desymmetrisation of prochiral diynes appeared in the literature.



Scheme 36: Cyanoacetate ester desymmetrisation.

Page and Stephenson reported the desymmetrisation of simple bis(alkynes) (scheme 36) prepared from the reaction between cyanoacetate esters and propargylic bromide.[36] Desymmetrisation with benzyl azide in the presence of copper(I) iodide and (–)-NORPHOS at -40 °C provided the monotriazole in 16% ee after stopping the reaction at 34% yield.

The laboratory of Zhou reported the CuAAC desymmetrisation of oxindole-derived dis(alkynes) with benzyl azide in high yields and enantioselectivities (scheme 37).[37]

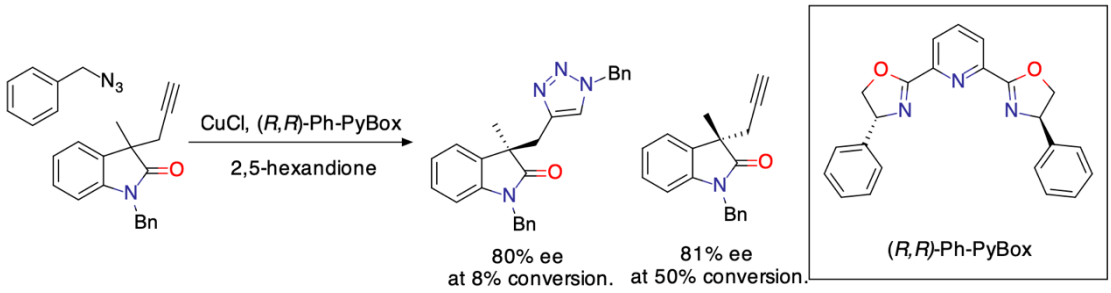


Scheme 37: Oxindole desymmetrisation.

This robust desymmetrisation provided high enantioselectivities and yields with a wide range of oxindole-derived bis(alkynes) and azides. The esoteric solvent, 2,5-hexanedione, was instrumental to the yields and enantioselectivities reported, with more common solvents giving comparatively poor results. The drastic increase of enantioselectivity and yield brought about by the use of 2,5-hexanedione as a solvent appears to be unique to this oxindole-derived class of

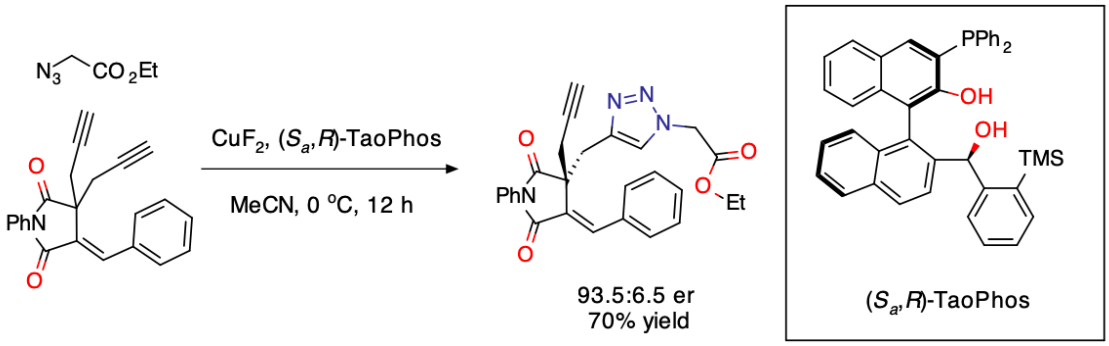
bis(alkynes), as the solvent results in racemic triazoles in the cases of the cyanoacetate ester-derived bis(alkynes) investigated by the groups of Page and Stephenson (unpublished work), and in the work reported within this thesis (chapter 2.2).

Brittain, Buckley, and Fossey applied the conditions reported by the laboratory of Zhou to the kinetic resolution of oxindole-derived monoalkynes with great success, recovering the unreacted starting material in 81% ee at 50% conversion (scheme 38).[38]



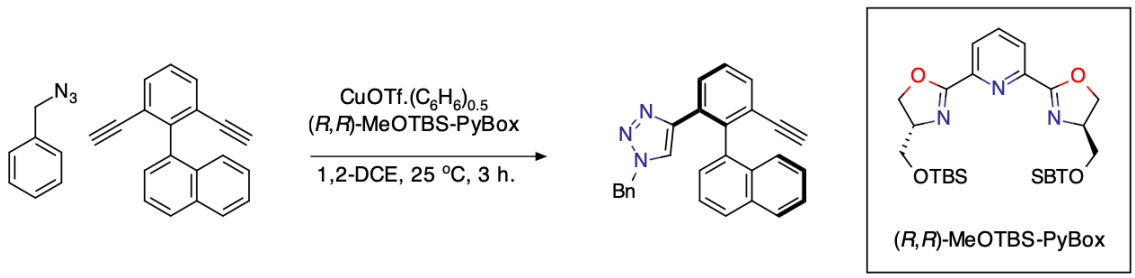
Scheme 38: Kinetic resolution of oxindoles.

The laboratory of Song successfully applied the Ar-BINMOL (TaoPhos) ligands they had previously developed for the enantioselective addition of zinc acetylides to aldehydes[39] to the desymmetrisation of meleimide-derived bis(alkynes)[40] (scheme 39). This reaction employed copper(II) fluoride as the source of copper, finding other copper(I) and copper(II) salts to give lower enantioselectivities. As well as having a notable effect on the enantioselectivity and yields of the desymmetrisation, the major enantiomer obtained was dependent on the choice of copper salt, with copper(II) fluoride, copper(II) acetate, and copper(I) oxide resulting in the opposite enantiomer to copper(I) chloride, copper(I) bromide, and tetrakis(acetonitrile)copper(I) hexafluorophosphate[41] highlighting the importance the choice of copper salt plays in asymmetric CuAAC reactions.



Scheme 39: Desymmetrisation of meleimides.

Deviating from the previous examples of enantioselective CuAAC desymmetrisations which all employ featuring a prochiral centre, the laboratory of Uozumi reported an elegant enantioposition-selective desymmetrisation of biaryls featuring axial prochirality[42] (scheme 40).



Scheme 40: Desymmetrisation of biaryls.

High yields and enantioselectivities were obtained with copper(I) triflate and the silylated serinol-derived PyBox ligand (*R*,*R*)-MeOTBS-PyBox as the catalytic system. Notably, this desymmetrisation proceeded rapidly, providing the triazole in 67% ee in three hours. The use of (*R*,*R*)-MeOTBS-PyBox showed a huge

improvement over the corresponding free alcohol (55% yield, 5% ee) and a significant improvement over (*R*,*R*)-Ph-PyBox (30% yield, 60% ee), the ligand utilised to great effect by the group of Zhou.

An asymmetric amplification[43], or *in situ* kinetic resolution, was observed when the equivalency of azide was increased from 1.0 to 1.5 resulting in an increase in the enantiomeric excess of the monotriazole to 91%.

The reaction is able to tolerate a both range of *para*-substituents on the phenyl ring and the replacement of the naphthyl ring by an *ortho*-methyl phenyl ring (figure 2) while retaining acceptable yields and high enantioselectivities.

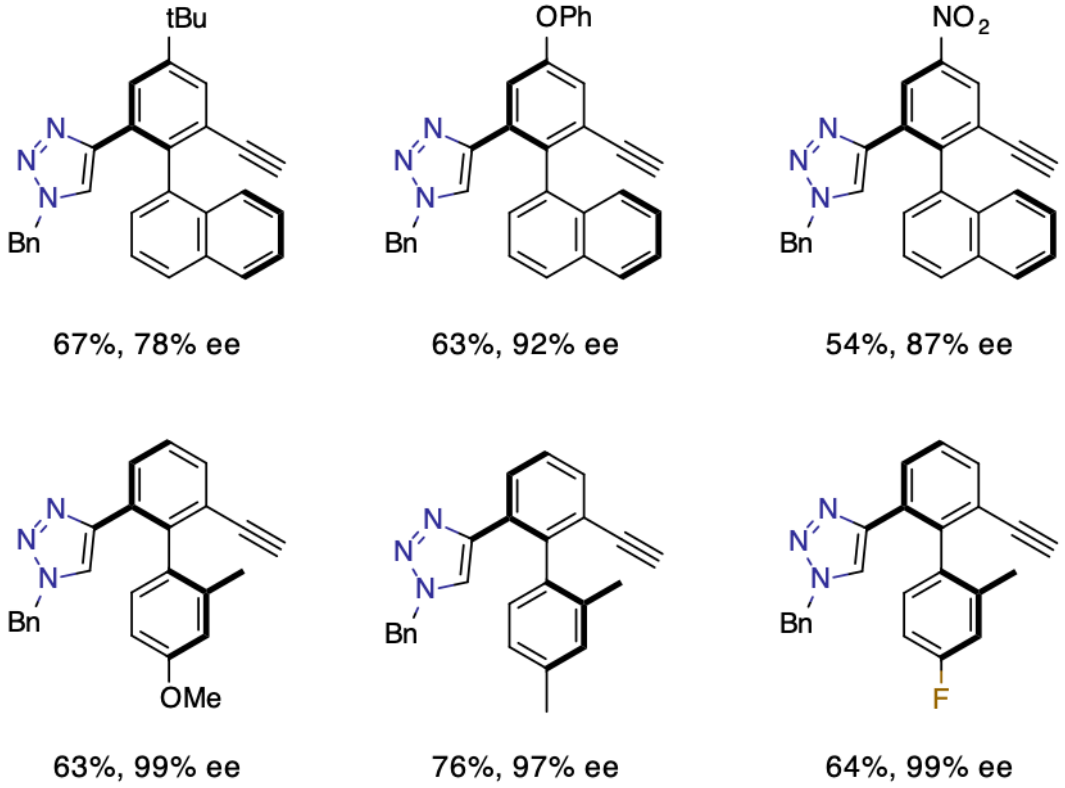
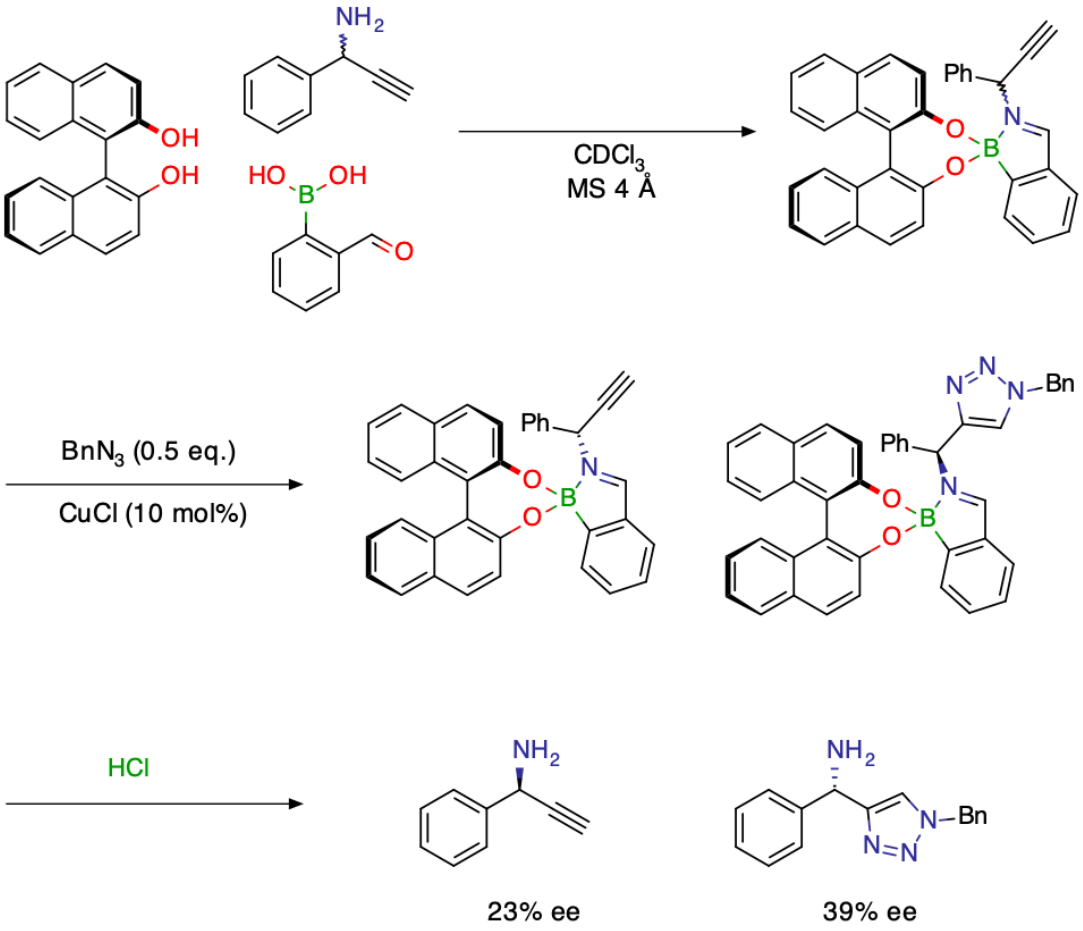


Figure 2: Uozumi enantioposition-selective CuAAC representative substrate scope.

A follow-up publication by Uozumi and Osako detailed negative non-linear effects with a fit in agreement with Kagan's model $(ML)_2$ systems,[44] providing further evidence for the role of dinuclear copper species as the active catalytic species in CuAAC reactions.

In 2016 Anslyn, Fossey, and coworkers[45] reported on the application of the Bull-James chiral auxiliary in the CuAAC kinetic resolutions of propargylic amines, publishing respectable enantiomeric excesses (scheme 41).

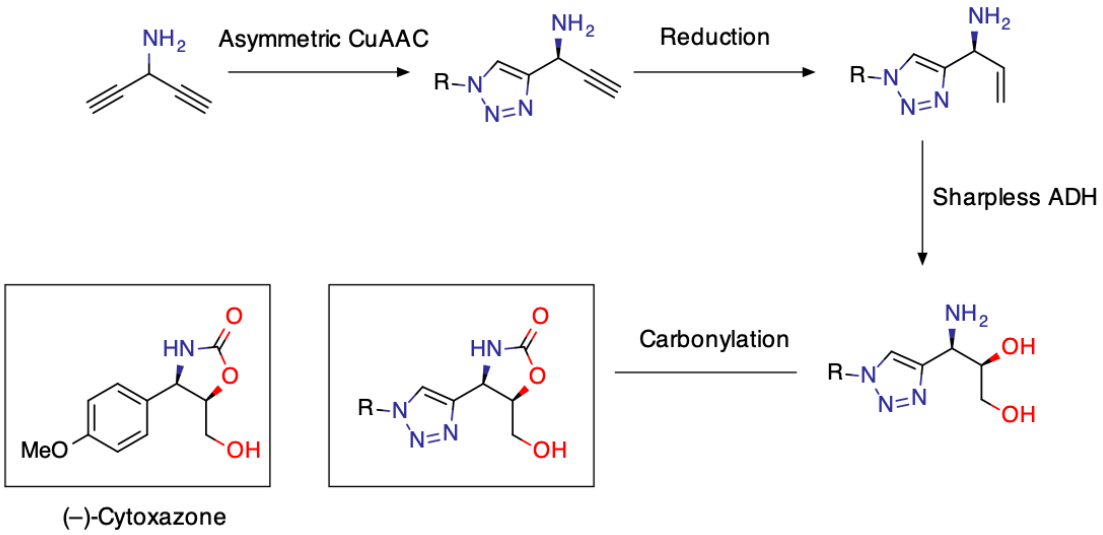


Scheme 41: Bull-James assembly in enantioselective CuAAC.

Results and Discussion.

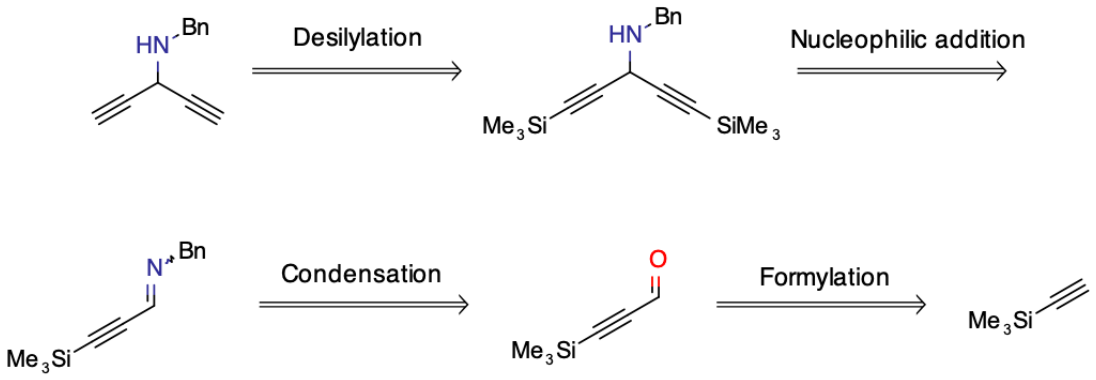
2.1 Bis(alkyne) Synthesis.

Building on the previous research into enantioselective copper-catalysed azide-alkyne desymmetrisation reactions performed by both our own laboratory and the laboratory of Zhou, we wished to apply the reaction to a total synthesis of natural product analogues. As a proof of concept we embarked on the design of a synthetic route to an analogue of cytoxazone, incorporating a 1,2,3-triazole in place of the methoxyphenyl and featuring an asymmetric CuAAC reaction as the key enantioselective step (scheme 42).



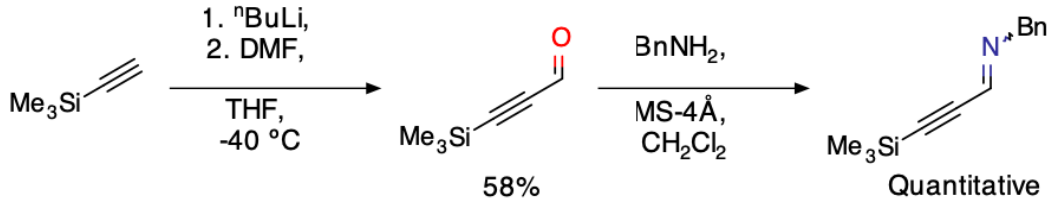
Scheme 42: Planned synthesis of cytoxazone analogues

We planned the synthesis of a diyne featuring an amine with an *N*-benzyl substituent, which we envisioned as being later removed under reductive conditions, ideally in the same step as the selective reduction of the remaining alkyne to the alkene. A retrosynthetic analysis (scheme 43) of this diyne led us to a propargylic imine, which boasted suitable functionality for the addition of the second alkyne and could be derived from readily available trimethylsilyl acetylene in two steps.



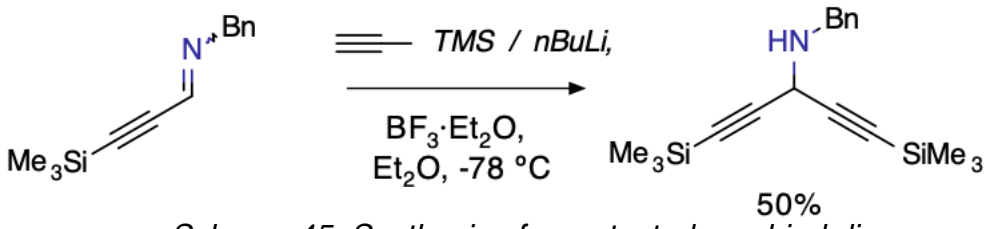
Scheme 43: Retrosynthesis of the prochiral diyne

To begin our synthesis of the diyne we first formylated trimethylsilylacetylene by deprotonation with ^{n}BuLi at 0 °C over 30 minutes followed by the addition of *N,N'*-dimethylformamide at -40 °C, providing the α-alkynylaldehyde in an acceptable yield. Condensation with benzylamine in the presence of molecular sieve furnished us with the desired imine as a mixture of stereoisomers in quantitative yield (scheme 44).



Scheme 44: Synthesis of the propargyl imine

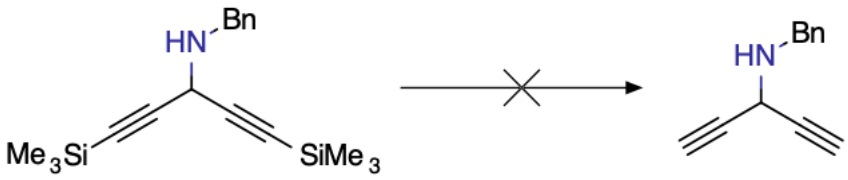
Addition of the second alkyne was successfully realised by the addition of lithium trimethylsilylacetylene, which had been prelithiated with ^{n}BuLi at 0 °C in diethyl ether, to the imine in the presence of boron trifluoride diethyl etherate at -78 °C (scheme 45).



Scheme 45: Synthesis of a protected prochiral diyne

With the silylated diyne in hand a simple desilylation would provide us with a suitable prochiral substrate for enantioselective desymmetrisation and continuation of the synthesis towards the proposed cytoxazone analogue.

To our surprise, desilylation with TBAF in THF did not yield the desired diyne, resulting instead in decomposition to many unidentified products even at reduced temperatures. A milder desilylation with catalytic potassium carbonate in methanol was attempted and appeared promising when the reaction was monitored by TLC, however attempts at isolating the product resulted in decomposition, similarly to the desilylation with TBAF (scheme 46).



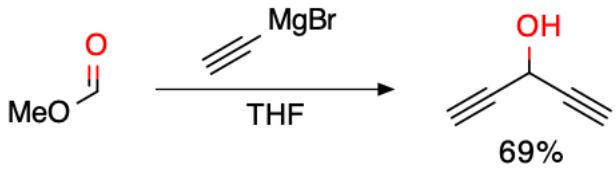
Scheme 46: Unsuccessful diyne desilylation

Upon encountering this hurdle we proposed to undertake the synthesis of a diyne which required fewer synthetic steps in order to facilitate an investigation into the necessary desilylation conditions to achieve the synthesis of the desired prochiral diyne and to gain an insight into the application of the enantioselective CuAAC reaction to this class of diyne.

By replacing the amino functional group with hydroxyl, as shown in figure 3**,** the number of synthetic steps to obtain a prochiral diyne could be significantly reduced.

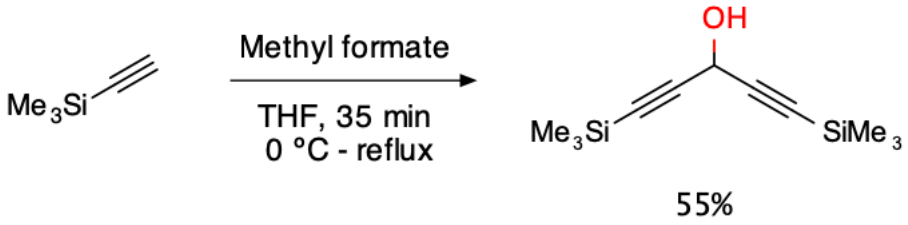
Figure 3: amino and hydroxyl diynes

The addition of ethynylmagnesium bromide as a 0.5 M solution in THF to methyl formate resulted in the desired diyne (scheme 20) after two days reaction at room temperature in a yield of 28% (scheme 47) after aqueous workup and purification by column chromatography.



Scheme 47: Synthesis of 1,4-pentadiyn-3-ol.

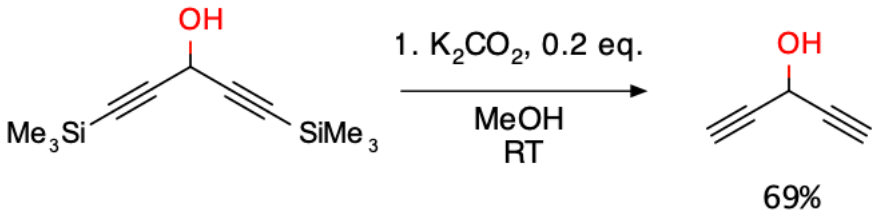
The inefficiency of the reaction due to the large volumes of THF used and non-trivial purification prompted the planning of an alternative route to the desired dialkyne. By lithiating trimethylethynylsilane with ^{n}BuLi at 0 °C over 30 minutes, and subsequently adding methyl formate before heating the mixture to near reflux for 5 minutes, yielded the desired (bis)TMS-protected diyne (scheme 48).



Scheme 48: Synthesis of the silylated precursor to 1,4-pentadiyn-3-ol.

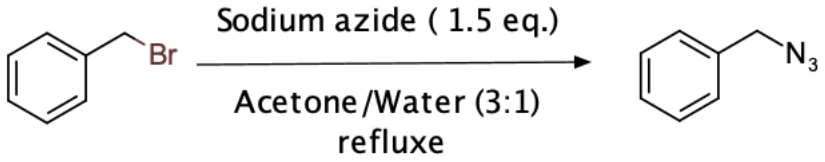
A simple desilylation would yield the desired prochiral diyne suitable for enantioselective desymmetrisation. Unfortunately, desilylation with TBAF in THF resulted in complete and rapid decomposition of the diyne to unidentified products even at reduced temperatures. Desilylation with catalytic potassium carbonate in methanol at room temperature was shown by TLC to proceed quickly and efficiently. However, upon concentrating the reaction mixture after filtration, decomposition was again observed. Performing an aqueous workup with ammonium chloride to avoid concentrating the desired diyne with residual

potassium carbonate resulted in the desired diyne sufficiently pure for further use, in the yield of 69% (scheme 49).



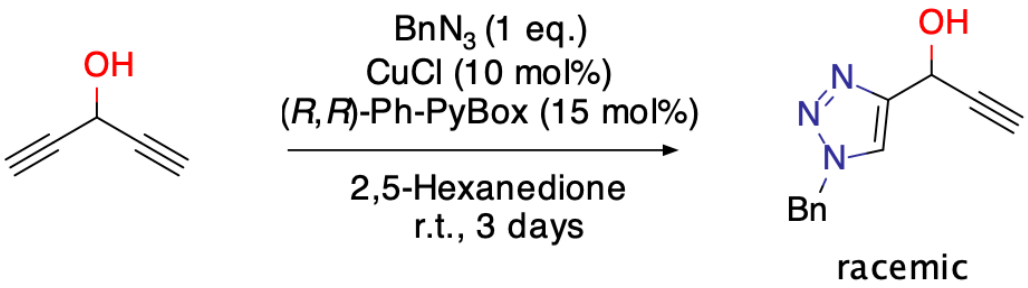
Scheme 49: Synthesis of 1,4-pentadiyn-3-ol.

We chose benzyl azide (scheme 50) as a simple, easily synthesised, and relatively stable cycloaddition partner suitable for investigations into enantioselective CuAAC reactions.



Scheme 50: Synthesis of benzyl azide.

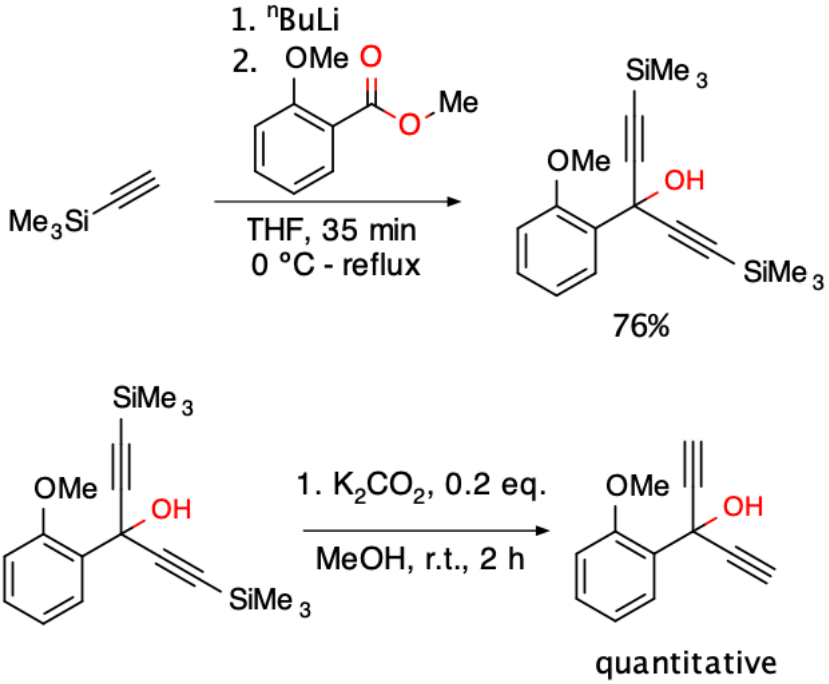
With both a prochiral (bis)alkyne and benzyl azide in hand we began our investigation into the asymmetric CuAAC desymmetrisation of geminal diynes (scheme 51).



Scheme 51: Enantioselective CuAAC: Zhou conditions.

When subjecting 1,4-pentadiyn-3-ol and benzyl azide to the enantioselective CuAAC conditions reported by Zhou's laboratory[37] the resulting benzyl triazole was isolated as the racemate. This unexpected and disappointing result made obvious the need to further develop and optimise the enantioselective CuAAC conditions for this class of diyne.

Due to the difficulties in handling 1,4-pentadiyn-3-ol, namely its tendency to decompose, we embarked upon the design of more stable quaternary diynes to facilitate the screening of reaction conditions (scheme 52).

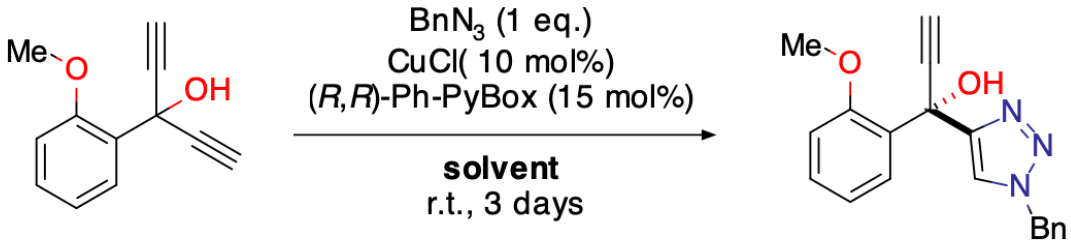


Scheme 52: Quaternary (bis)alkyne synthesis.

We synthesised a prochiral diyne featuring an aromatic group using the same methodology we found effective for the synthesis of 1,4-pentadiyn-3-ol. Our assumption that a higher molecular weight quaternary derivative would prove less demanding to handle was immediately confirmed. The purification of the isolated silylated diyne was produced in a higher yield after a relatively trivial purification and the desilylation proceeded quickly, cleanly, and quantitatively.

Building on the results of Zhou, these diynes were subjected to initial solvent screening using coper(I) chloride and (*R*)-Ph-PyBox as the catalyst.

2.2 Solvent Screening.



Scheme 53: Solvent screening reaction.

As with the 1,4-pentadiyn-3-ol, the reaction of the 2-methoxyphenyl substituted diyne with one equivalent of benzyl azide in the presence of copper(I) chloride and (*R*,*R*)-PhPyBox in 2,5-hexanedione resulted in the desired triazole in 26% yield as the racemate. Similarly, the other coordinating solvents screened, acetone and acetonitrile, also resulted products as, or close to (<5% ee), racemic mixtures in similar yields.

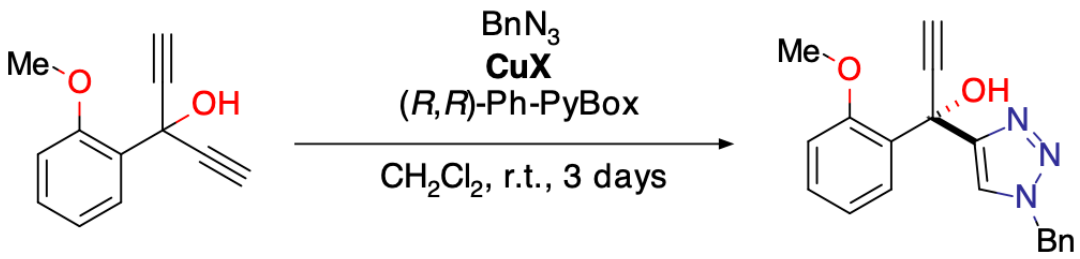
Table 1: Table of copper screening results.

Solvent	Yield	% ee
DCM	32%	14%
MeCN	28%	0%
Acetone	30%	0%
2,6-Hexanedione	26%	0%
Toluene	23%	14%
DCE	20%	11%

When the reaction was carried out in non-coordinating solvents the enantiomeric excess increased. Dichloromethane and toluene both gave promising yields and enantioselectivity, however the reaction in toluene appeared to proceed slowly, as determined by the consumption of benzyl azide by TLC.

Despite our fears that the lability of the hydroxyl group provided by the stability of the resulting tertiary carbocation could result in racemisation of the monotriazole, we found no decrease in enantiomeric excess was observed when stirring an enantioenriched sample of the triazole with copper(I) chloride overnight. Furthermore, and more extraordinarily, treating the triazole with catalytic trifluoroacetic acid under anhydrous conditions also resulted in no change to the enantiomeric excess.

2.3 Copper Screening.



Scheme 54: Copper screening reaction.

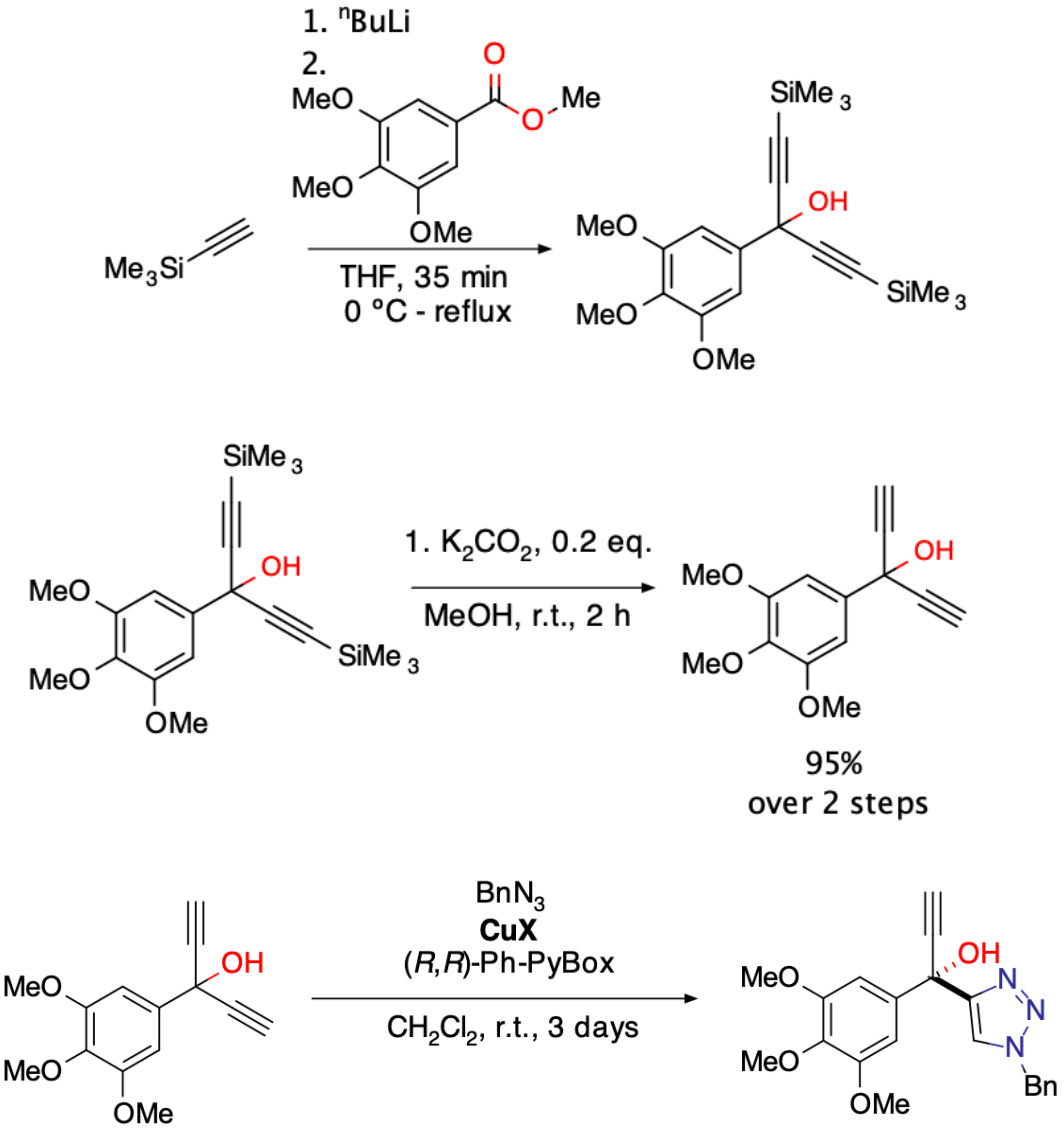
For the copper(I) halides, enantiomeric excess decreased with the mass of the halide, with copper(I) chloride providing the triazole in 32% yield at 14% ee. Copper(I) iodide, used by Fokin,[35] gave poorer results than copper(I) chloride and slightly poorer results than CuBr, in terms of both yield and enantioselectivity. Copper(I) thiophene-2-carboxylate provided remarkably similar results to copper(I) chloride.

Table 2: Table of copper screening results with (2-methoxyphenyl)penta-1,4-diyn-3-ol

CuX	Yield	% ee
CuCl	32%	14%
CuBr	16%	13%
CuI	12%	8%
CuTC	37%	14%

During the copper screening process, we synthesised a second quaternary (bis)alkyne to investigate. Desymmetrisations performed on the 3,4,5-trimethoxyphenyl-substituted (bis)alkyne showed the same trend across the copper(I) salts screened, however the resulting triazoles were isolated in significantly higher yields and enantiomeric excesses. In the case of copper(I)

chloride both the yield and enantiomeric excess of the triazole was more than doubled to a respectable 71% and 36% ee, respectively, providing us with a



Scheme 55: (3,4,5-Trimethoxyphenyl)penta-1,4-diyn-3-ol synthesis and copper screening reaction.

promising starting point to begin ligand screening and optimisation. In contrast to the findings reported by the laboratory of Tao Song, copper(II) fluoride provided a racemic product, though at a brilliant yield of 90%. The high selectivity for the monotriazole over the (bis)triazole provided by these conditions is interesting due to the problems that can be encountered when attempting to synthesis monotriazoles from (bis)alkynes. It was found that substituting the phenyl ring with three methoxy groups in the 3, 4, and 5 positions (scheme 55) greatly increased both the enantiomeric excess to 36% ee and the yield of the desired

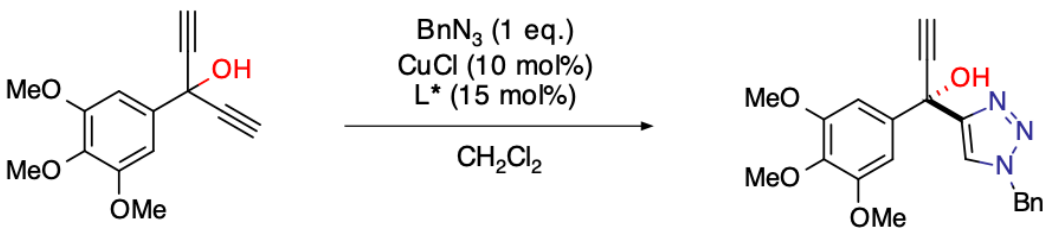
mono-triazole to 71%, compared to the diyne with only one methoxy substituent in the 2 position. Ligand screening was undertaken on the diyne containing the trimethoxyphenyl motif.

Table 3: Table of copper screening results with (3,4,5-trimethoxyphenyl)penta-1,4-diyn-3-ol

CuX	Yield	% ee
CuCl	71%	36%
CuBr	36%	21%
CuI	18%	8%
CuF_2	90%	0%
CuTC	71%	30%

3 Ligand Screening.

Having settled on copper(I) chloride and dichloromethane as the copper salt and solvent of choice, ligand screening began (scheme 56). The quaternary prochiral (bis)alkyne shown in scheme 56 was chosen as our desymmetrisation substrate as we envisioned the steric differentiation between the aromatic and hydroxyl groups providing favourable and noticeable initial results upon which we could capitalize; it also boasted ease of handling and a straightforward and high yielding synthesis. Benzyl azide was our azide of choice due to its safe-handling compared to aliphatic and aromatic azides and the availability of its component starting materials.



Scheme 56: General ligand screening reaction.

We chose to begin our investigation by screening oxazoline ligands, as other groups working in the field of asymmetric CuAAC reactions had reported great success with the use of (bis)oxazoline ligands; however, we also planned to investigate phosphine based ligands as our own group had previously found promising results applying C_2-symmetric phosphine ligands from the BINAP and NORPHOS family of ligands.

3.1 Oxazoline Ligands.

Table 4: Table of oxazoline ligand screening results.

Entry	Ligand	% Yield	%ee[a]
L1	(*R*,*R*)-Ph-PyBox	71	36 (+)
L2	(*S*,*S*)-^{i}Pr-PyBox	36	18 (-)
L3	(*S*,*S*)-Indenyl-PyBox	36	13 (+)
L4	(*S*)-^{i}Pr-PyOx	52	4 (-)
L5	(*S*)-^{i}Pr-PhosOx	51	3 (-)
L6	(*R*,*R*)-Ph-Box	44	11 (+)
L7	(*S*,*S*,*S*)-Indenyl-TrisOx	54	13 (+)
L8	(*Rp*,*S*,*S*)-Ph-SpiroBox	26	4 (+)
L9	(*Sp*,*S*,*S*)-Ph-SpiroBox	51	24 (+)

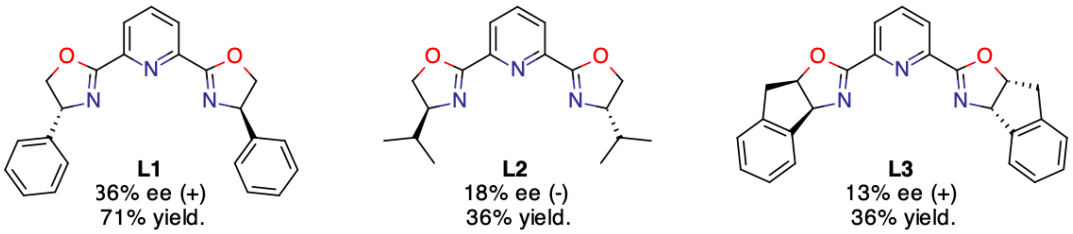
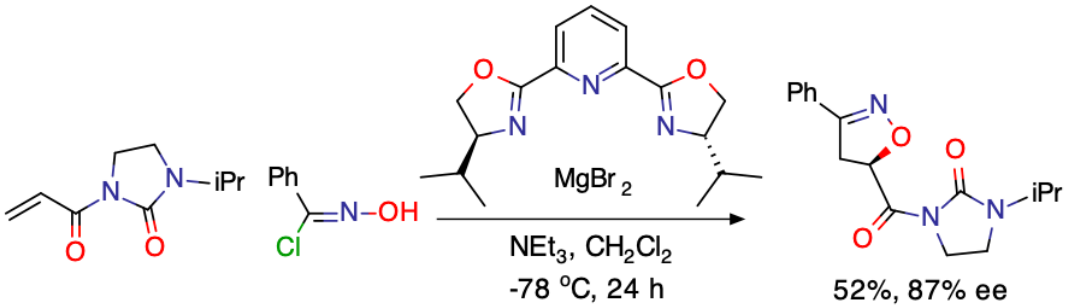


*Figure 4: PyBox ligands **L1**, **L2** and **L3***

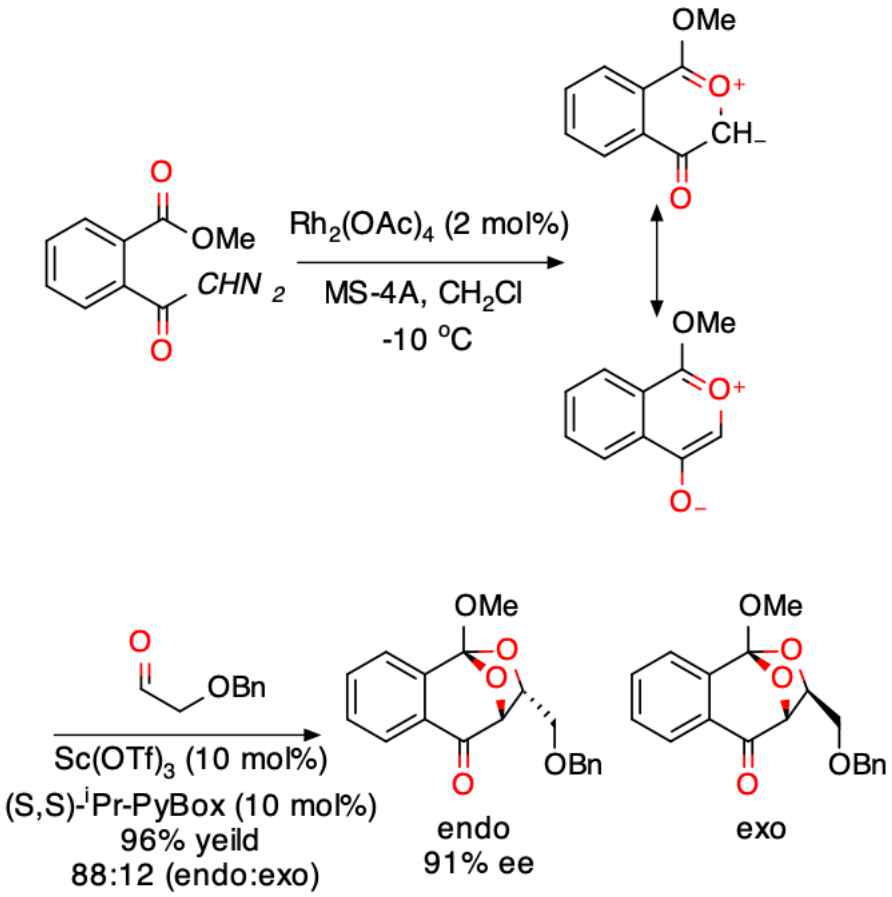
We began our screening of the oxazoline family of ligands with PyBOx ligands due the success this ligand family has exhibited in both asymmetric CuAAC reactions and other asymmetric 1,3-dipolar cycloadditions. (*R*,*R*)-Ph-PyBox **L1** (figure 4) was used to great success by the group of Zhou in their work on the CuAAC desymmetrisation of oxindole-derived bis(alkynes)[37] and later by Buckley[38] for the kinetic resolution of chiral alkynes. During their initial ligand screening for asymmetric CuAAC reactions Uoxumi and Osako reported only 23% yield and 12% ee with (*R*,*R*)-^{i}Pr-PyBox.[42] This ligand has, however, provided high enantioselectivities for other asymmetric 1,3-dipolar cycloadditions.

Yamamoto and colleagues reported in 2007 the synthesis of isooxazolines from nitrile oxides with up to 87% ee[46] (scheme 57) using $MgBr_2$ and (S,S)-^{i}Pr-PyBox as the catalyst.



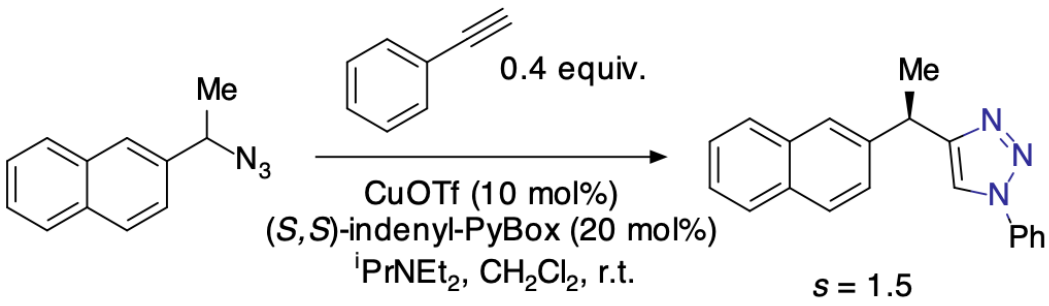
Scheme 57: Asymmetric nitrile oxide cycloaddition.

In 2002 Suga and coworkers[47] reported the asymmetric 1,3-dipolar cycloadditions of 2-benzopyrylium-4-olate (scheme 58) in a one-pot procedure starting with the diazoacetophenone and utilising scandium(III) triflate and (*S*,*S*)-^{i}Pr-PyBox as the enantioselective catalytic system providing cycloadducts in up to 91% ee.



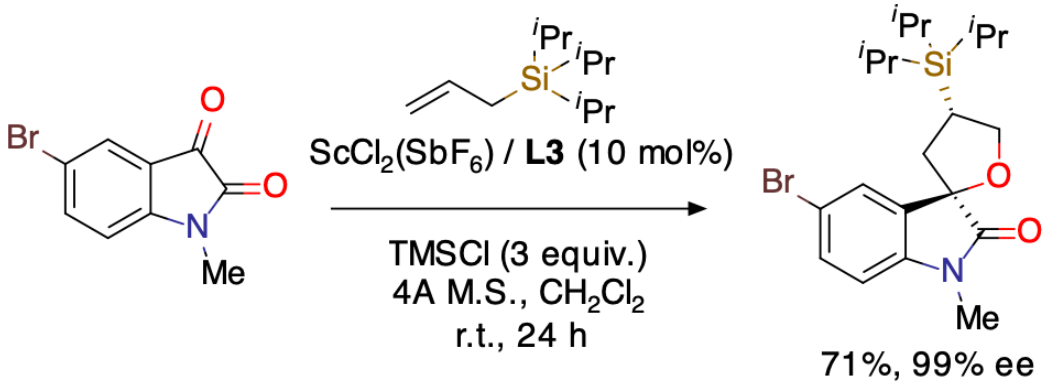
Scheme 58: Enantioselective carbonyl ylide 1,3-dipolar cycloaddition.

The use of (*S*,*S*)-Indenyl-PyBox **L3** was investigated by Fokin and Finn[35] during ligand screening for asymmetric CuAAC reactions. **L3** gave a selectively of only 1.5 ($s = 1.5$, conversion = 40%) in the kinetic resolution of 1-(2-napthyl)ethyl azide with phenylacetylene (scheme 59).



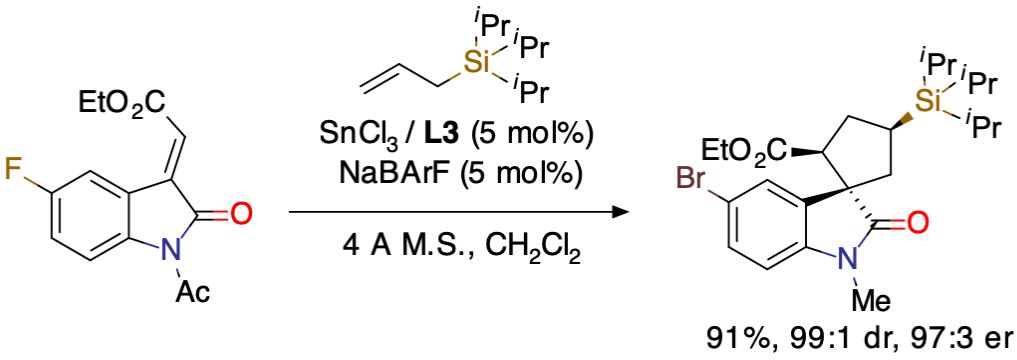
Scheme 59: Kinetic resolution of racemic azides.

(*S*,*S*)-Indenyl-PyBox **L3** has recently been used to great effect in [3+2] annulation reactions. Franz and colleagues reported[49] that scandium/(*S*,*S*-indenyl-PyBox)-catalysed [3+2] annulations of allylsilanes with isatins provided spirooxindoles in up to 99% ee (scheme 60).



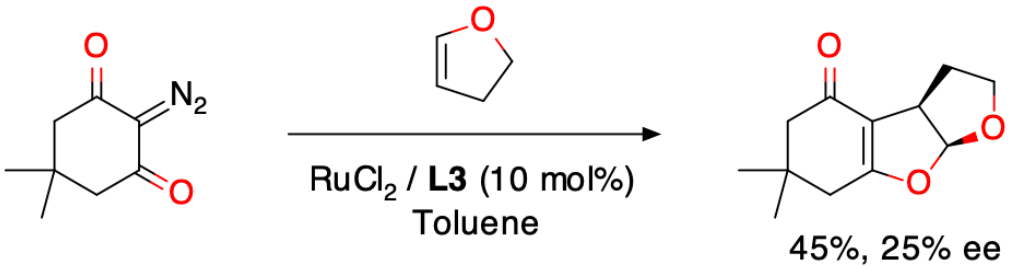
Scheme 60: Enantioselective [3+2] annulation of isatin with allylsilane.

In 2014 Franz[50] and colleagues followed up this work with the enantioselective carboannulation of oxindole derivatives with allylsilanes (scheme 61) catalysed by scandium(III) chloride in the presence of (*S*,*S*)-indenyl-PyBox and Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate to give spirooxindoles in up to 97:3 er (94% ee).



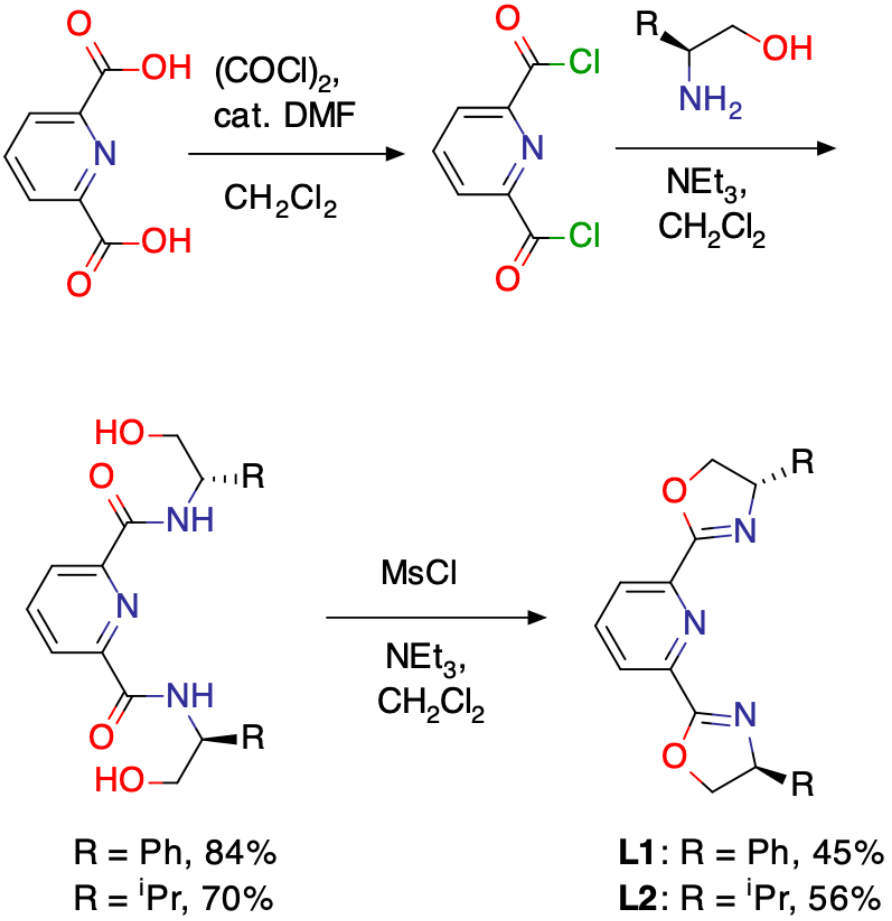
Scheme 61: Enantioselective [3+2] carboannulation with allylsilane.

(*S*,*S*)-Indenyl-PyBox **L3** has also seen use in 1,3-dipolar cycloadditions.[48] While reporting only 45% yield and 25% ee in the 1,3-dipolar cycloaddition between 2-Diazo-5,5-dimethyl-cyclohexane-1,3-dione and 2,3-dihydrofuran (scheme 62), Müller and Chappellet demonstrated that indenyl-PyBox is capable of producing enantiomeric excess in 1,3-dipolar cycloadditions.



Scheme 62: $RuCl_2$ / (*S*,*S*)-indenyl-PyBox-catalysed 1,3-dipolar cycloaddition.

(*R*,*R*)-Ph-PyBox **L1** and (*S*,*S*)-^{i}Pr-PyBox **L2** (figure 4) were synthesised starting from 2,6-dipicolinic acid (scheme 63), using a method in which the volatiles from the chlorination were removed under reduced pressure and the amid was isolated prior to cyclisation.



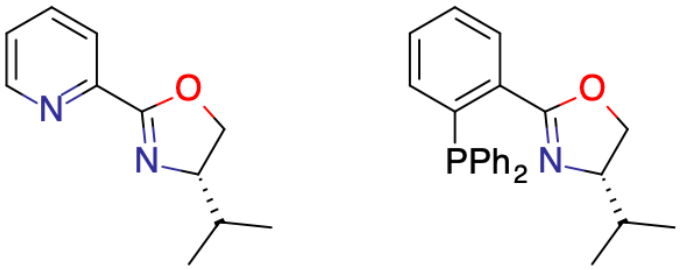
Scheme 63: Synthesis of PyBox ligands.

The desymmetrisation reaction of our 1,3-diyne in the presence of (*R*)-Ph-PyBox **L1** (figure 4) produced the desired chiral triazole in a promising 71% yield and 36% ee. Encouraged by this result we quickly moved to investigate other members of the PyBox family, starting with (*S*,*S*)-^{i}Pr-PyBox **L2** (figure 4). We found that changing the PyBox chiral oxazoline groups from phenyl to *iso*-propyl had a detrimental effect on our enantioselective CuAAC reaction, halving both the enantiomeric excess and yield to 18% ee and 36%, respectively.

After the disappointing results encountered with ^{i}Pr-PyBox **L1** we investigated (*S*,*S*)-indenyl-PyBox **L3** (figure 4), hoping that the more rigid structure would provide improved enantioselectivity in comparison to Ph-PyBox **L1**.

Unfortunately, the more rigid (*S*,*S*)-indenyl-PyBox ligand **L3** yielded the desired triazole in only 13% ee and 36% yield when employed in our screening reaction. Interestingly, when compared to Ph-PyBox, **L3** was selective for the opposite enantiomer, suggesting the possibility of a precipitous relationship determining the enantioselectivity of this reaction system with PyBox ligands.

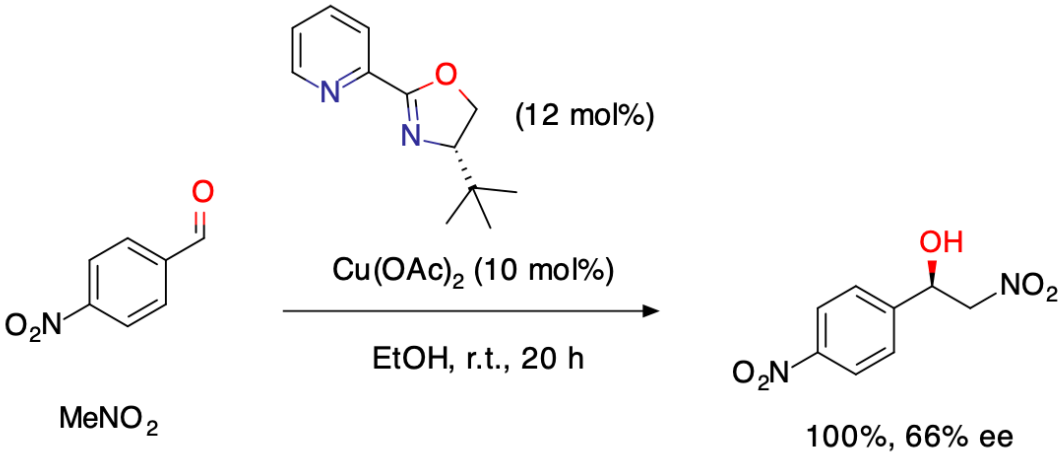
Having promising initial results but little follow-up success with PyBox ligands, and with the drastic differences in enantioselectivity we observed in mind, we investigated the non-C_2-symmetric sibling family of the PyBox Family, the PyOx family.



L4 **L5**

*Figure 5: Non-C_2-symmetric oxazoline ligands **L4** and **L5** .*

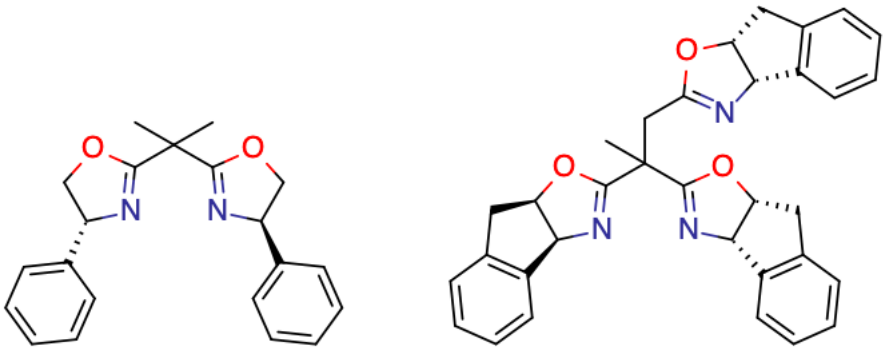
Ligands of the PyOx family have found application in asymmetric copper-catalysed addition reactions. In 2008 Koskinen[51] utilised a copper(II) acetate/(*S*)-^{t}Bu-PyOx system to catalyse the Henry reaction between *para*-nitrobenzaldehyde and nitromethane, quantitatively yielding the α-nitroalcohol with 66% ee (scheme 64).



Scheme 64: Copper-catalysed asymmetric Henry reaction.

We were envisioning the less rigid and spatially greedy ligands providing freedom during the desymmetrisation process that could result in more readily forming the lower energy transition states and intermediates, providing greater enantioselectivity. We synthesised (*S*)-^{i}Pr-PyOx **L4** (figure 5) from 2-picolinic acid following the same procedure used for (*S*,*S*)-^{i}Pr-PyBox **L2** with adjusted equivalencies. (*S*)-^{i}Pr-PyOx **L4** performed poorly as a chiral ligand in the enantioselective desymmetrisation of our prochiral diyne, yielding the triazole in only 4% ee. Similarly poor enantioselectivity resulted when another non-C_2-symmetric oxazoline was used. The triphenylphosphine-derivative **L5** provided the chiral triazole in 3% ee and 51% yield.

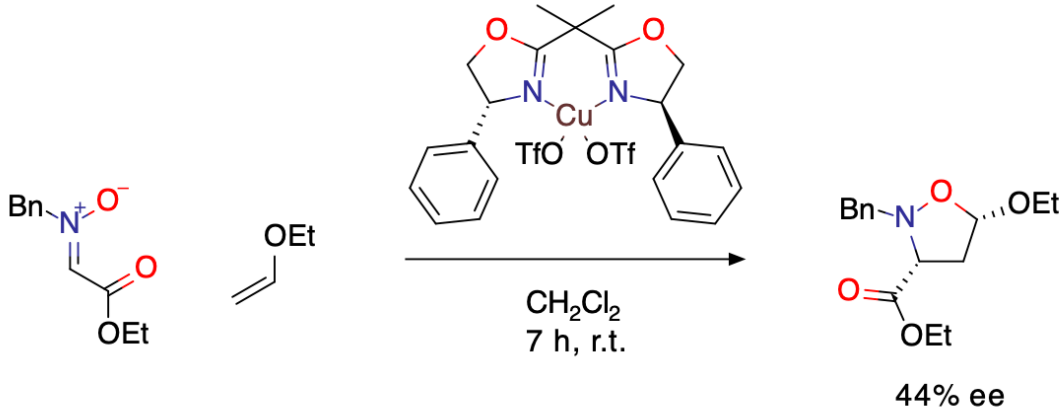
The disappointing results obtained with non-C_2-symmetric oxazoline ligands and the promising results obtained with (*R*),(*R*)-Ph-PyBox **L1** made (*R*),(*R*)-Ph-Box **L6** (figure 6) the obvious next choice for screening.



L6 **L7**

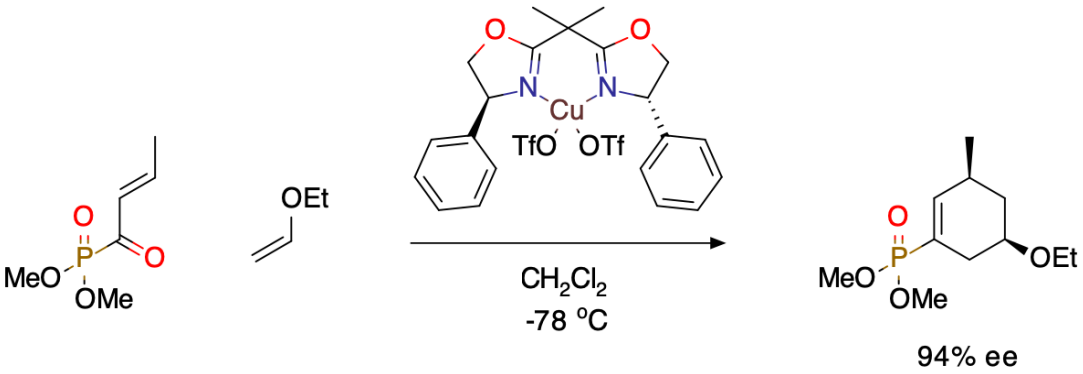
*Figure 6: Box **L6** and Tox **L7** ligands.*

Bis(oxazoline) ligands exhibit the C_2-symmetry present in PyBox ligands, but with one less heteroatom for potential chelation and a narrower bite angle. Much like the PyBox family of ligands bis(oxazoline) ligands have also seen extensive use in asymmetric copper-catalysed transformations, including copper catalysed 1,3-dipolar cycloadditions.



*Scheme 65: Jørgensen's copper(II) triflate / Ph-Box **L6** catalysed enantioselective 1,3-dipolar cycloaddition*

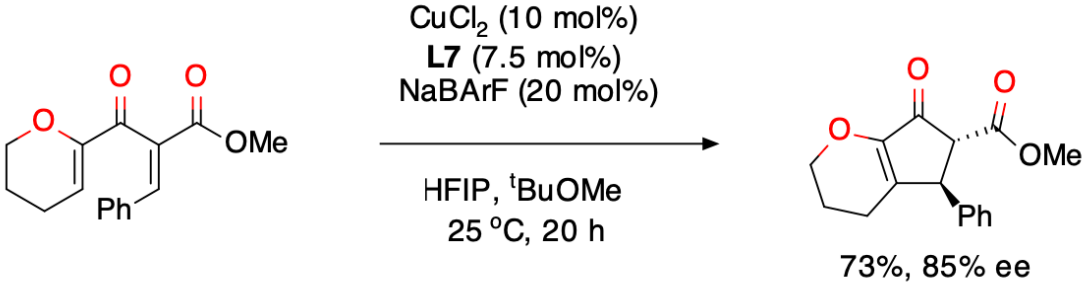
Jørgensen and coworkers[52] reported that copper(II) triflate/Ph-Box **L6** catalysed 1,3-dipolar cycloaddition of imine oxides and enolate ethers (scheme 66) proceeded with up to 44% ee.



*Scheme 66: Evans' copper(II) triflate / Ph-Box **L6** catalysed enantioselective hetero-Diels-Alder*

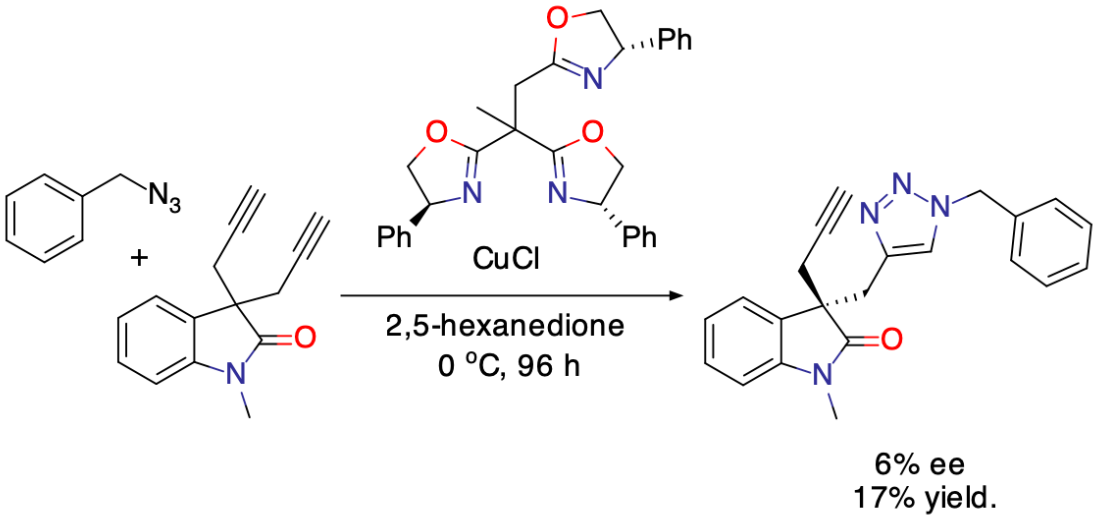
Evans and colleagues[53] reported that the same catalytic system mediated asymmetric hetero-Diels-Alder reactions with high enantioselectivity (scheme 66).

Related to the bis(oxazoline) family of ligands are the tris(oxazoline) ligands, which feature an additional chiral oxazoline for potential chelation. Though tris(oxazoline) ligands are not as ubiquitous as bis(oxazoline) ligands they have seen use in asymmetric copper-catalysed transformations.



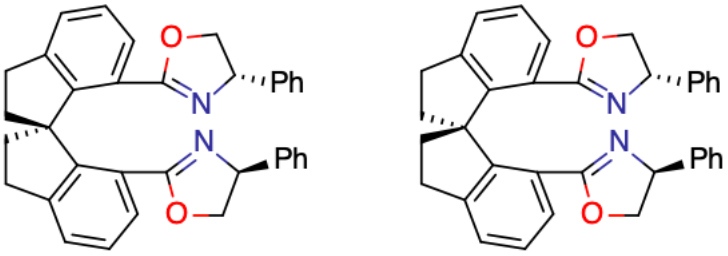
*Scheme 67: Tang's copper(II) chloride / TrisOx **L7** catalysed enantioselective Nazarov reaction*

Tang and coworkers applied tris(oxazoline) **L7** to asymmetric Nazarov reactions with great success,[54] (scheme 67) finding that the (*S,S,R*') diastereomer provided higher yields and enantioselectivity (90%, 92% ee) than the (*S,S,S*') diastereomer (73%, 85% ee). Zhou and coworkers[37] also chose to include a tris(oxazoline) ligand, (*S,S,S*')-Ph-TrisOx, in their enantioselective CuAAC ligand screening investigation (scheme 65).



Scheme 68: Zhou's coppper(I) chloride / TrisOx catalysed enantioselective CuAAC

When applied as the chiral ligand our desymmetrisation, (*R*),(*R*)-Ph-Box **L6** (figure 6) provided the desired triazole in an acceptable yield of 44%, but at only 11% ee. (*S,S,S'*)-naphthyl-TrisOx **L7** (figure 6) performed slightly better, providing the chiral triazole in 53% yield and 13% ee when used in our screening reaction. While better results than both bis(oxazoline) **L6** and the naphthyl-PyBox **L3**, the enantioselectivity was still unsatisfactory, being much lower than what was achieved with the use of Ph-PyBox **L1**.



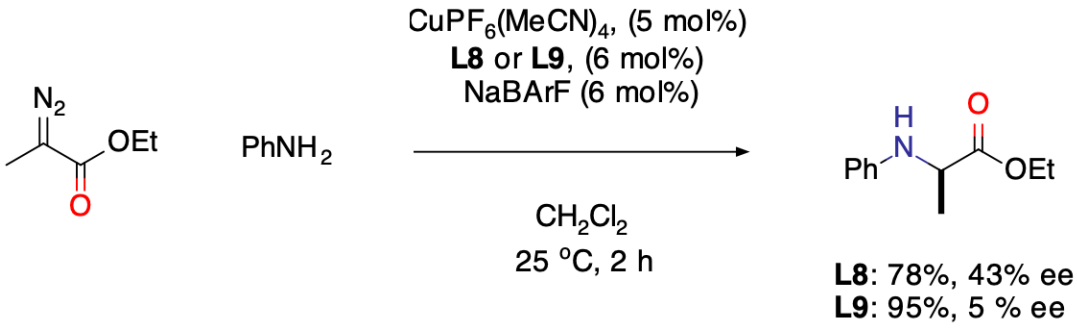
L8 **L9**

*Figure 7: SpirOx ligands **L8** (Sp,S,S) and **L9** (Rp,S,S)*

Noting that the ligands which we reasoned would be less enveloping of the copper(II) centre were performing worse in our screening reaction, for example

the higher bite angle and more compact Ph-Box ligand providing less enantioselectivity than the higher bite angle Ph-PyBox ligand, we turned our attention to the SpirOx family of oxazoline ligands (figure 7). As with the Box and PyBox ligands we previously investigated, SpirOx ligands are C_2-symmetric ligands with two oxazoline rings suitable for metal chelation; however we reasoned that their structure may allow for greater envelopment of the copper(II) centre, possibly conferring greater enantioselectivity to the desymmetrisation process.

SpirOx ligands **L8** and **L9** (figure 7) have seen use in the asymmetric copper-catalysed amination of diazo species. Optimisation resulted in enantioselectivities and yield improving to up to 94% yield and 98% ee and providing high yields (scheme 69) and enantioselectivities across a broad scope of substrates.



Scheme 69: Amination of diazo species catalysed by copper(I) / SpirOx systems

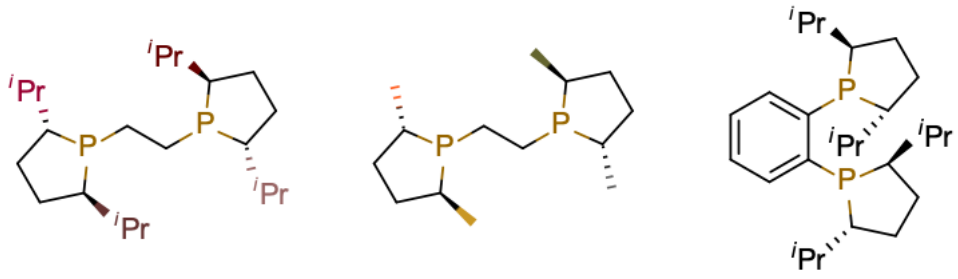
We investigated both diastereomers of the Ph-SpiroBox ligand, (*R*),(*R*)-Ph-Box **L6** and (*Sp*,*S*,*S*)-Ph-SpiroBox **L8** (figure 7), expecting one to give improved enantioselectivity in comparison to the other. When utilized in our screening reaction, (*Rp*,*S*,*S*)-Ph-SpiroBox **L9** provided the desired product with 26% yield at only 4% ee. (*Sp*,*S*,*S*)-Ph-SpiroBox **L8** performed better, providing the desired product in a much improved 51% yield at 24% ee, showing the (*Sp*,*S*,*S*) configuration to be the “matched” configuration for our screening reaction.

Satisfied with the breadth of oxazoline ligands investigated but unsatisfied with

the desymmetrisation results they provided, the best ligand thus far being (*R*)-Ph-PyBox **L1** (figure 4) with 71% yield and 36% ee, we looked towards phosphine ligands as possible screening candidates.

3.2.1 Phosphine Ligands: Literature Review.

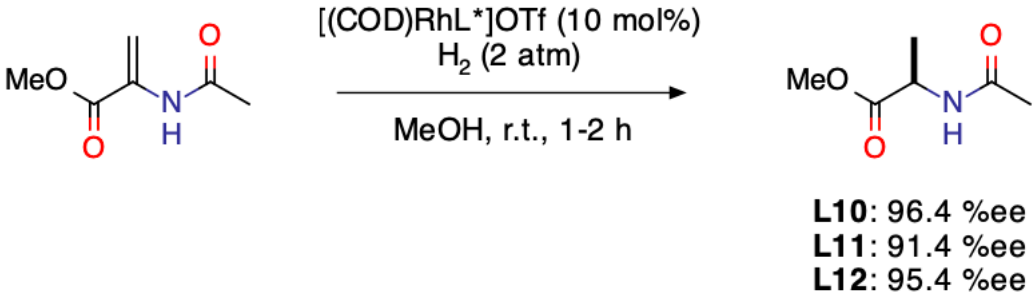
Having little success with C_2-symmetric bis(oxazoline) ligands after our initial screening with Ph-PyBox **L1**, we moved on to investigating the yields and enantioselectivities when phosphine ligands were used in our screening reaction. We had utilised the C_2-symmetric phosphine ligands in our previous work on the enantioselective-CuAAC desymmetrisation of cyanoacetate-derived (bis)propargyls;[36] additionally, Song and coworkers[40] had reported the successful desymmetrisation of meleimide-derived bis(alkynes) using a chiral ligand featuring a diphenylphosphine moiety (scheme 39), as discussed in the previous chapter. While phosphine ligands tend not to be the first choice for the asymmetric copper catalysis of cycloaddition reactions, the wide variety of chiral phosphine ligands and their widespread use in asymmetric metal catalysis, including copper catalysis, made this broad class of ligands a worthwhile target for screening. Through perusal of the literature we began to compile a collection of phosphine ligands we believed may show potential in our screening reaction, favouring ligands that had seen successful use in copper catalysis or catalytic cycloaddition reactions.



L10 **L11** **L12**

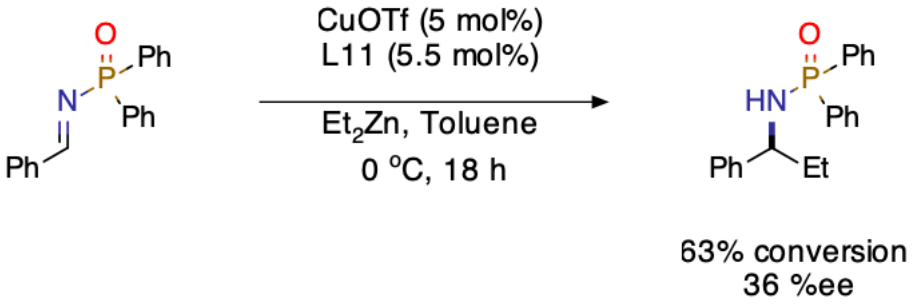
Figure 8: Selected phosphine ligands.

BPE (**L10**, **L11**) and DuPhos (**L12**) ligands are popular choices for rhodium-catalysed asymmetric hydrogenation reactions, and have been shown to result in very high enantioselectivites (scheme 70).



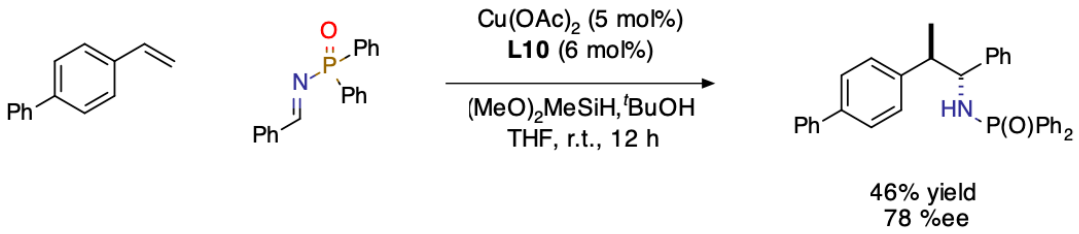
Scheme 70: Asymmetric rhodium-catalysed hydrogenation with BPE and DuPhos ligands

BPE ligands have also been utilised to various success in copper(I)- and copper(II)-catalysed reactions. The laboratory of Charette reported in 2003[55] the application of (*S*,*S*)-Me-BPE **L11** in the copper(I)-catalysed addition of diethylzinc to *N*-phosphinoyl imines (scheme 71). (*R*,*R*)-^{i}Pr-DuPhos was also included in the screening, though it resulted in a very low yield (<10%).



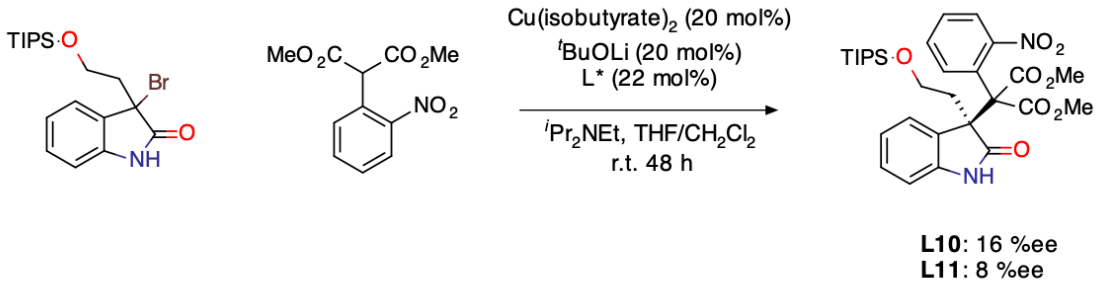
Scheme 71: Enantioselective copper(I) Triflate / (*S*,*S*)-Me-BPE **L11** mediated addition of ethyl zinc to *N*-phosphinoyl imines

The laboratory of Buchwald[56] reported another copper-catalysed addition to *N*-phosphinoyl imines in 2016. Using copper(II) acetate in the presence of (*R*,*R*)-^{i}Pr-BPE as the catalytic system the group were able to demonstrate an elegant generation of an alkyl cuprate by the hyrdocupration of styrenes, followed by enantioselective addition to the imine (scheme 72). Similarly to the work reported by Charette. DuPhos **L12** was also screened but again resulted in poor yields (<5%).

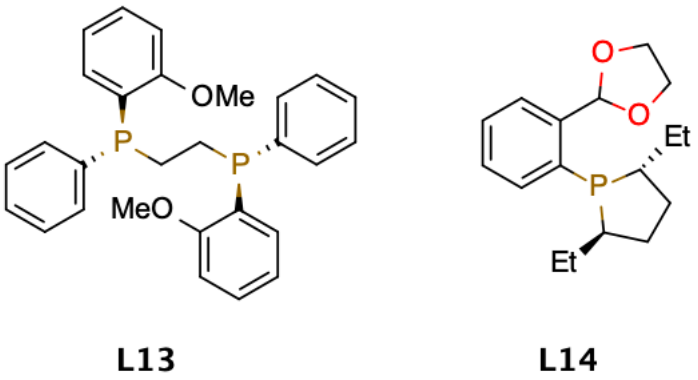


Scheme 72: Enantioselective copper(II) acetate / BPE mediated addition of styrene to N-phosphinoyl imines

The laboratory of Stoltz[57] reported the use of BPE ligands **L10** and **L11** in the asymmetric copper(II)-catalysed synthesis of quaternary oxindoles (scheme 73), albeit in low enantiomeric excess.



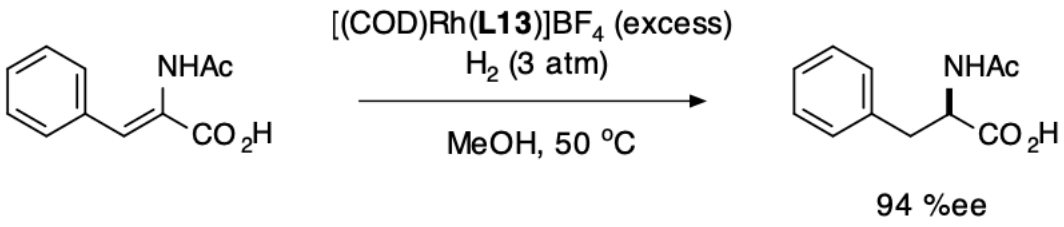
Scheme 73: Asymmetric BPE / copper(II)-catalysed synthesis of quaternary oxindoles



L13 **L14**

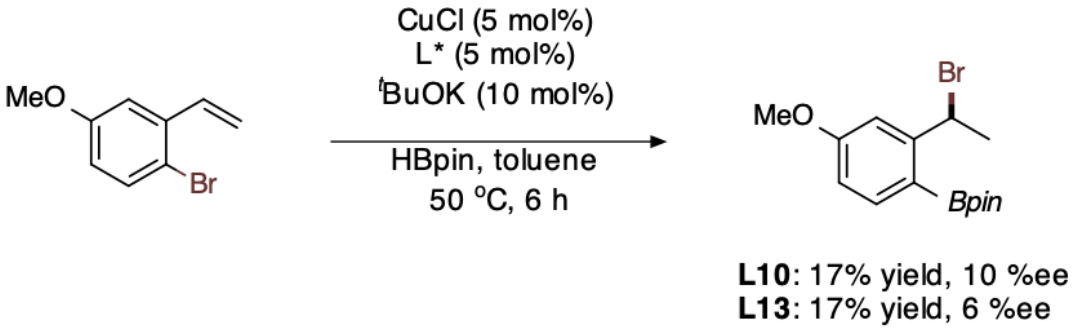
*Figure 9: (-)-DIPAMP **L13** and (R,R)-Et-PhosPD **L14***

(-)-DIPAMP **L13** (figure 9) is another ligand more commonly seen in asymmetric rhodium-catalysed hydrogenations. Knowles[58] demonstrated that a pre-generated (-)-DIPAMP-rhodium(I) complex mediated selective alkene hydrogenation with great enantioselectivity (scheme 74).



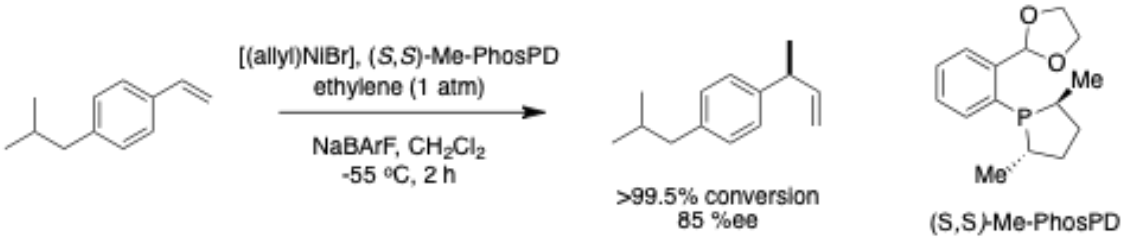
*Scheme 74: Enantioselective rhodium / DIPAMP **L13** catalysed alkene hydrogenation*

As with BPE and DuPhos ligands (-)-DIPAMP **L13** has found its way into the ligand screening libraries of chemists working on asymmetric copper catalysis. In 2014, the laboratory of Schomaker reported[59] a very interesting copper(I)-catalysed migratory bromination of styrenes which featured (-)-DIPAMP **L13** in the ligand screening process (scheme 75).

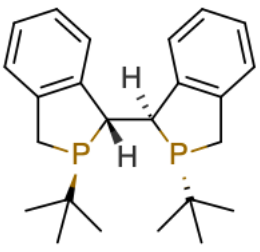


Scheme 75: Enantioselective DIPAMP / copper(I) chloride catalysed bromination

We also had an interest in the non-C_2-symmetric phosphine ligand (*R*,*R*)-Et-PhosPD **L14** due to its structural similarity to DuPhos **L12**, which had so far performed marginally better than other phosphine ligands in this screening. (*S*,*S*)-Me-PhosPD has been used by RajanBabu[60] and coworkers in the nickel-catalysed asymmetric vinylation of styrenes (scheme 76).



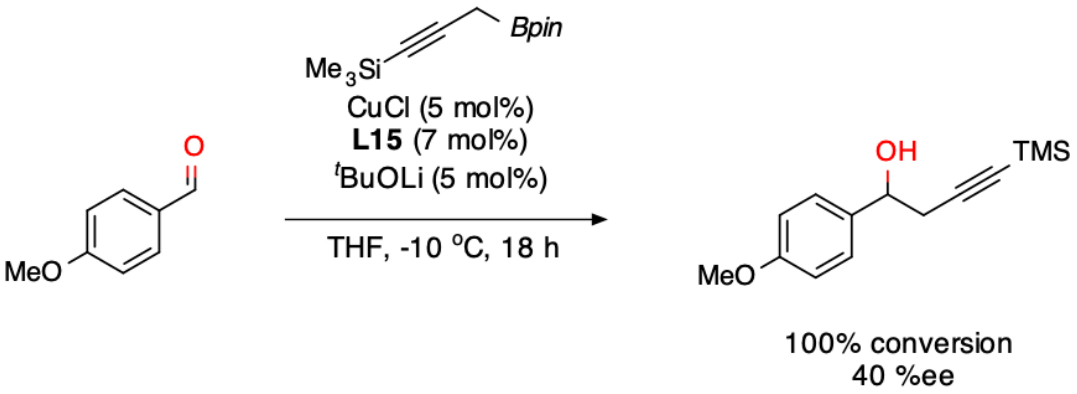
*Scheme 76: PhosPD **L14** / nickel-catalysed asymmetric vinylation of styrenes*



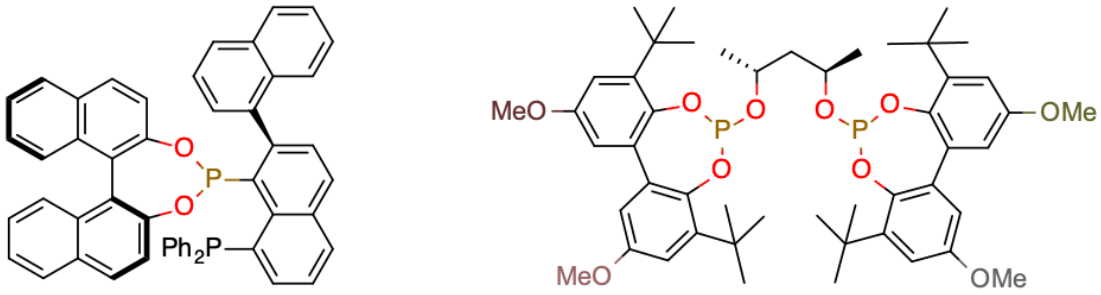
L15

*Figure 10: (R,R,S,S)-DuanPhos **L15***

Continuing with the screening of phosphine ligands, we moved onto the C_2-symmetric ligand (*R*,*R*,*S*,*S*)-DuanPhos **L15** (figure 10), which has seen some use in asymmetric copper catalysis. Fandrick and colleagues[61] reported in 2014 the copper(I) catalysed asymmetric propargylation of aldehydes, for which (*R*,*R*,*S*,*S*)-DuanPhos **L15** provided the product in 40% ee (scheme 77).



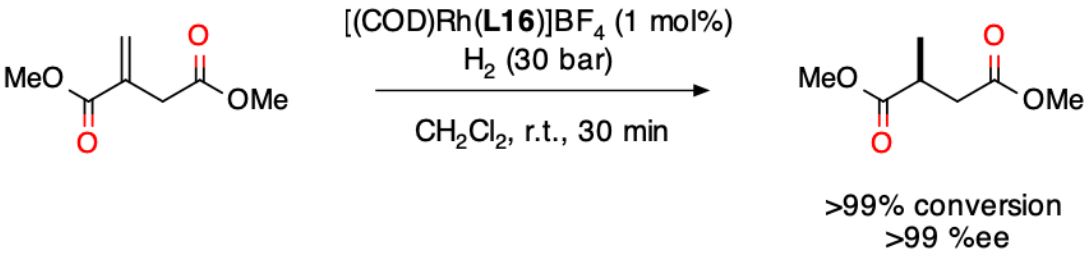
*Scheme 77: (R,R,S,S)-DuanPhos **L15** copper(I) catalysed asymmetric propargylation of aldehydes*



L16 **L17**

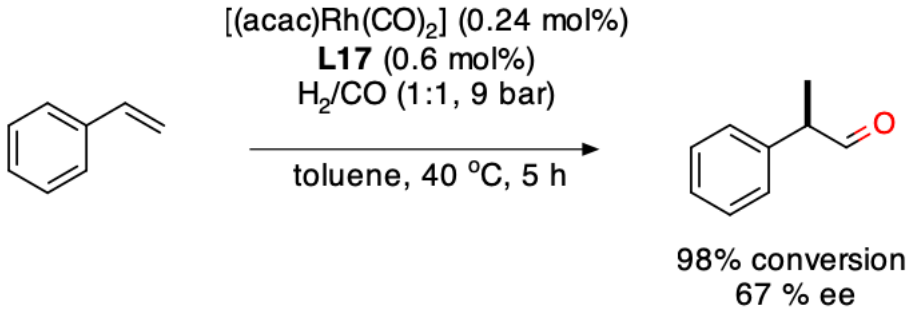
*Figure 11: (S_a,R_c)-(1-Nph)-Quinaphos **L16** and (R,R)-Chiraphite **L17***

We hoped the steric bulk of the ligands (S_a,R_c)-(1-Nph)-Quinaphos **L16** and (*R*,*R*)-Chiraphite **L17** (figure 11) would result in higher enantioselectivities than we had seen with the other phosphine ligands. Both ligands have seen use in asymmetric catalysis.

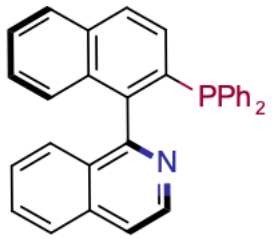


*Scheme 78: Enantioselective rhodium / (S_a,R_c)-(1-Nph)-Quinaphos **L16** catalysed hydrogenation*

The groups of Franciò and Leitner[62] reported the use of (S_a,R_c)-(1-Nph)-Quinaphos **L16** (scheme 78) resulting in great enantioselectivity in a hydrogenation similar to the work of Knowles[58] (scheme 74) mentioned above. The laboratory of Leeuwen reported the use of (*R*,*R*)-Chiraphite **L17** in an asymmetric hydroformylation of styrene[63] (scheme 79).



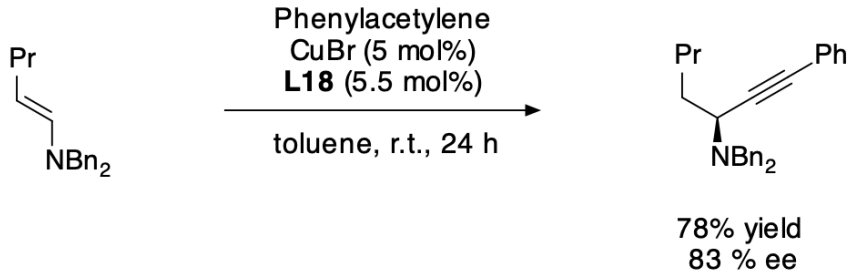
Scheme 79: Enantioselective rhodium / (*R*,*R*)-Chiraphite **L17** catalysed hydroformylation



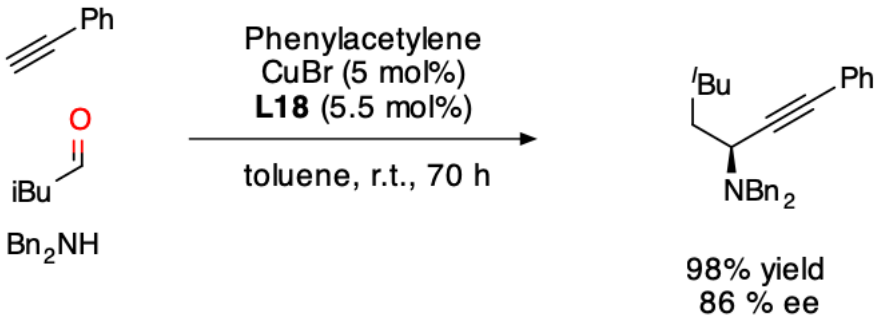
L18

*Figure 12: (S)-QUINAP **L18***

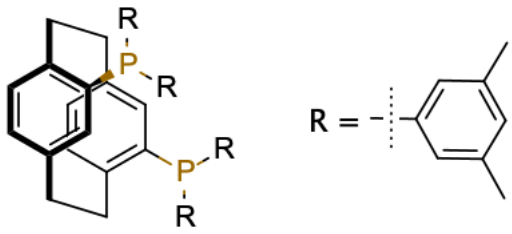
(*S*)-QUINAP **L18** (figure 12) was used by the group of Knochel in 2002 in the copper(I) bromide catalysed asymmetric addition of terminal alkynes to enamines, producing propargylic amines in high enantiomeric excess (scheme 80).[64] A year later in 2003 the laboratory of Knochel published[65] a highly enantioselective three-component variant of the reaction, also using (*S*)-QUINAP **L18** (scheme 81).



*Scheme 80: Enantioselective copper / (S)-QUINAP **L18** catalysed alkynylation*



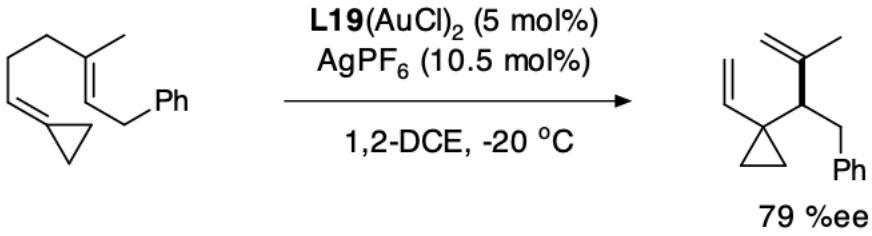
*Scheme 81: Enantioselective copper / (S)-QUINAP **L18** catalysed 3-component propargylamine synthesis*



L19

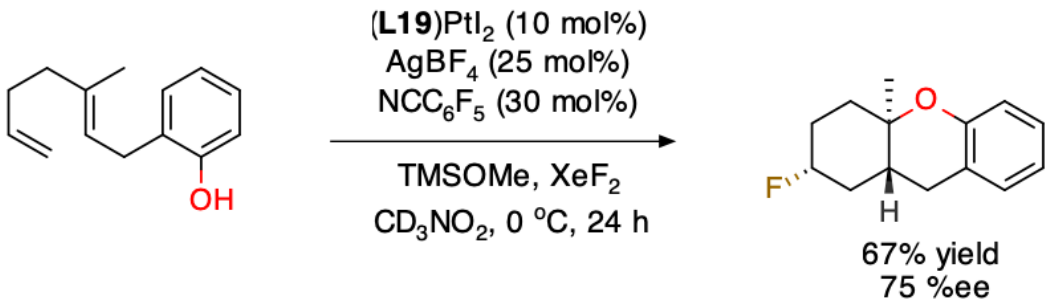
*Figure 13: (R)-xylyl-PhanePhos **L19***

The laboratories of Tantillo and Gagné published[66] a gold(I) catalysed Cope rearrangement (scheme 82) in which high enantioselectivities were obtained when (*R*)-xylyl-PhanePhos **L19** (figure 13) was used as the ligand.



*Scheme 82: Enantioselective (R)-xylyl-PhanePhos **L19** / gold(I) catalysed Cope rearrangement*

The group of Gagné[67] also utilised (*R*)-xylyl-PhanePhos **L19** to great effect in a very interesting platinum catalysed asymmetric cascade-cyclisation and fluorination reaction (scheme 83).



*Scheme 83: Enantioselective (R)-xylyl-PhanePhos **L19** / platinum catalysed cascade-cyclisation and fluorination reaction*

3.2.2 Phosphine Ligands: Asymmetric CuAAC.

Table 5: Ligands.

L	Ligand	% Yield	%ee
L10	(*R*,*R*)-^{i}Pr-BPE	20	4 (+)
L11	(S,S)-Me-BPE	53	4 (+)
L12	(*R*,*R*)-^{i}Pr-DuPhos	31	10 (+)
L13	(-)-DIPAMP	70	racemic
L14	(*R*,*R*)-Et-PhosPD	52	4 (-)
L15	(*R*,*R*,*S*,*S*)-DUANPHOS	56	7 (-)
L16	(Sa,Rc)-(1-Nph)-Quinaphos	46	12 (+)
L17	(*R*,*R*)-Chiraphite	5	7 (+)
L18	(*S*)-Quinap	44	2 (+)
L19	(*R*)-xylyl-PhanePhos	28	22 (-)

We began our screening of phosphine ligands with (*R*,*R*)-^{i}Pr-BPE **L10** and (*R*,*R*)-Me-BPE **L11**, being drawn to these ligands due to the possibility of screening a library of BPE ligands exhibiting a range of substituents on the phospholane rings with the goal of optimising the enantioselectivity and yield should we encounter promising initial results.

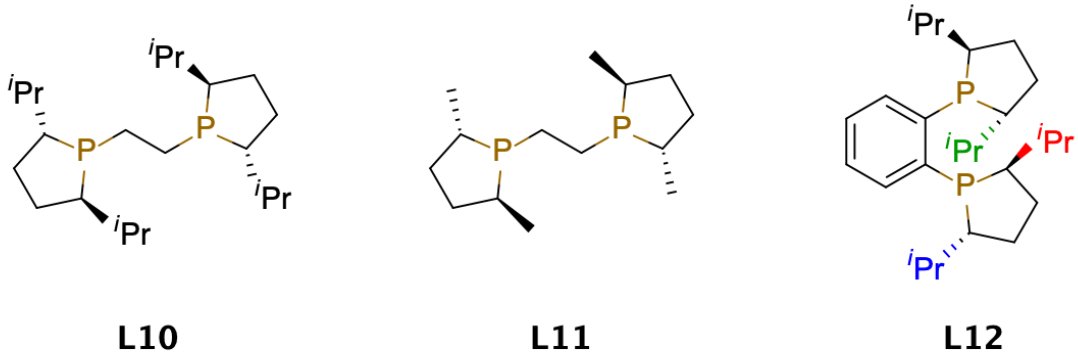
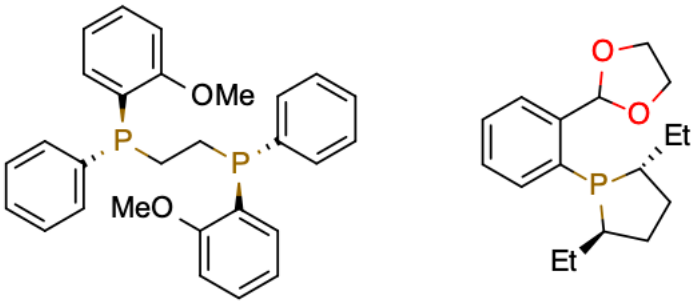


Figure 14: Selected C_2-symmetric phospholane ligands.

When screened against our standard CuAAC desymmetrisation reaction both (*R*,*R*)-^{i}Pr-BPE **L10** and (*R*,*R*)-Me-BPE **L11** gave the very low enantioselectivity of 4% ee. (*R*,*R*)-Me-BPE **L11** did, however, provide the desired triazole in with a yield of 53%, compared to the 20% yield resulting from the use of (*R*,*R*)-Me-BPE **L11**. The third chiral phosphine ligand we screened, (*R*,*R*)-^{i}Pr-DuPhos **L12**, featured a similar (bis)phospholane structure to (*R*,*R*)-^{i}Pr-BPE **L10** and (*R*,*R*)-Me-BPE **L11**. We hoped that the more rigid structure of (*R*,*R*)-^{i}Pr-DuPhos **L12** when compared to (*R*,*R*)-^{i}Pr-BPE **L10** and (*R*,*R*)-Me-BPE **L11** due to the comparatively inflexible benzene backbone would provide less freedom for the disfavoured configurations during the desymmetrisation process to find lower spatial energy arrangements, leading to a greater energetic difference between the favoured and unfavoured configurations and ultimately higher enantioselectivity. Used in our asymmetric CuAAC screening reaction, (*R*,*R*)-^{i}Pr-DuPhos **L12** provided the triazole with 10% ee in 31% yield. While showing an improvement in enantioselectivity in comparison to the phospholane ligands **L10** and **L11** we had previously screened, the enantioselectivity provided by (*R*,*R*)-^{i}Pr-DuPhos **L12** left much to be desired.

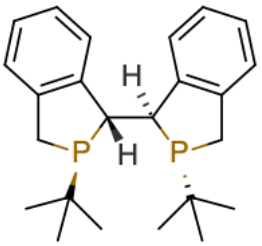
As with our screening on oxazoline ligands, we wished to investigate the enantioselectivity provided by a non-C_2-symmetric analogue of (*R*,*R*)-Et-PhosPD **L14** and turned our attention towards (*R*,*R*)-Et-PhosPD **L14** (figure 15). With the results from our screening of (*S*)-^{i}Pr-PyOx **L4** (figure 5) in mind, we were not surprised when we isolated the triazole from the asymmetric CuAAC with only 4% ee.



L13 **L14**

*Figure 15: (-)-DIPAMP **L13** and (R,R)-Et-PhosPD **L14***

Considering our lack of success with the phospholane ligands **L10**, **L11**, **L12**, and **L14**, we moved away from that class of ligand and turned our attention towards (-)-DIPAMP **L13**, a ligand that features chiral phosphorous centres. We were curious whether bringing the chiral centres of the ligand as closer to the catalytic copper centre would result in a more robust chiral induction. Unfortunately, (-)-DIPAMP **L13** was unsuitable as the chiral ligand in our asymmetric CuAAC screening reaction, providing the triazole as a racemic product. (-)-DIPAMP **L13** was, however, much more selective towards the desired monotriazole than the majority of ligands we had previously screened, providing the desired monotriazole in 70% yield, a potentially significant result considering the tendency for CuAAC reactions preformed on (bis)alkynes to often result the bis(triazole) as the major product.



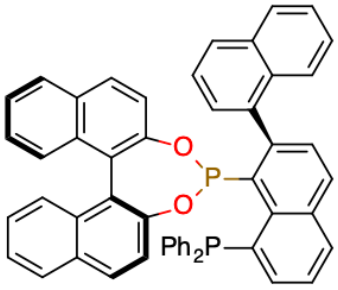
L15

*Figure 16: (R,R,S,S)-DuanPhos **L15***

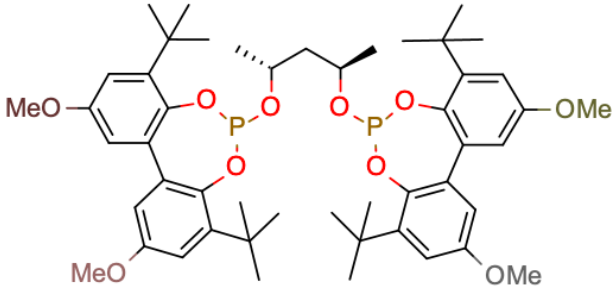
Despite our lack of success with (-)-DIPAMP **L13**, we wished to investigate another phosphine ligand exhibiting chiral phosphorous. (*R*,*R*,*S*,*S*)-DuanPhos

L15 caught our attention as a chiral ligand for use in asymmetric CuAAC reactions as its structure reminded us of the binaphthyl derived ligands our group had previously seen potentially promising results with asymmetric CuAAC reactions.[36] We envisioned the bulky tertiary butyl groups enveloping the catalytic copper centre, similarly to how we envisioned the phenyl groups of Ph-PyBox **L1** behaving, and as such had high hopes for the performance of (*R*,*R*,*S*,*S*)-DuanPhos **L15** in our asymmetric CuAAC reaction. Unfortunately, (*R*,*R*,*S*,*S*)-DuanPhos **L15** performed poorly in terms of enantioselectivity, producing the desired triazole in an acceptable 50% yield but at only 7% ee.

Considering our lack of success with lower molecular weight chiral phosphine ligands, we turned our attention to (S_a,R_c)-(1-Nph)-Quinaphos **L16** and (*R*,*R*)-Chiraphite **L17** (figure 17), two ligands with higher molecular weights and more steric bulk than the phosphine ligands we had previously screened.



L16



L17

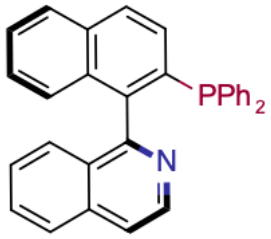
*Figure 17: (S_a,R_c)-(1-Nph)-Quinaphos **L16** and (R,R)-Chiraphite **L17***

(S_a,R_c)-(1-Nph)-Quinaphos **L16** does not feature the C_2-symmetry we have noted in the ligands we have found most of our success with; however, we reasoned that the size of the molecule may overcome this potential shortcoming and result in promising enantioselectivity. Used in our asymmetric CuAAC screening reaction (S_a,R_c)-(1-Nph)-Quinaphos **L16** provided the desired monotriazole in 46% yield and 12% ee, boasting the highest enantioselectivity among the ligands

without C_2-symmetry that we have screened possibly vindicating our line of thinking that sufficient steric bulk could break the pattern of non-C_2-symmetric ligands providing next to no enantioselectivity and showcasing non-C_2-symmetric as a potential avenue of investigation for asymmetric CuAAC reactions, a conclusion that may be drawn with more strength from the work of Song and colleagues[40] who used the non-C_2-symmetric ligand (S_a,*R*)-TaoPhos (scheme 34) to great success in their asymmetric CuAAC investigation.

Like (*R*,*R*)-Chiraphite **L17**, (*R*,*R*)-Chiraphite **L17** (figure 17) also exhibits a higher molecular weight and more steric bulk than many of the other ligands we have screened. We hoped that large steric bulk featured on a C_2-symmetric ligand would result in favourable enantioselectivity. To our disappointment, (*R*,*R*)-Chiraphite **L17** performed particularly poorly, being very selective for the undesired (bis)triazole and providing the triazole in the very low yield of 5% at 7% ee. This poor enantioselectivity may be due to the flexibility of the ligand's propyl backbone resulting in poor energetic differentiation between the two alkynes. Due to the high ratio of bis to mono product, it is also a distinct possibility that the observed poor enantioselectivity is a result of an *in situ* kinetic resolution in which the enantiomer produced in excess by the desymmetrisation is preferentially brought forward to the bis product leading to a dampening of observed enantioselectivity.

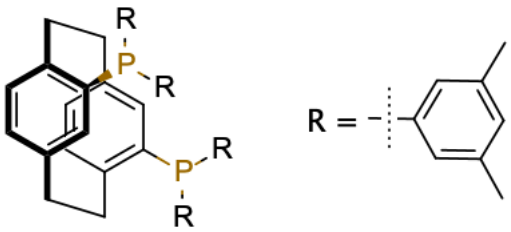
(*S*)-QUINAP **L18** (figure 18) was chosen for screening as we wished to further investigate whether binaphthyl-reminiscent structures have a positive influence on the enantioselectivity of asymmetric CuAAC reactions, as we had seen promise of with (S_a,R_c)-(1-Nph)-Quinaphos **L16** in this work and the BINAP family of ligands in our previous work.[36] (*S*)-QUINAP **L18** proved to follow the trends set by the other non-C_2-symmetric ligands without significantly enveloping steric bulk previously investigated in this work, providing the desired monotriazole with only 2% ee in 44% yield.



L18

*Figure 18: (S)-QUINAP **L18***

Considering the lack of success we had encountered screening the lower molecular weight, flexible, or non-C_2-symmetric ligands described in this chapter, we opted to investigate a C_2-symmetric phosphine ligand featuring a rigid backbone and steric bulk, envisioning a 'critical mass' of features our investigation had thus far led us to believe are beneficial to good enantioselectivites in our screening reaction.



L19

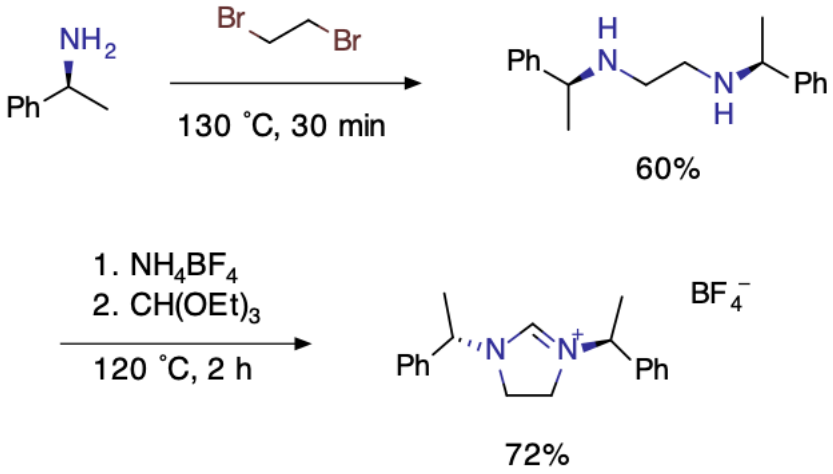
*Figure 19: (R)-xylyl-PhanePhos **L19***

We were pleased to find (*R*)-xylyl-PhanePhos **L19** (figure 19) perform far better than any of the other phosphine ligands and most of the oxazoline ligands we had screened. While the desired triazole was only isolated in 29% yield, it was obtained at 22% ee, providing enantioselectivity similar to our most successful results thus far and highlighting the potential of asymmetric CuAAC reactions to provide enantiomerically enriched triazoles when rigid and bulky C_2-symmetric chiral ligands are used in the reaction.

Although find (*R*)-xylyl-PhanePhos **L19** (figure 19) provided us with a promising result and useful information with which to make our future decisions regarding ligand choice, we felt that the enantioselectivity and yield it provided was not remarkable enough to continue investigation into paracyclophane-derived ligands. We reasoned that the phosphine ligands we had screened to this point did not show enough potential as chiral ligands in our asymmetric CuAAC screening reaction to temp us to continue screening phosphine ligands, and believed our investigation would be better served by moving our investigation on towards other classes of ligands.

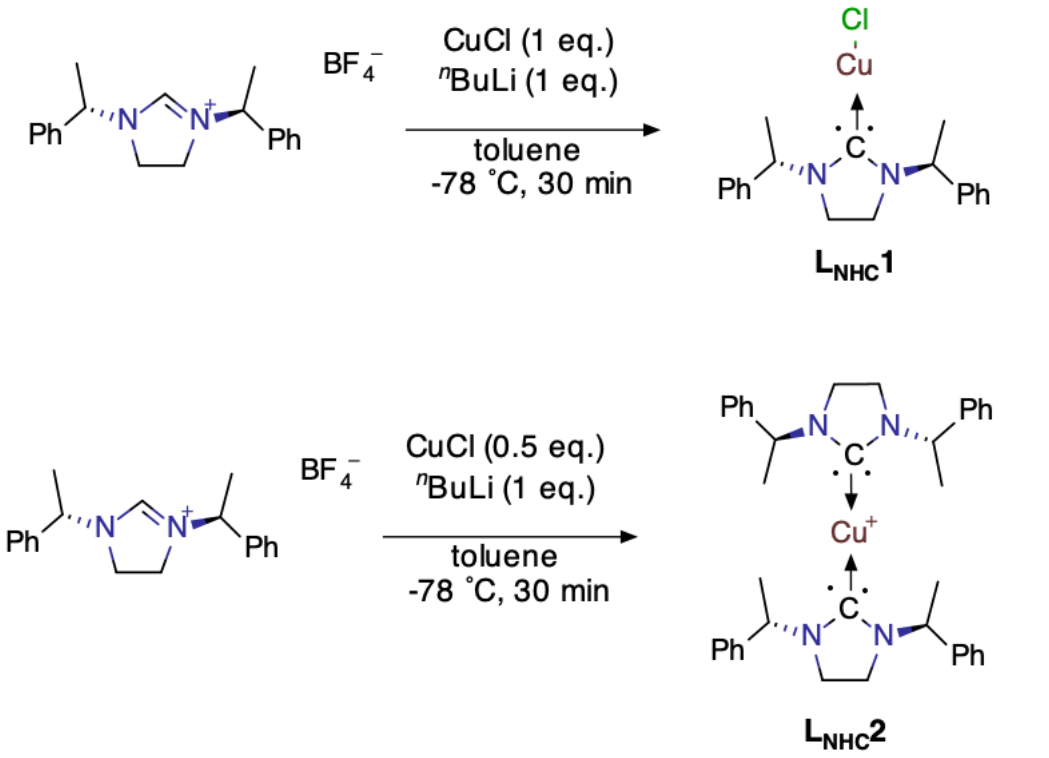
3.3 Chiral copper N-heterocyclic carbenes.

The high catalytic activity of copper *N*-heterocyclic carbenes in CuAAC reactions[68] prompted us to include an example of chiral *N*-heterocyclic carbene-copper complexes in our ligand screening. The chiral imidazolium salt was obtained over two steps starting from (*S*)-(-)-phenylethylamine (scheme 84).



Scheme 84: Chiral imidazolium salt synthesis

With the imidazolium salt in hand, we examined the enantioselectivity of Cu(NHC) $\mathbf{L_{NHC}1}$ and $[Cu(NHC)_2]^+$ $\mathbf{L_{NHC}2}$ in our screening reaction. Following the generation of copper-carbene complexes *in-situ* (scheme 85), the prochiral bis(alkyne) and benzyl azide were added.



Scheme 85: In-situ chiral copper-carbene formation

While the use of both **L_{NHC}1** and **L_{NHC}2** delivered the desired triazole in 36% and 62%, respectively, the isolated product was found to be racemic. We noted that the reaction went to completion swiftly, with the starting material having being completely consumed within several hours, as opposed to reaction times of up to 3 days we observed while screening many other ligands. This fast reaction matches the high catalytic activity of *N*-heterocyclic carbene-copper complexes reported in the literature,[68] which in turn provides a possible explanation for the complete lack of enantioselectivity we observed.

4.1 C_2-Symmetric Ferrocenyl Ligands.

Table 6: C_2-symmetric Ferrocenyl Ligands.

L21	(*S*,*S*)-^{i}Pr-BisFox	38	37 (-)
L22	(*S*,*S*)-^{t}Bu-BisFox	15	27 (-)
L23	(*R*,*R*)-Ph-BisFox	60	racemic
L24	(*S*,*S*)-CPh_2OH-BisFox	21	racemic
L25	(*Sp*,*Sp*)-Me-(*S*,*S*)-^{i}Pr-BisFox	35	53 (-)
L26	(*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox	31	60 (-)
L27	(*Rp*,*Rp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox	51	20 (+)

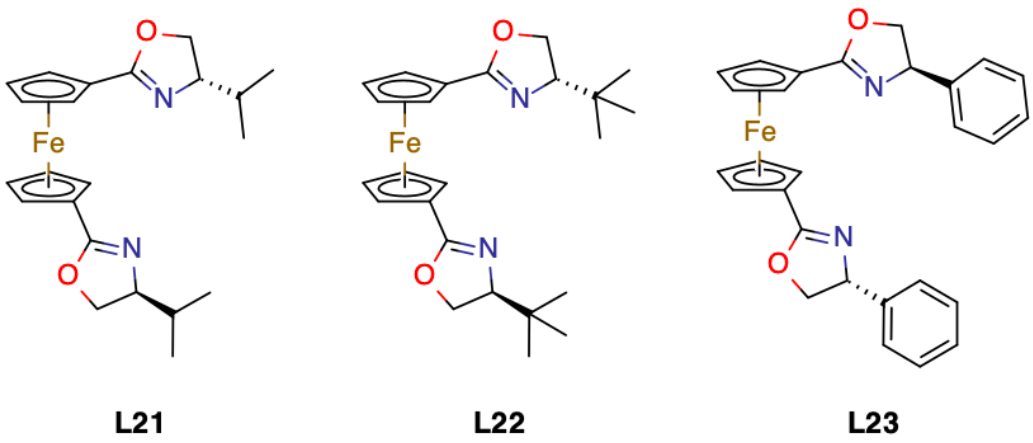


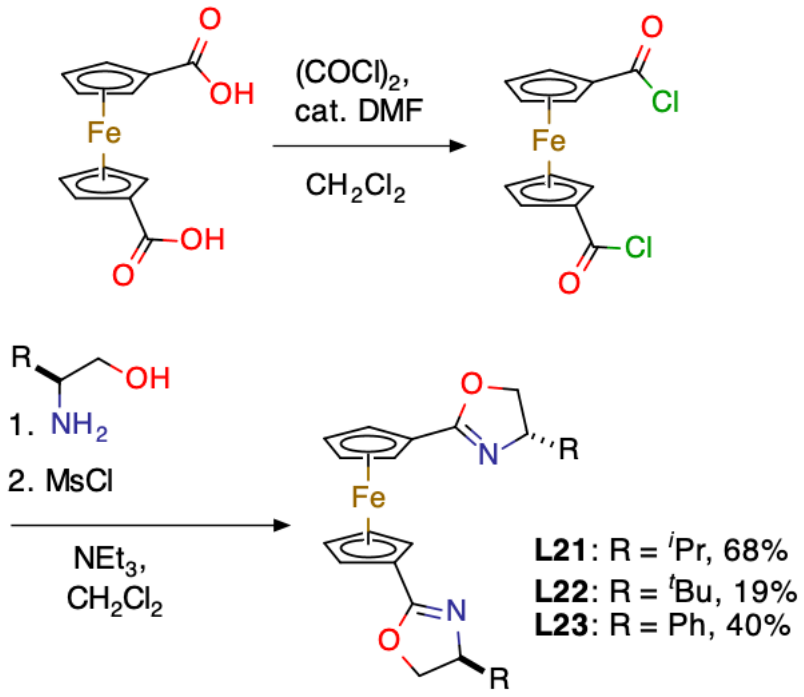
*Figure 20: (S,S)-^{i}Pr-BisFox **L21**, (S,S)-^{t}Bu-BisFox **L22**, and (R,R)-Ph-BisFox **L23***

We took an interest in C_2-symmetric ferrocene-derived bis(oxazoline), "BisFox", ligands (figure 20) as they represent a family of ligands with similarities to the PyBox and SpirOx ligands with which we had previously found success. As with PyBox and SpirOx, BisFox ligands are C_2-symmetric bis(oxazoline) ligands with appendages that we envision protruding well beyond the copper(I) centre allowing them to have significant impact on the desymmetrisation of our bis(alkyne).

These ligands were synthesised (scheme 86) using a similar method to our PyBox ligand synthesis, the only notable difference being that the ethanolamide intermediate was not isolated. Unlike the PyBox syntheses, taking the

ethanolamide forward in a one-pot process did not lead to a significant reduction of final product yield.

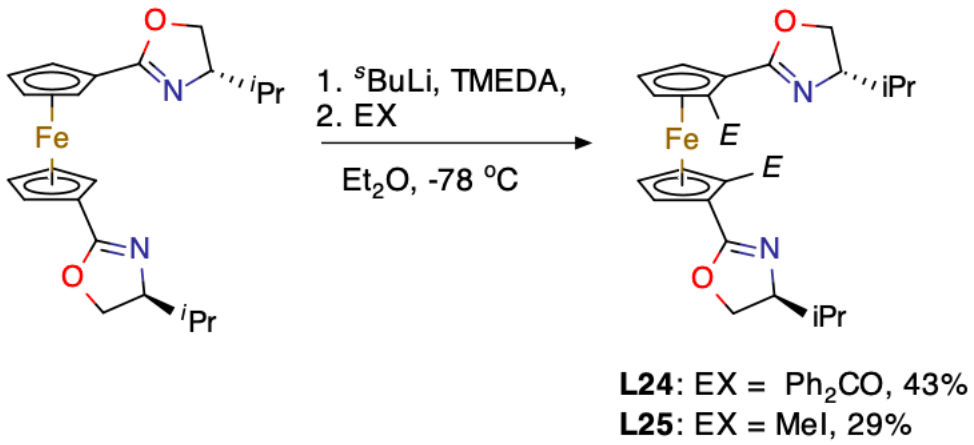
The use of (*S*,*S*)-^{i}Pr-BisFox **L21** in our screening reaction resulted in the desired triazole being isolated in 39% yield and 37% ee, providing what we considered to be our most exciting result thus far. (*S*,*S*)-^{t}Bu-BisFox **L22** also provided promising results, though lower in both yield and enantioselectivity than (*S*,*S*)-^{i}Pr-BisFox **L21**, with the triazole being isolated in 15% yield and 27% ee, revealing BisFox ligands to be a highly promising avenue of research. Remarkably the use of (*R*,*R*)-Ph-BisFox **L23** resulted in no enantioselectivity, putting it in stark contrast to the BisFox ligands **L21** and **L22**. We noted, however, that **L23** proved to exhibit much improved selectivity for the desired monotriazole.



*Scheme 86: Synthesis of BisFox ligands **L21**, **L22**, and **L23***

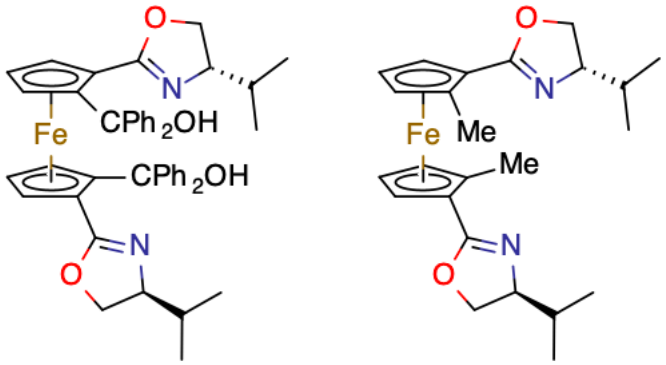
The promising results obtained by (*S*,*S*)-^{i}Pr-BisFox **L21** led us to begin investigating modification of the ligand, employing diastereoselective lithiations (scheme 87) of ferrocenes first reported in 1995 independently by the laboratories of Richards,[69] Uemura[70] and Sammkia[71] and expanded in 1996 to include double lithiations by the laboratory Ikeda[72] to produce a set of BisFox ligands exhibiting both the chiral centre of the oxazoline and planar chirality on the ferrocenyl rings. The ability to diastereoselective introduce further chirality and steric bulk into

these BisFox ligands by lithiation followed by quenching with electrophiles provides a wide variety of ligands potential screening candidates and presents the very enticing possibility of ligand fine-tuning, allowing us to investigate "matched" and "mismatched" chirality and various oxazoline and ferrocene substituents in order to work towards optimisation.



*Scheme 87: Diastereoselective lithiation of (S,S)-^{i}Pr-BisFox **L21***

Several BisFox derivatives are readily accessible by lithiation with *sec*-butyl lithium followed by a quench with an electrophile (scheme 87), opening up the avenue towards a library of diastereomeric ferrocenyl ligands. We first employed benzophenone and methyl iodide as our electrophilic quenching agent, installing a diphenyl carbinol moiety in 43% yield and a methyl in 29% yield, respectively. In contrast, we found that efficiently installing bulkier silanes through reaction with chlorotriethylsilane and chloro-triisopropylsilane proved difficult, often resulting in the non-C_2-symmetric mono-substituted species as the major product. Attempts at further modification of the carbinol moiety of **L24** (figure 21) by either methylation or silylation also met with failure.



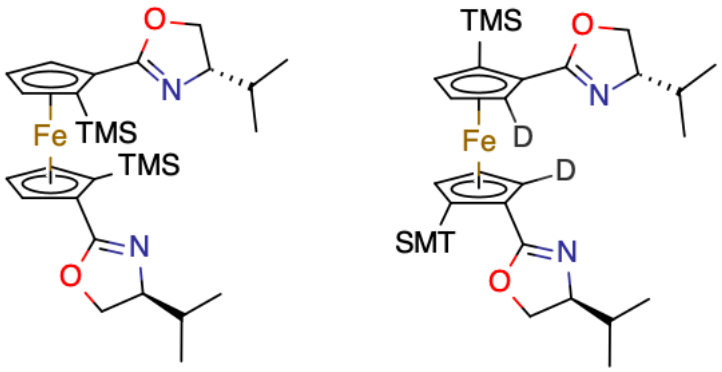
L24 **L25**

*Figure 21: (S,S)-CPh₂OH-BisFox **L24** and (Sp,Sp)-Me-(S,S)-ⁱPr-BisFox **L25***

(*S*,*S*)-ⁱPr-BisFox **L21** modified with benzophenone, (*S*,*S*)-CPh₂OH-BisFox **L24**, (figure 21) resulted in a racemic product at the low yield of 20%. It is possible that the shear bulk of this ligand significantly impeded the progression of the CuAAC reaction. The considerably less bulky methylated ligand, (*Sp*,*Sp*)-Me-(*S*,*S*)-ⁱPr-BisFox **L25** (figure 21) retained a similar yield to the unmodified (*S*,*S*)-ⁱPr-BisFox **L21** of 35%, but increased the enantiomeric excess of the product to 53% ee, prompting us to halt our attempts at installing substituents with great steric bulk onto the ferrocene and instead consider substituents with more steric bulk than methyl but less than the triethylsilyl group we had previously been attempting to install.

To our satisfaction, increasing the steric bulk of the 2-substitution by installing a trimethylsilyl group, (*Sp*,*Sp*)-TMS-(*S*,*S*)-ⁱPr-BisFox **L26** (figure 22), provided an increase of enantioselectivity without overly harming the yield of the desired product, resulting in the triazole being isolated in 31% yield and 60% ee. The other diastereomer, (*Rp*,*Rp*)-TMS-(*S*,*S*)-ⁱPr-BisFox **L27** (figure 22), developed by the laboratory of Richards[83] through exploiting the far slower aromatic lithiation of deuterated positions by quenching (*Sp*,*Sp*)-Li-(*S*,*S*)-ⁱPr-BisFox with deuterium oxide and performing a second lithiation that favoured the non-deuterated position, resulted in a higher yield and an inversion of enantioselectivity, providing the triazole as the opposite enantiomer in 51% yield and at 20% ee, revealing (*Rp*,*Rp*)-TMS-(*S*,*S*)-ⁱPr-BisFox **L27** to be the “mismatched” enantiomer. This

observed inversion of stereochemistry points towards the planar chirality as being more influential than the oxazoline in dictating the chiral induction.

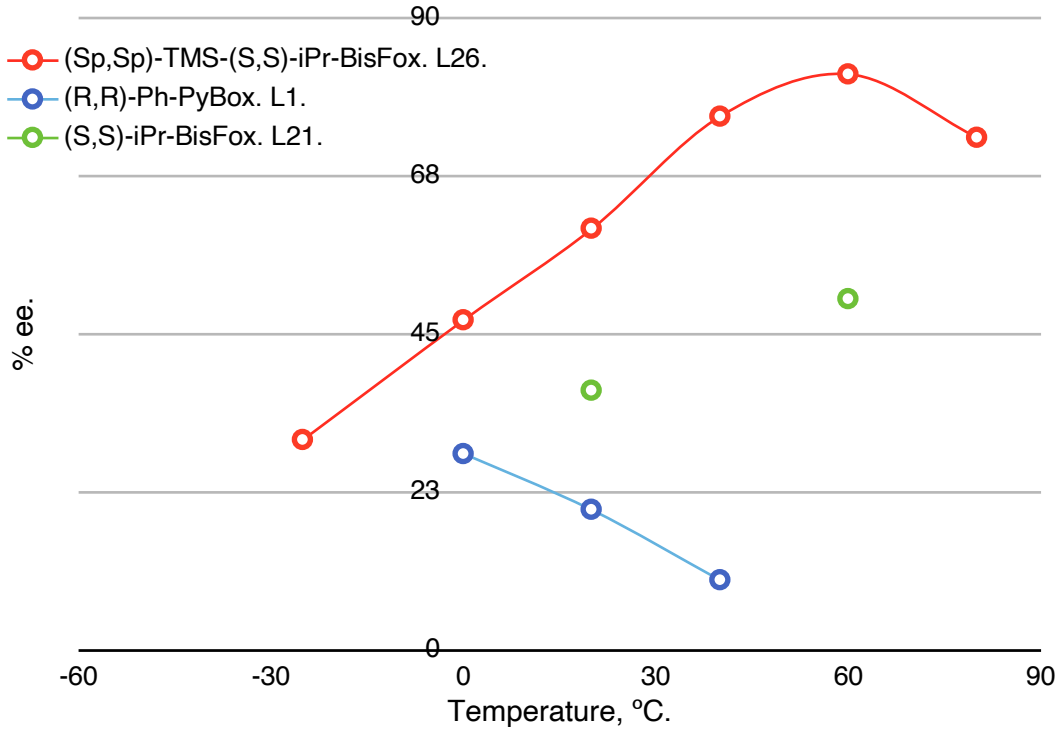


L26 **L27**

*Figure 22: (Sp,Sp)-TMS-(S,S)-^{i}Pr-BisFox **L26** and (Rp,Rp)-TMS-(S,S)-^{i}Pr-BisFox **L27***

4.2 Temperature Studies and Kinetic Resolution.

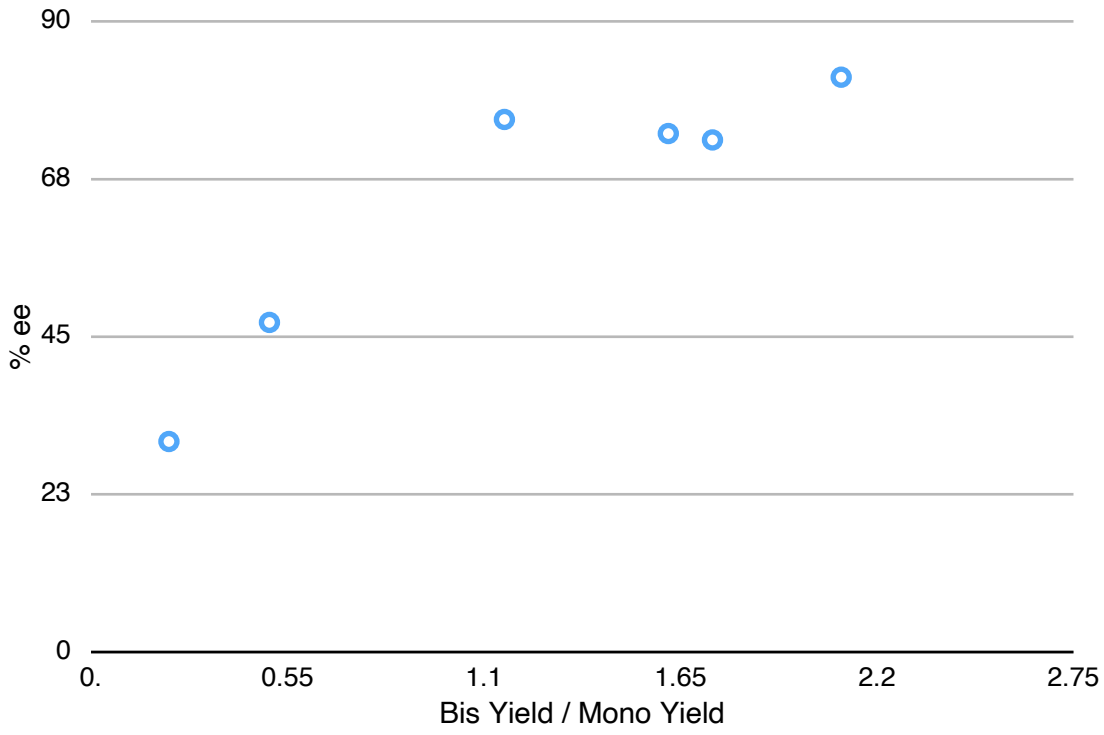
Graph 1: Desymmetrisation Temperature Dependence.



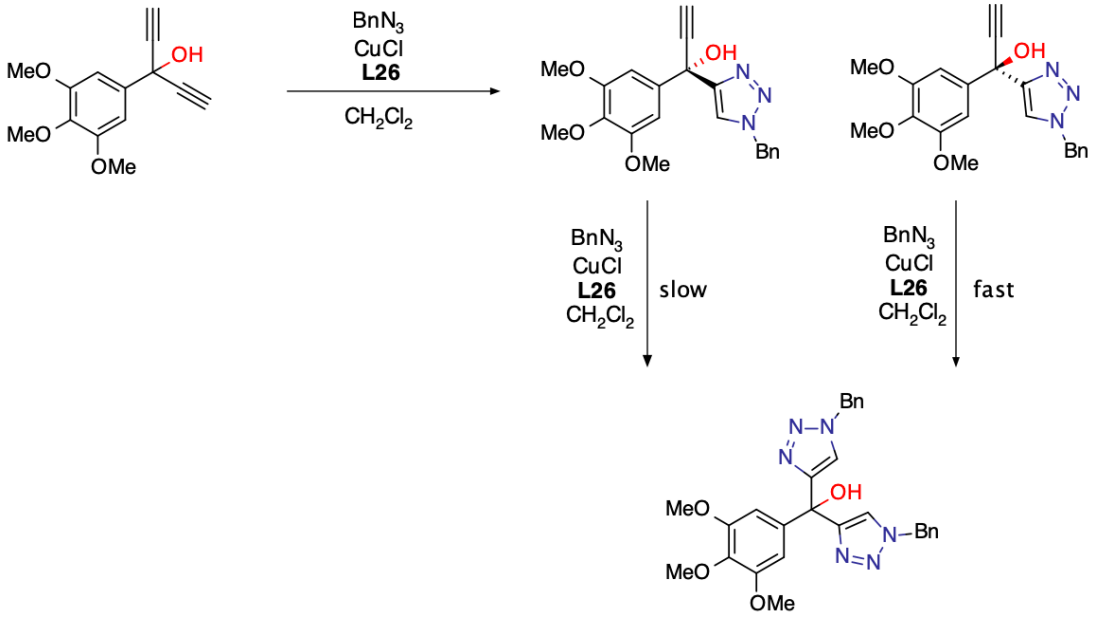
With the promising results from (*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox **L26** (figure 22) in hand we began to investigate the effect of temperature on the reaction with the goal of optimising for yield and enantioselectivity, expecting a lower temperature to provide higher enantioselectivity and higher selectivity for the desired monotriazole. Surprisingly, lowering the temperature to 0 ˚C with (*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox **L26** resulted in decreased enantioselectivity, providing the triazole at 47% ee. Further reduction of the temperature to -25 ˚C reduced the enantiomeric excess of the product to only 30% ee, however, a higher yield of the monotriazole to 39% was also observed. Increasing the temperature resulted in an increase of the enantiomeric excess of the monotriazole at the cost of yield, at 60 ˚C the enantiomeric excess of the product was 82% ee but isolated in only 10% yield. With further elevation of the reaction temperature to 80 ˚C the enantiomeric excess fell to 73% ee and the yield rose to 23%, similar to the results obtained at 40 ˚C. A similar trend was observed with (*S*,*S*)-^{i}Pr-BisFox **L21**, which resulted in an enantiomeric excess of 50% ee when the reaction temperature was elevated to 60 ˚C. To investigate whether this unexpected

temperature-dependent behaviour was unique to the BisFox ligands in our asymmetric CuAAC screening reaction we ran the reaction with our most successful PyBox ligand, (*R,R*)-Ph-PyBox **L1**. In contrast to the BisFox ligands, and as expected, higher reaction temperatures resulted in lower enantiomeric excess; the chiral monotriazole product was isolated in only 10% ee from reactions run with (*R,R*)-Ph-PyBox **L1** at 40 ˚C and lowering the reaction temperature resulted in product with greater enantiomeric excess.

Graph 2: Enantiomeric Excess vs. Product Ratio.



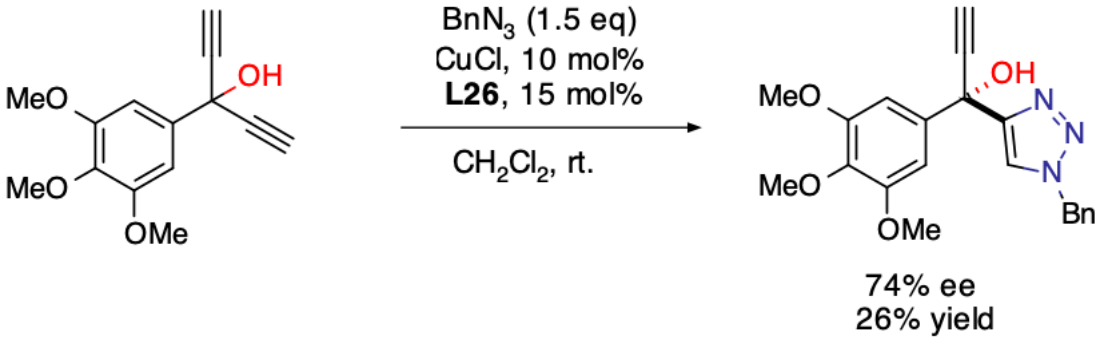
As (*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox **L26** resulted in an increase of the enantiomeric excess and decrease in the yield of the monotriazole alongside an increase in the yield of the bis(triazole) with increasing temperature we believed it possible that the high enantiomeric excess obtained at elevated temperature was a result of an *in situ* kinetic resolution (scheme 88). This would also explain the results we observed with (*R*,*R*)-Ph-BisFox **L23**, which gave little to no enantioselectivity, but produced the monotriazole in high yield. With this result in mind, we considered it possible that the majority of the observed enantioselectivity was due to an *in situ* kinetic resolution and that the desymmetrisation itself was responsible for very little of the enantiomeric excess.



Scheme 88: In-situ kinetic resolution of a geminal bis(alkyne).

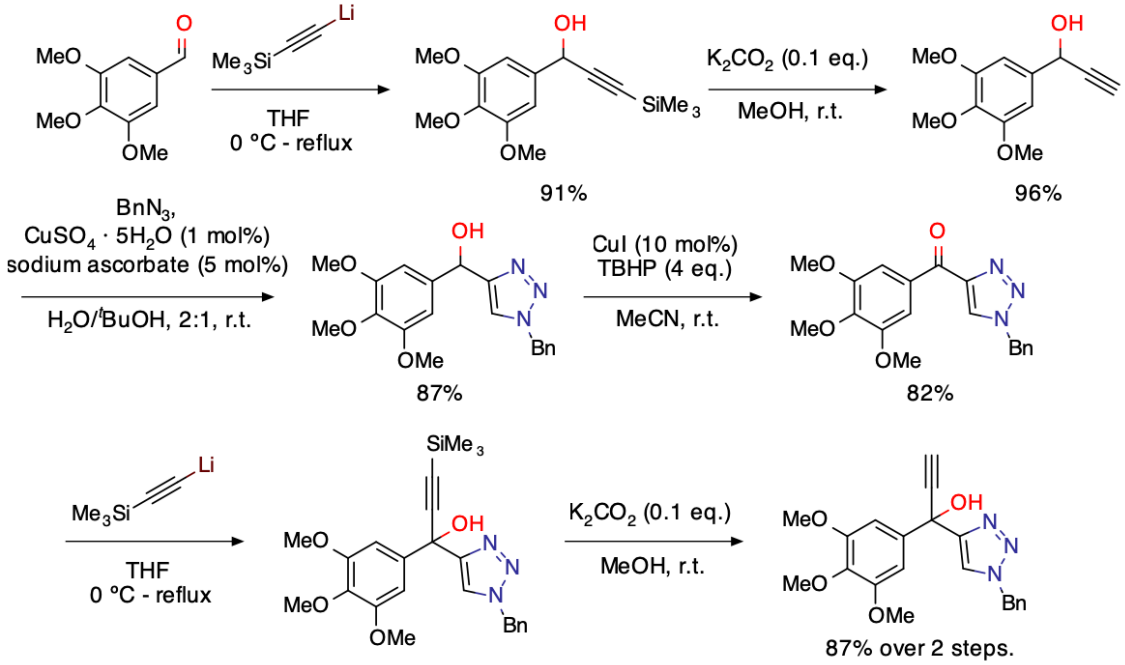
In a situation where the reaction of the first alkyne in the initial desymmetrisation step is fast compared to the reaction of the second alkyne, the kinetic resolution or kinetic amplification step, an increase in temperature would result in an increase of the rate of the resolution step relative to the desymmetrisation step, shifting the product ratio towards the bis(triazole). If the apparent enantioselectivity of the reaction was a result of the second kinetic resolution step an increase in temperature could also be expected to result in an increase in enantiomeric excess. The fall off in enantiomeric excess observed at 80 ˚C may be a result of the detrimental effect of the increasing temperature on the enantioselectivity of the kinetic resolution outstripping the beneficial effect of a relatively faster second step.

To initially investigate this hypothesis, we performed the reaction at room-temperature while increasing the equivalency of benzyl azide to 1.5 equivalents, resulting in an increase of the enantiomeric excess of the product to 74% (scheme 89).



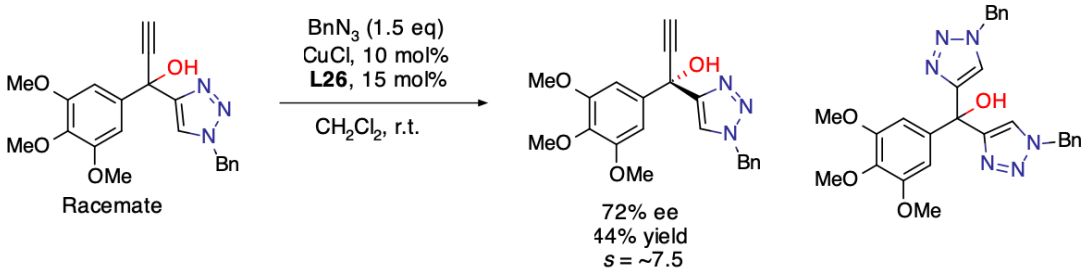
Scheme 89: Reaction of bis(alkyne) with 1.5 equivalents of benzyl azide

To further investigate this hypothesis we embarked upon the synthesis of the monotriazole as a racemate (scheme 90). Lithiation of trimethylsilylacetylene with ^{n}butyl lithium followed by addition of the resulting lithium acetylide to 3,4,5-trimethylbenzaldehyde proceeded in high yield to the silyl-protected propargylic alcohol. Potassium carbonate mediated desilylation progressed cleanly to provide the terminal alkyne in 96% yield, which was then subject to CuAAC conditions in the presence of benzyl azide to yield the triazole in 87%. A copper(I) iodide catalysed oxidation of the alcohol to a ketone with ^{t}butyl hydroperoxide proceeded in good yield. A second addition of lithiated trimethylsilylacetylene followed by a second desilylation provided the desired racemic monotriazole in 87% yield over the two steps.



Scheme 90: Racemic mono-alkyne synthesis

With the racemic monotriazole in hand a kinetic resolution was attempted using (*Sp*,*Sp*)-TMS-(*S*,*S*)-*i*Pr-BisFox **L26** and copper(I) chloride with half an equivalent of benzyl azide (scheme 91). After complete consumption of the azide, the remaining monotriazole was recovered with an enantiomeric excess of 72% in an isolated recovery of 44% (an estimated selectivity factor of 7.5).

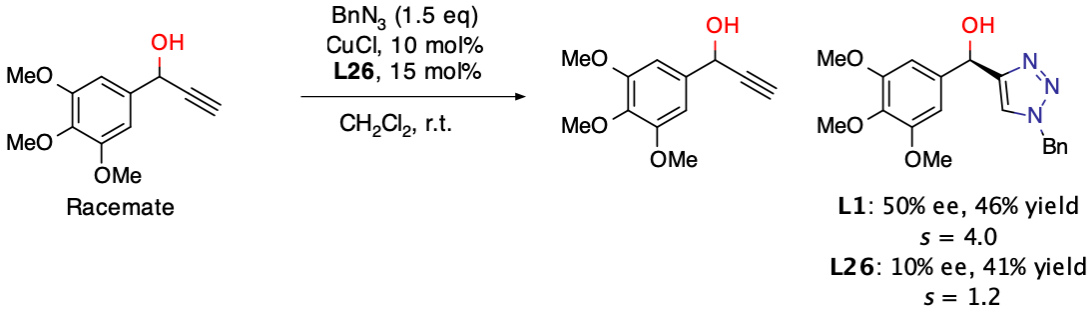


Scheme 91: Kinetic resolution of racemic mono-alkyne with (Sp,Sp)-TMS-(S,S)-^{i}*Pr-BisFox **L26***

In contrast to (*Sp*,*Sp*)-TMS-(*S*,*S*)-*i*Pr-BisFox **L26** which exhibited good enantioselectivity, when (*R*,*R*)-Ph-PyBox **L1** was employed as the ligand in the same kinetic resolution the monotriazole was recovered as the racemate. This result points towards the observed enantioselectivity in the desymmetrisation

reaction when (*R*,*R*)-Ph-PyBox **L1** being wholly determined in the desymmetrisation step.

However, (*R*,*R*)-Ph-PyBox **L1** did exhibit enantioselectivity in the kinetic resolution of another alkyne (scheme 92), providing the triazole in 46% isolated yield at 50% ee (an estimated selectivity factor of 4.0).



*Scheme 92: Kinetic resolution of racemic mono-alkyne with (R,R)-Ph-PyBox **L1***

(*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox **L26** was far less effective in the kinetic resolution of this substrate, providing the triazole in only 10% ee isolated in 41% yield (an estimated selectivity factor of 1.2). These findings point towards a situation in which the initial desymmetrisation of the bis(alkyne) used in the ligand screening proceeds with low enantioselectivity in the presence of (*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox **L26**, the majority of the enantiomeric excess resulting from the enantioselective formation of the second triazole on the remaining alkyne. Conversely, it appears that the enantiomeric excess observed when (*R*,*R*)-Ph-PyBox **L1** is used as the ligand wholly results from the initial desymmetrisation.

A brief investigation into the effect of the identity of the copper(I) salt on formal asymmetric desymmetrisations performed in the presence of (*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox **L26** highlighted the importance of the copper species in the reaction.

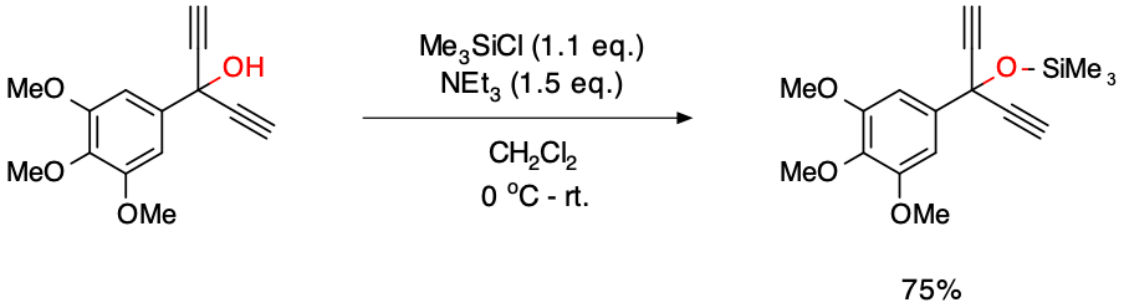
CuX	Yield	% ee
$CuPF_6(MeCN)_4$	75%	0%
Cu_2O	72%	0%
CuCl	23%	60%
CuTC	51%	0%

Table 7: Table of copper(I) screening results.

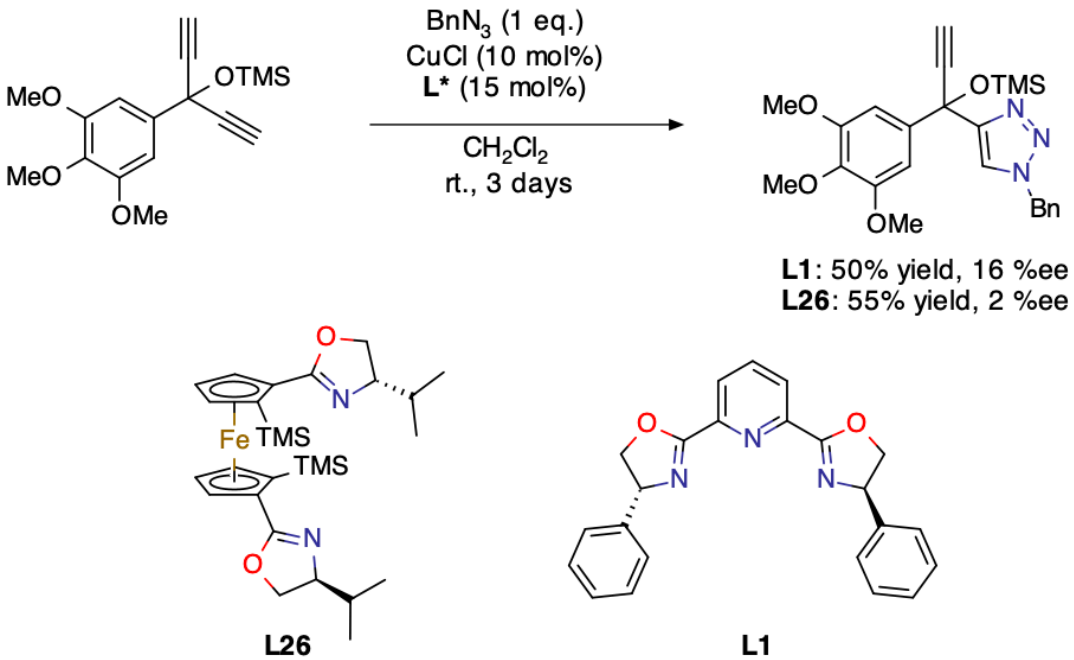
Interestingly, when copper(I) thiophene-2-carboxylate is used as the source of copper(I) a large difference in enantioselectivity is observed between (*R*,*R*)-Ph-PyBox **L1** and (*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox **L26**. (*R*,*R*)-Ph-PyBox **L1** with copper(I) thiophene-2-carboxylate resulted in very similar product yield and enantiomeric excess to copper(I) chloride, where (*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox **L26** with copper(I) thiophene-2-carboxylate resulted in a racemic product. Tetrakiss(acetonitrile) copper(I) hexafluorophosphate and copper(I) oxide also both resulted in racemic triazoles, but in decent yields, highlighting the importance of the identity of the copper(I) salt source in asymmetric CuAAC reactions.

5 Substrate Scope.

In order to deepen our understanding of the asymmetric copper-catalysed azide-alkyne cycloaddition reaction in the desymmetrisation of geminal bis(alkynes) we wished to expand the scope of substrates investigated. Firstly, we were interested in removing the alcohol functionality from the bis(alkyne). Various attempts at replacing the hydroxyl with something of a similar or smaller size, including reductions with hydrosilanes; transformations to sulfonates, esters and halogens to facilitate displacement by a nucleophile, were met with either no reaction or decomposition. Ultimately we settled for simply masking the hydroxyl as a silyl ether (scheme 93).



Scheme 93: Trimethylsilylation of (3,4,5-Trimethoxyphenyl)penta-1,4-diyn-3-ol.

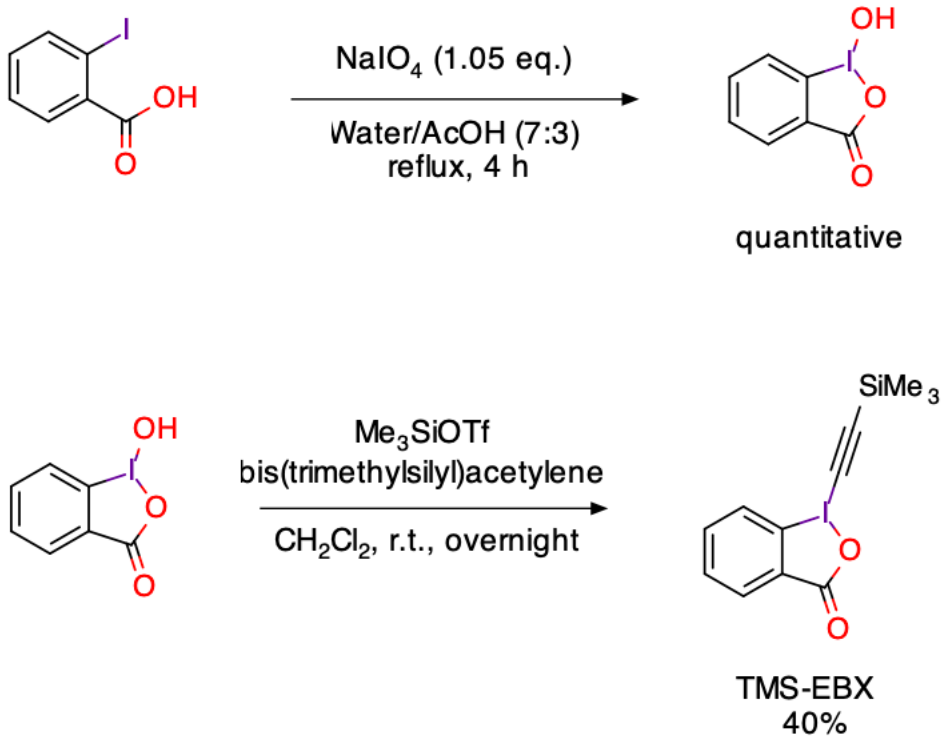


Scheme 94: Enantioselective CuAAC with a bis(alkyne) featuring a silyl ether

The bis(alkyne) featuring the silyl ether was subjected to enantioselective CuAAC conditions in the presence of (*R*,*R*)-Ph-PyBox **L1** and (*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox **L26** (scheme 94).

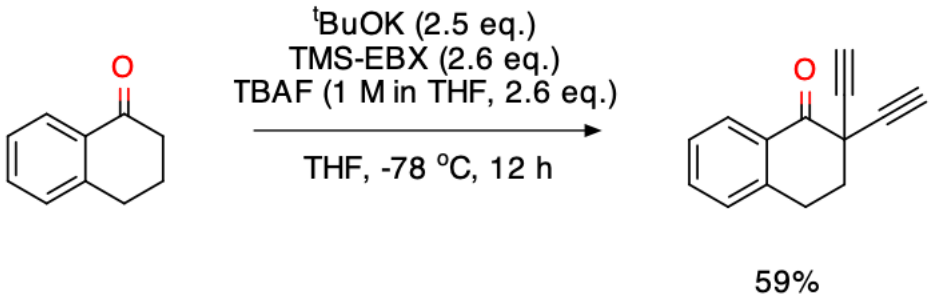
Silylating the alcohol resulted in a drop in enantioselectivity in both cases. The use of (*R*,*R*)-Ph-PyBox **L1** yielded the desired triazole at 16% ee, compared to 36% ee for the free alcohol. A much more pronounced drop in enantiomeric excess was observed in the case of (*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox **L26**, which produced a triazole at only 2% ee. Unfortunately, due to the bulk of the trimethylsilyl group no conclusions can be safely drawn from these results regarding any potential role of the alcohol in the reaction.

We envisioned that a cyclic substrates featuring a quaternary geminal bis(alkyne) would result in higher enantioselectivities than the non-cyclic substrates we had been investigating. In 2014 the laboratory of Silva reported the alkynylation of ketones using 1-(trimethylsilyl)ethynyl-1,2-benziodoxol-3-one, (TMS-EBX).[75] The synthesis of TMS-EBX began with the oxidation of 2-iodobenzoic acid to 1-hydroxy-1,2-benziodoxol-3-one with sodium periodate, reaction with bis(trimethylsilyl)acetylene under acidic conditions resulted in TMS-EBX as reported by Wasa and coworkers[74] in 40% yield (scheme 95).



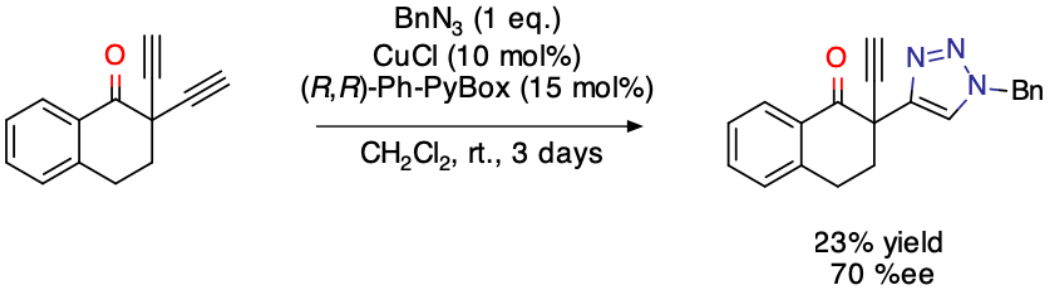
Scheme 95: Synthesis of TMS-EBX

The double alkynylation of 1-tetralone proceeded smoothly to deliver 2,2-diethynyl-1-tetralone in 59% yield. (scheme 96).



Scheme 96: Synthesis of 2,2-diethynyl-1-tetralone.

We initiated our investigation into the asymmetric CuAAC desymmetrisation of 2,2-diethynyl-1-tetralone by reaction with benzyl azide using copper(I) chloride with (*R*,*R*)-Ph-PyBox **L1** as the ligand (scheme 97).



*Scheme 97: Enantioselective desymmetrisation of 2,2-diethynyl-1-tetralone catalysed by CuCl / **L1***

To our gratification the reaction appeared to be far more enantioselective than with the previously screened substrates, unfortunately the yield was a disappointingly low 23%. Emboldened by the result a brief ligand screening was undertaken with the aim of optimising the yield and enantiomeric excess of the product.

Table 8: Table of 2,2-diethynyl-1-tetralone ligand screening results

Entry	Ligand	Yield	% ee
1	(*R*,*R*)-Ph-PyBox **L1**	23%	70
2	(*S*,*S*)-^{i}Pr-PyBox **L2**	20%	46
3	(*S*,*S*)-indenyl-PyBox **L3**	16%	39
4	(*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox **L26**	64%	8

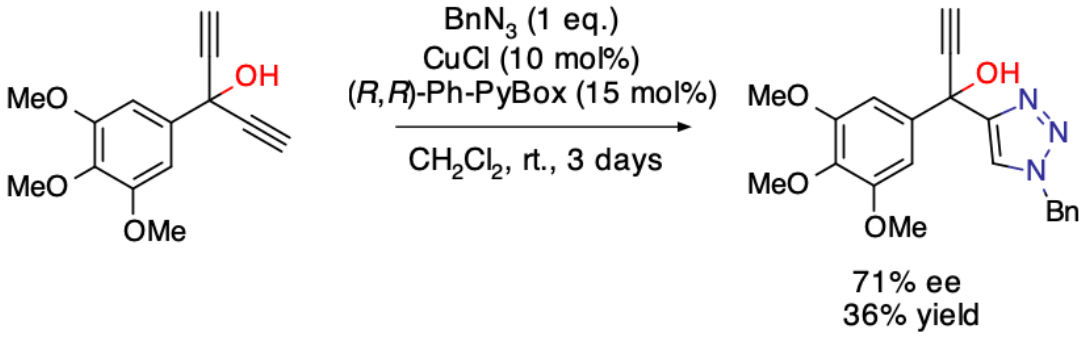
Reminiscent of our ligand screening for the desymmetrisation of the ester-derived geminal bis(alkynes), (*R*,*R*)-Ph-PyBox **L1** gave the best results among the bis(oxazoline) ligands screened. Both (*S*,*S*)-^{i}Pr-PyBox **L2** and (*S*,*S*)-indenyl-PyBox **L3** gave lower yields and significantly lower enantioselectivity. While (*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox **L26** provided the monotriazole in a greater yield (64%) than the other ligands screened, in terms of enantioselectivity (*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox **L26** performed poorly in the desymmetrisation of 2,2-diethynyl-1-tetralone, providing the triazole in only 8% ee.

Conclusions

6 Conclusion.

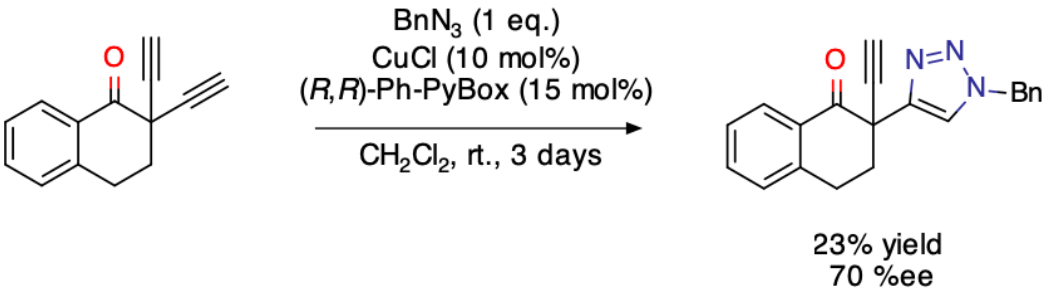
Research into enantioselective copper-catalysed azide-alkyne cycloaddition reactions has been undertaken by only a handful of laboratories and is a reaction that has not yet been solved. The reactions are proving remarkably substrate dependent, exhibiting large differences in both enantiomeric excess and yield as a result of the species of bis(alkyne) used or substrate modification. The choice of solvent, copper source, ligand, and temperature can result in drastic and unexpected changes to the outcome of the reaction.

In this thesis, (*R*,*R*)-Ph-PyBox **L1** has been demonstrated to afford enantioenriched triazoles in the desymmetrisation of prochiral bis(alkynes) with an enantioselective CuAAC reaction, representing the first examples of enantioselective CuAAC desymmetrisations of geminal alkynes (scheme 98).



Scheme 98: The enantioselective desymmetrisation of prochiral geminal alkynes.

We report both the enantioselective desymmetrisation of (3,4,5-trimethoxyphenyl)penta-1,4-diyn-3-ol in up to 71% yield and 36% ee and the enantioselective desymmetrisation of 2,2-diethynyl-1-tetralone in up to 23% yield and 70% ee (scheme 99).

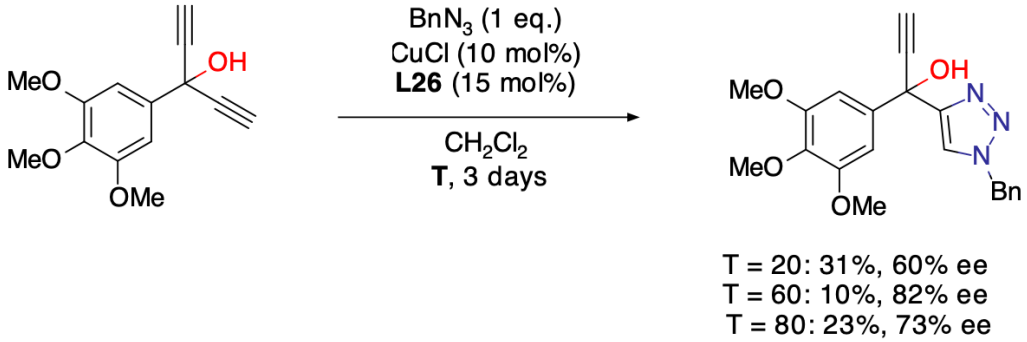


Scheme 99: The enantioselective desymmetrisation of prochiral geminal alkynes on a tetralone core.

These desymmetrisations represent a solid foundation upon which further optimisation may be built and highlight PyBox ligands as a robust starting point for investigations into asymmetric CuAAC reactions. Examination of a wider variety of PyBox ligands, particularly Ar-PyBox ligands, may reveal a ligand or set of ligands that can be utilised in asymmetric CuAAC reactions to furnish chiral triazoles in respectable yield and enantiomeric excess from a variety of bis(alkyne) substrates.

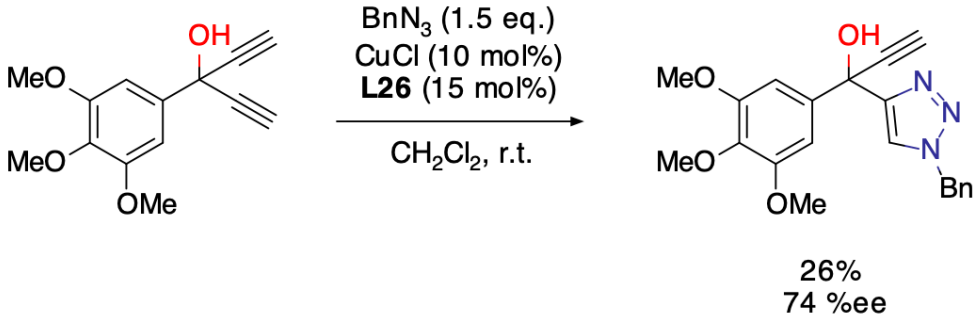
The enantioselective CuAAC desymmetrisation of 2,2-diethynyl-1-tetralone with (*R*,*R*)-PhPyBox **L1** used as the chiral ligand exhibited good enantioselectivity with the pursuit of very little optimisation. Modification of the reaction conditions has the potential to result in a reaction that exhibits outstanding product yield and enantiomeric excess. There is also much room for modification of the bis(alkyne) substrate; investigation into the desymmetrisation of 2,2-diethynyl-1-indanone and 2,2-diethynyl-1-benzosuberone as well as the variety of possible related substrates featuring 3,3-disubstitutions would be an interesting avenue of research that would provide a respectable substrate scope.

We also report the novel use of BisFox ligands in asymmetric CuAAC reactions with the temperature-dependent formal desymmetrisation of (3,4,5-trimethoxyphenyl)penta-1,4-diyn-3-ol with (*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox **L26** in 31% yield and 60% ee and in 23% yield and 73% ee at 20 ˚C and 80 ˚C, respectively. Temperature optimisation for enantiomeric excess allows for the triazole to be isolated at 82% ee at the cost of yield (scheme 100).



Scheme 100: Prochiral geminal alkyne desymmetrisation and enantioenrichment by in-situ kinetic resolution.

The application of (*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox **L26** in the formal desymmetrisation of (3,4,5-trimethoxyphenyl)penta-1,4-diyn-3-ol with higher equivalencies of azide can also provide triazoles in respectable enantiomeric excess (scheme 101).

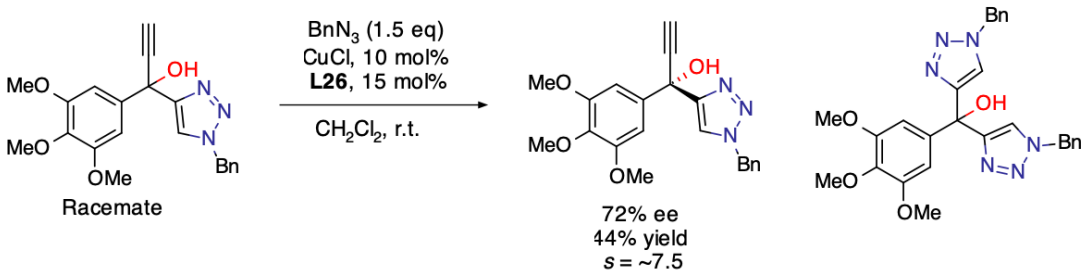


Scheme 101: Prochiral geminal alkyne desymmetrisation and enantioenrichment by in-situ kinetic resolution with 1.5 equivalents of azide.

Our investigations into the application of ferrocenyl ligands in desymmetrising asymmetric CuAAC reactions has also led to an effective enantioenrichment of chiral alkynes by kinetic resolution (scheme 102).

These results highlight (*Sp,Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox as a great chiral ligand for use in the asymmetric CuAAC reactions investigated within this thesis, capable of maintaining respectable enantioselectivity at high reaction temperatures. Investigation into this highly modifiable class of ligand has the potential to reveal BisFox ligands as a robust tool for asymmetric CuAAC reactions. Furthermore,

the success resulting from the use of (*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox described in this thesis make the BisFox class of ligands a potentially enticing avenue of research within investigations of other asymmetric copper-catalysed reactions.



*Scheme 102: Kinetic resolution with (Sp,Sp)-TMS-(S,S)-^{i}Pr-BisFox **L26**.*

The dichotomy between (*R*,*R*)-PhPyBox **L1** and (*Sp*,*Sp*)-TMS-(*S*,*S*)-^{i}Pr-BisFox **L26** observed in both the desymmetrisations of prochiral bis(alkynes) and the kinetic resolutions of chiral monoalkynes illustrates the specificity between substrate and ligand required to provide high enantioselectivities in asymmetric copper-catalysed azide-alkyne cycloaddition reactions. The research detailed in this thesis revealed asymmetric CuAAC conditions that yield respectable enantioselectivities for desymmetrisations and kinetic resolutions for a few substrates, representing a step towards a set of general conditions that may be broadly applied to asymmetric copper-catalysed azide-alkyne cycloaddition reactions.

Experimental Procedures.

7.1 General Procedures.

Enantiomeric excess of (1-Benzyl-1H-1,2,3-triazol-4-yl)(3,4,5-trimethoxyphenyl)methanone was determined by HPLC, using a Chiralpak® AD-H column, eluting at 11 and 15 minutes with hexane/isopropanol 70:30 at a flow rate of 1 ml/minute, and detected by UV light (230 nm). Enantiomeric excess of 2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-2-ethynyl-1-tetralone was determined by HPLC, using a Chiralpak® OJ column, eluting at 27 and 66 minutes with hexane/isopropanol 60:40 at a flow rate of 1 ml/minute, and detected by UV light (230 nm). Enantiomeric excess of (1-Benzyl-1H-1,2,3-triazol-4-yl)(3,4,5-trimethoxyphenyl)methanol was determined by HPLC, using a Chiralpak® AD-H column, eluting at 8 and 11 minutes with hexane/isopropanol 70:30 at a flow rate of 1 ml/minute, and detected by UV light (230 nm). Reactions were magnetically stirred and monitored by thin-layer chromatography using silica gel pre-coated aluminium plates which were visualised with UV light and potassium permanganate stain. Flash column chromatography was performed using silica gel (230-400 mesh particle size). Reagents were purchased from Sigma-Aldrich and used without further purification. Chiral ligands were purchased from Stem Chemicals, Inc. and used without further purification. Ferrocene ligands, L21, L26 and L27, were generously provided by Dr Chris Richards and Dr Ross Arthurs. Solvents were purchased from Fisher Scientific. Tetrahydrofuran and diethyl ether were distilled over sodium/benzophenone, toluene was distilled over sodium, and dichloromethane was distilled over calcium hydride. All other solvents were used without further purification or drying. 1H NMR and 13C NMR were acquired at 500 MHz and 126 MHz, respectively, on a Bruker 500 machine. 1H NMR and 13C NMR were obtained for all final compounds. Structural confirmation of intermediates lacking a full suite of spectral characterisation was inferred from characterisation of products from subsequent transformations. Melting points are reported as the average of three melting observations; melting points were not obtained for compounds afforded through enantioselective CuAAC reactions due to the low scale and low product quantities of the reactions.

General procedure A for CuAAC desymmetrisations. A sealable was tube charged with prochiral diyne (1.0 mmol, 1.0 eq.) copper(I) salt (0.10 mmol, 0.10 eq.) and ligand (0.15 mmol, 0.15 eq.), sealed, and flushed with argon. Solvent (0.1 M) was added, and the mixture stirred for one hour or until the copper(I) salt had dissolved indicating ligation. Benzyl azide (1.0 mmol, 1.0 eq.) was added and the reaction was stirred for 3 days until the benzyl azide was consumed as determined by TLC. The reaction mixture was loaded directly onto a silica column (Pet Ether/EtOAc) for purification.

General procedure B for CuAAC kinetic resolutions. A sealable was tube charged with racemic alkyne (1.0 mmol, 1.0 eq.) copper(I) salt (0.10 mmol, 0.10 eq.) and ligand (0.15 mmol, 0.15 eq.), sealed, and flushed with argon. Solvent (0.1 M) was added, and the mixture stirred for one hour or until the copper(I) salt had dissolved indicating ligation.Benzyl azide (0.50 mmol, 0.50 eq.) was added and the reaction was stirred for 3 days until the benzyl azide was consumed as determined by TLC. The reaction mixture was loaded directly onto a silica column (Pet Ether/EtOAc) for purification.

General procedure C for RuAAC desymmetrisations. A sealable was tube charged with prochiral diyne (1.0 mmol, 1.0 eq.) Cp*RuCl[COD] (0.10 mmol, 0.10 eq.) and ligand (0.15 mmol, 0.15 eq.), sealed, and flushed with argon. Solvent (0.1 M) was added, and the mixture stirred for one hour. Benzyl azide (1.0 mmol, 1.0 eq.) was added and the reaction was stirred for 3 days until the benzyl azide was consumed as determined by TLC. The reaction mixture was loaded directly onto a silica column (Pet Ether/EtOAc) for purification.

General procedure D for prochiral carbinol-diyne synthesis. A flame dried flask fitted with a magnetic stirrer bar and flushed with argon was charged with trimethylsilylacetylene (15 mmol, 2.2 eq.) and THF (0.3 M). The mixture was cooled to 0 °C, ^{n}Buli 1.6 M in hexanes (15 mmol, 2.2 eq.) was added dropwise and the reaction was stirred for 30 minutes at 0 °C. An appropriate methyl ester or formate (6.8 mmol, 1.0 eq.) was added and after the mixture was allowed to

warm it was heated to near reflux with a heat gun for ca. 5 minutes. The mixture was allowed to cool and added to a mixture of sat. aqueous NH_4Cl / EtOAc (1:1). The phases were separated and the organic washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo to yield red oils. Purified by column chromatography (Pet Ether/EtOAc) where necessary.

General procedure E for chiral carbinol-alkyne synthesis. A flame dried flask fitted with a magnetic stirrer bar and flushed with argon was charged with trimethylsilylacetylene (15 mmol, 1.1 eq.) and THF (0.3 M). The mixture was cooled to 0 ºC, ^{n}Buli 1.6 M in hexanes (15 mmol, 1.1 eq.) was added dropwise and the reaction was stirred for 30 minutes at 0 ºC. An appropriate aldehyde (14 mmol, 1.0 eq.) was added and after the mixture was allowed to warm it was heated to near reflux with a heat gun for ca. 5 minutes. The mixture was allowed to cool and added to a mixture of sat. aqueous NH_4Cl/EtOAc (1:1). The phases were separated and the organic washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo to yield red oils. Purified by column chromatography (Pet Ether/EtOAc) where necessary.

General procedure F for alkyne desilylation. Trimethylsilyl-protected alkyne (5 mmol, 1.0 eq.) and K_2CO_3 (0.1 eq. per silane) were dissolved in methanol (0.3 M) and stirred for 1-12 hours until the reaction was complete as determined by TLC. The mixture was diluted with EtOAc and washed with water and brine. Dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (Pet Ether/EtOAc) or recrystallisation from methanol.

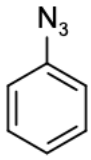
General procedure G for pyridine-2,6-bis(ethanolamide) synthesis. To a suspension of pyridine-2,6-dicarboxylic acid (10 mmol, 1.0 eq.) in CH_2Cl_2 (0.2 M) was added oxalyl chloride (30 mmol, 3.0 eq.) and DMF (1 drop) the reaction was stirred overnight until the suspension had dissolved to form a yellow solution. Volatiles were removed in vacuo. The resulting pyridine-2,6-dicarboxylic chloride was redissolved in CH_2Cl_2 (0.35 M) and added at 0 ºC to a flask charged with a chiral amino alcohol (30 mmol, 3.0 eq.) triethylamine (6.0 eq.) and CH_2Cl_2 (0.25 M). The reaction was allowed to warm to room temperature and stirred overnight. Purified by column chromatography (Pet Ether/EtOAc).

General procedure H for PyBox ligand synthesis. To a flask charged with a pyridine-2,6-bis(ethanolamide) (10 mmol, 1.0 eq.) triethylamine (100 mmol, 10 eq.) and CH_2Cl_2 (0.1 M) was added MsCl (22 mmol, 2.2 eq.) and the mixture stirred at room temperature for 16 hours followed by reflux for 16 hours. The mixutre was diluted with CH_2Cl_2 and washed with 5% aqueous NaOH, water, and brine. Dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (pet ether/EtOAc) or recrystallisation from methanol.

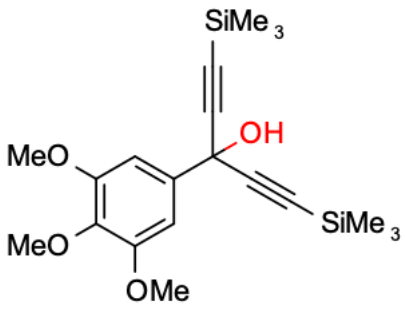
General procedure I for ferrocene-1,1'-bis(ethanolamide) synthesis. To a suspension of ferrocene-1,1'-dicarboxylic acid (10 mmol, 1.0 eq.) in CH_2Cl_2 (0.2 M) was added oxalyl chloride (30 mmol, 3.0 eq.) and DMF (1 drop) the reaction was stirred overnight until the suspension had dissolved to form a red solution. Volatiles were removed in vacuo. The resulting ferrocene-1,1'-dicarboxylic chloride was redissolved in CH_2Cl_2 (0.35 M) and added at 0 ºC to a flask charged with a chiral amino alcohol (30 mmol, 3.0 eq.) triethylamine (60 mmol, 6.0 eq.) and CH_2Cl_2 (0.25 M). The reaction was allowed to warm to room temperature and stirred overnight. Purified by column chromatography (Pet Ether/EtOAc).

General procedure J for BisFox ligand synthesis. To a flask charged with a ferrocene-1,1'-bis(ethanolamide) (10 mmol, 1.0 eq.) triethylamine (100 mmol, 10 eq.) and CH_2Cl_2 (0.1 M) was added MsCl (22 mmol, 2.2 eq.) and the mixture stirred at room temperature for 16 hours followed by reflux for 16 hours. The mixture was diluted with CH_2Cl_2 and washed with 5% aqueous NaOH, water, and brine. Dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (pet ether/EtOAc).

7.2 Compound Syntheses.

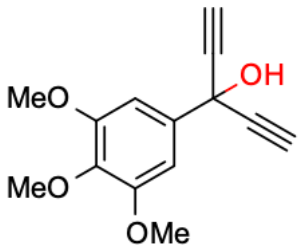


Benzyl azide. According to the preparation reported by Wilkening.[88] To a solution of NaN_3 (1.5 g, 23 mmol) in water (10 ml) was added acetone (30 ml) followed by benzyl bromide (1.8 ml, 15mmol). The reaction mixture was heated to reflux for 18 hours, allowed to cool, diluted with EtOAc (100 ml) and washed with water (50 ml) and brine (50 ml). Dried over $MgSO_4$ and concentrated in vacuo to yield 2.0 g (quant.) of benzyl azide as a colourless liquid. Obtained spectroscopic data was consistent with that reported in the literature.[88] 1H NMR (500 MHz, CDCl3) δ 7.42 – 7.31 (m, 5H), 4.34 (s, 1H). 13C NMR (126 MHz, CDCl3) δ 135.51, 128.92, 128.39, 128.31, 54.83.

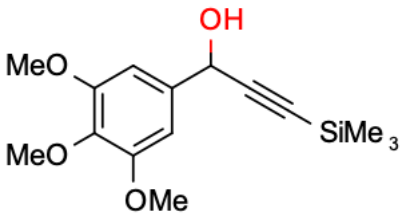


3-(3,4,5-Trimethoxyphenyl)-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-ol. A solution of trimethylsilylacetylene (3.0 ml, 21 mmol) in THF (50 ml) was cooled to 0 °C. ^{n}Buli 2.5 M solution in hexanes (8.4 ml, 21 mmol) was added dropwise and the reaction was stirred for 30 minutes at 0 °C. Methyl 3,4,5-trimethoxybenzoate (2.3 g, 10 mmol) was added and the reaction mixture was heated to near reflux with a heat gun for 5 minutes. The mixture was allowed to cool and added to a mixture of sat. aqueous NH_4Cl (50 ml) and EtOAc (50 ml). The phases were separated and the organic washed with water (50 ml) and brine (50 ml), dried over $MgSO_4$ and concentrated in vacuo to yield 4.0 g (quant.) of the product as a

red oil. Obtained spectroscopic data was consistent with the title compound. The title compound was successfully used in subsequent transformations. 1H NMR (500 MHz, CDCl3) δ 7.08 (s, 2H), 3.88(s, 6H), 3.85 (s, 3H), 0.22 (s, 18H), 13C NMR (126 MHz, CDCl3) δ 154.15, 153,22, 137.16, 135.37, 105.80, 105.76, 82.11, 81.98, 75.6, 61.30, 57.80, 56.23, -0.02.

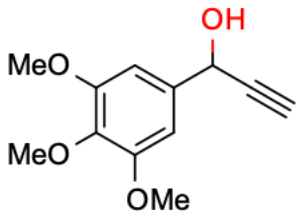


3-(3,4,5-Trimethoxyphenyl)penta-1,4-diyn-3-ol. To a solution of 3-(3,4,5-Trimethoxyphenyl)-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-ol (4.0 g, 10 mmol) in methanol (50 ml) was added K_2CO_3 (0.14 g, 1.0 mmol). After stirring for 5 hours the reaction mixture was diluted with EtOAc (100 ml) and washed with water (2 x 30 ml) and brine (30 ml). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (pet ether/EtOAc, 5:1) yielded 2.5 g (quant.) of the product as a white solid. 1H NMR (500 MHz, CDCl3) δ 7.04 (s, 2H), 3.89 (s, 6H), 3.85 (s, 3H), 3.01 (s, 1H), 2.80 (s, 2H). 13C NMR (126 MHz, CDCl3) δ 153.31, 138.62, 136.30, 103.26, 83.51, 73.85, 64.84, 61.00, 56.36. HRMS (NSI) *m/z* calcd. for $C_{14}H_{14}O_4$ $(M+Na)^+$ 269.0790, found 269.0787. IR neat / cm^{-1} 3385, 3277, 3263, 2937, 1596, 1501, 1460, 1415, 1326, 1238, 1224, 1124, 996, 846, 830, 765, 732, 705.

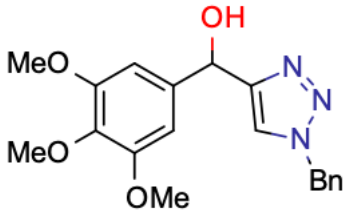


1-(3,4,5-trimethoxyphenyl)-3-(trimethylsilyl)prop-2-yn-1-ol. A flame dried flask fitted with a magnetic stirrer bar and flushed with argon was charged with trimethylsilylacetylene (1.5 g, 15 mmol, 1.1 eq.) and THF (50 ml). The mixture

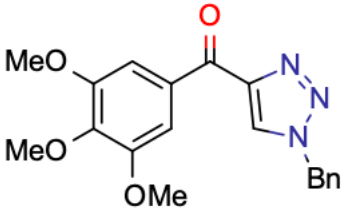
was cooled to 0 °C, ^{n}Buli 1.6 M in hexanes (9.4 ml, 15 mmol, 1.1 eq.) was added dropwise and the reaction was stirred for 30 minutes at 0 °C. Methyl 3,4,5-trimethoxybenzaldehyde (2.8 g, 14 mmol, 1.0 eq.) was added and after the mixture was allowed to warm it was heated to near reflux with a heat gun for ca. 5 minutes. The mixture was allowed to cool and added to a mixture of sat. aqueous NH_4Cl/EtOAc (1:1). The phases were separated and the organic washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo to afford 3.5 g (86%) of the title product as a red oil. 1H NMR (500 MHz, CDCl3) δ 6.80 (s, 2H), 5.39 (d, J = 5.1 Hz, 1H), 3.87 (s, 6H), 3.84 (s, 3H), 2.30 (d, J = 6.3 Hz, 1H), 0.21 (s, 9H). 13C NMR (126 MHz, CDCl3) δ 153.40 , 138.07 , 136.06 , 105.06 , 103.99 , 91.94 , 65.22 , 61.01 , 56.22 , -0.01 .



1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-ol. To a solution of 1-(3,4,5-trimethoxyphenyl)-3-(trimethylsilyl)prop-2-yn-1-ol (3.5 g, 12 mmol) in methanol (50 ml) was added K_2CO_3 (0.14 g, 1.0 mmol). After stirring for 5 hours the reaction mixture was diluted with EtOAc (100 ml) and washed with water (2 x 30 ml) and brine (30 ml). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (pet ether/EtOAc, 5:1) yielded 2.4 g (92%) of the product as a colourless oil. 1H NMR (500 MHz, CDCl3) δ 6.78 (s, 2H), 5.40 (d, J = 2.3 Hz, 2H), 3.88 (s, 6H), 3.84 (s, 3H), 2.68 (d, J = 2.2 Hz, 1H), 2.40 (s, 1H). 13C NMR (126 MHz, CDCl3) δ 153,23, 138.01, 133.80, 132.16, 127.54, 125.58, 122,80, 103.52, 73.98, 61.03, 57.12.

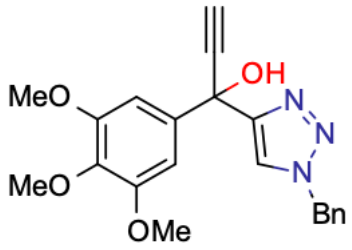


(1-Benzyl-1H-1,2,3-triazol-4-yl)(3,4,5-trimethoxyphenyl)methanol. To a solution of 1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-ol (1.0 g, 4.5 mmol), sodium ascorbate (0.089 g, 0.45 mmol) and $CuSO_4 \cdot (H_2O)_5$ (0.011 g, 0.045 mmol) in ^{t}butanol/water 1:1 (18 ml, 0.25 M) was added Benzyl azide (0.56 ml, 4.5 mmol). The reaction mixture was stirred at room temperature for 16 hours. The mixture was diluted with EtOAc (60 ml) and washed with water (2 x 40 ml) and brine (40 ml). The organic phase was dried over $MgSO_4$ and concentrated in vacuo without further purification to yield 1.4 g (87%) of the product as a white solid. HRMS (NSI) *m/z* calcd. for $C_{14}H_{14}O_4$ $(M+H)^+$ 356.1610, found 356.1607. 1H NMR (500 MHz, CDCl3) δ 7.36 (dq, *J* = 4.5, 2.8, 2.1 Hz, 3H), 7.27 – 7.22 (m, 3H), 6.65 (s, 2H), 5.94 (s, 1H), 5.49 (s, 2H), 3.82 (s, 3H), 3.81 (s, 6H). IR neat / cm^{-1} 3378, 2943, 2836, 1593, 1506, 1458, 1423, 1323, 1241, 1214, 1147, 1121, 1056, 1026, 997, 964, 854, 817, 769, 723.



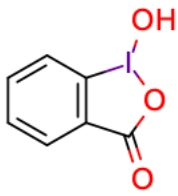
(1-Benzyl-1H-1,2,3-triazol-4-yl)(3,4,5-trimethoxyphenyl)methanone. To a round bottomed flask charged with (1-benzyl-1H-1,2,3-triazol-4-yl)(3,4,5-trimethoxyphenyl)methanol (0.52 g, 1.5 mmol), CuI (0.028 g, 0.15 mmol) and MeCN (5 ml, 0.3 M) was added ^{t}butylhydrogen peroxide 70% in water (0.81 ml, 5.8 mmol) and the reaction mixture was stirred overnight. Water (30 ml) was added and the reaction was extracted with EtOAc (2 x 40 ml). The combined organic was washed with brine (40 ml), dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (pet ether/EtOAc, 4:1, R_f: 0.13)

yielded 0.42 g (80%) of the product as an off-white solid. 1H NMR (500 MHz, CDCl3) δ 8.17 (s, 1H), 7.88 (s, 2H), 7.44 – 7.39 (m, 3H), 7.37 – 7.33 (m, 2H), 5.61 (s, 2H), 3.95 (s, 9H). 13C NMR (126 MHz, CDCl3) δ 184.05, 153.07, 148.92, 143.06, 133.82, 131.55, 129.56, 129.42, 128.63, 108.47, 61.16, 56.49, 54.74. IR neat / cm^{-1} 3128, 3008, 2949, 2840, 1630, 1579, 1501, 1456, 1417, 1350, 1310, 1122, 1044, 1003, 818, 759, 731.

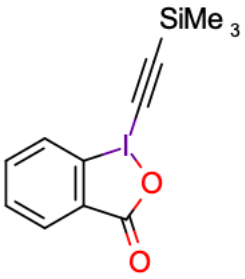


1-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-ol. A solution of trimethylsilylacetylene (0.16 ml, 1.1) in THF (3.8 ml, 0.3 M) was cooled to 0 °C. ^{n}Buli 1.6 M in hexanes (0.7 ml, 1.14 mmol) was added dropwise and the reaction was stirred for 30 minutes at 0 °C. (1-benzyl-1H-1,2,3-triazol-4-yl)(3,4,5-trimethoxyphenyl)methanone (0.366 g, 1.04 mmol) was added. After the mixture was allowed to warm it was heated to near reflux with a heat gun for ca. 5 minutes. The mixture was allowed to cool and added to a mixture of sat. aqueous NH_4Cl (15 ml) and EtOAc (15 ml). The phases were separated and the organic washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$ and concentrated in vacuo to yield 0.43 g of 1-(1-benzyl-1H-1,2,3-triazol-4-yl)-1-(3,4,5-trimethoxyphenyl)-3-(trimethylsilyl)prop-2-yn-1-ol and 1-(1-benzyl-1H-1,2,3-triazol-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-ol as a 4:1 mixture. The mixture was taken up in methanol (3 ml, 0.3 M) and K_2CO_3 (0.013 g, 0.096 mmol) was added. The reaction was stirred overnight, diluted with EtOAc (10 ml), washed with water (5 ml) and brine (5 ml). Dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (pet ether/EtOAc 1:1, R_f: 0.29) yielded 3.4 g (87%) the product as a yellow solid. 1H NMR (500 MHz, CDCl3) δ 7.37 (m, 3H), 7.32 (s, 1H), 7.28 – 7.25 (m, 2H), 6.90 (s, 2H), 5.50 (s, 2H), 3.83 (s, 3H), 3.82 (s, 6H), 2.84 (s, 1H). HRMS (NSI) *m/z* calcd. for $C_{21}H_{21}N_3O_4$ $(M+H)^+$

380.1610, found 380.1607. IR neat / cm^{-1} 3419, 3250, 2937, 2114, 1592, 1501, 1456, 1415, 1321, 1233, 1116, 1081, 1046, 996, 932, 841, 797, 763, 719.

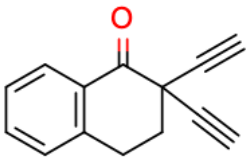


1-Hydroxy-1,2-benziodoxol-3-one. Following the procedure reported by Waser,[74] a suspension of 2-iodobenzoic acid (8.0 g, 32 mmol) and $NaIO_4$ (7.24 g, 0.34 mmol). in water/AcOH 7:3 (50 ml) was refluxed with vigorous stirring for 4 hours. The reaction mixture was allowed to cool, cold water (180 ml) was added and the mixture was allowed to stand for 3 hours. The resulting solid was collected by vacuum filtration, washed with ice-water (2 x 20 ml), cold acetone (2 x 20 ml) and air-dried on the filter paper in the dark to yield 9.4 g (quant.) of the product as a white solid. Obtained spectroscopic data was consistent with that reported in the literature.[74] 1H NMR (500 MHz, DMSO-d6) δ 8.01 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.95 (ddd, *J* = 8.6, 7.2, 1.5 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.70 (td, *J* = 7.4, 1.0 Hz, 1H). IR neat / cm^{-1} 3083, 2812, 2401, 1585, 1563, 1438, 1338, 1301, 1148, 1112, 1017, 834, 739, 693, 580, 543, 474.

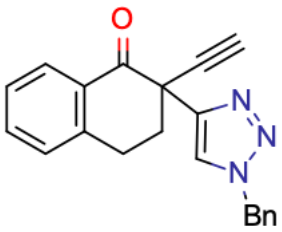


1-(Trimethylsilyl)ethynyl-1,2-benziodoxol-3-one. Following a procedure reported by Waser.[74] to a suspension of 1-Hydroxy-1,2-benziodoxol-3-one (1.94 g, 7.4 mmol) in CH_2Cl_2 (22 ml) was added TMSOTf (1.5 ml, 8.1 mmol). After stirring at room temperature for 1 hour bis(trimethylsilyl)acetylene (1.8 ml, 8.1 ml)

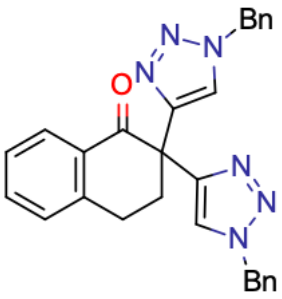
was added dropwise. The reaction mixture was stirred overnight and sat. aqueous $NaHCO_3$ (40 ml) was added with vigorous stirring. After the solid had dissolved the phases were separated, and the aqueous extracted again with CH_2Cl_2 (50 ml). The combined organics were washed with sat. aqueous $NaHCO_3$ (50 ml), dried over $MgSO_4$ and concentrated in vacuo to yield a yellow solid. Recrystallisation from hot MeCN yielded 1.9 g (40%) of the product as a white solid. Obtained spectroscopic data was consistent with that reported in the literature.[74] 1H NMR (500 MHz, CDCl3) δ 8.43 – 8.40 (m, 1H), 8.21 – 8.18 (m, 1H), 7.81 – 7.74 (m, 2H), 0.32 (s, 9H). 13C NMR (126 MHz, CDCl3) δ 166.55, 135.04, 132.71, 131.80, 131.53, 126.23, 117.35, 115.60, 64.37, -0.22. IR neat / cm^{-1} 1603, 1582, 1558, 1436, 1327, 1298, 1249, 845, 826, 745, 686.



2,2-Diethynyl-1-tetralone. Following the procedure reported by Silva, [75] to a solution of 1-tetralone (0.45 g, 3.1 mmol) in THF (30 ml) was added potassium *tert*-butoxide (0.86 g, 7.7 mmol). The reaction was stirred at room temperature for 1 hour and then cooled to -78 ˚C and TMS-EBX (2.75 g, 8.0 mmol) was added followed by TBAF, 1 M in THF (8.0 ml, 8.0 mmol). The reaction was stirred at -78 ˚C for 12 hours, at which point silica gel was added and the mixture concentrated in vacuo. Purification by column chromatography (pet ether/EtOAc 7:3) yielded 0.36 g (59%) of 2,2-diethynyl-1-tetralone as a viscous off-white oil. Obtained spectroscopic data was consistent with that reported in the literature.[75] 1H NMR (500 MHz, CDCl3) δ 8.11 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.52 (td, *J* = 7.5, 1.4 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 0H), 3.20 (t, *J* = 6.2 Hz, 2H), 2.55 – 2.52 (t, *J* = 6.2 Hz, 2H), 2.43 (s, 2H).

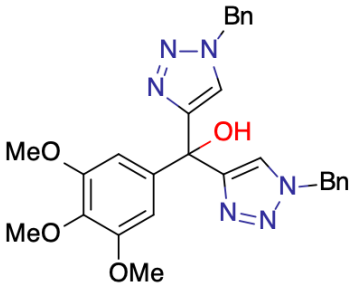


2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-2-ethynyl-1-tetralone. A sealable was tube charged with 2,2-diethynyl-1-tetralone (19 mg, 0.1 mmol), copper(I) chloride (1 mg, 0.01 mmol) and (*R*,*R*)-Ph-PyBox (5.5 mg, 0.015 mmol), sealed, and flushed with argon. CH_2Cl_2 (1 ml) was added, and the mixture stirred for one hour or until the copper(I) salt had dissolved indicating ligation. Benzyl azide (12 mg, 0.1 mmol) was added and the reaction was stirred for 3 days until the benzyl azide was consumed as determined by TLC. The reaction mixture was loaded directly onto a silica column (Pet Ether/EtOAc) for purification to afford the title compound (7.5 mg, 23%). HRMS (NSI) *m/z* calcd. for $C_{21}H_{17}N_3O$ $(M+H)^+$ 328.1450, found 328.1447. 1H NMR (500 MHz, CDCl3) δ 8.07 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.69 (s, 1H), 7.52 (td, *J* = 7.5, 1.5 Hz, 1H), 7.41 – 7.27 (m, 8H), 5.57 (d, *J* = 14.9 Hz, 1H), 5.51 (d, *J* = 14.9 Hz, 1H), 3.46 (ddd, *J* = 16.8, 11.2, 4.4 Hz, 1H), 3.07 (dt, *J* = 17.0, 4.4 Hz, 1H), 2.98 (ddd, *J* = 13.5, 11.2, 4.2 Hz, 1H), 2.65 (dt, *J* = 13.5, 4.4 Hz, 1H), 2.33 (s, 1H). 13C NMR (126 MHz, CDCl3) δ 197.6, 142.3, 133.9, 133.7, 133.2, 130.7, 128.6, 128.0, 127.7, 127.6, 125.9, 125.7, 122.9, 71.3, 64.0, 57.3, 55.6, 33.2, 24.8. IR neat / cm^{-1} 3262, 2924, 2854, 1685, 1599, 1455, 1290, 1219, 1056, 889, 737, 719, 667.

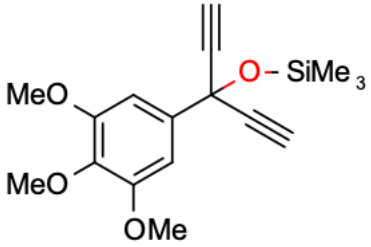


2,2-bis(1-Benzyl-1H-1,2,3-triazol-4-yl)-1-tetralone. A sealable was tube charged with 2,2-diethynyl-1-tetralone (19 mg, 0.1 mmol), copper(I) chloride (1 mg, 0.01 mmol) and (*R*,*R*)-Ph-PyBox (5.5 mg, 0.015 mmol), sealed, and

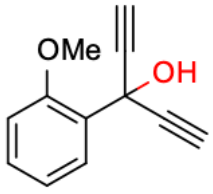
flushed with argon. CH_2Cl_2 (1 ml) was added, and the mixture stirred for one hour or until the copper(I) salt had dissolved indicating ligation. Benzyl azide (12 mg, 0.1 mmol) was added and the reaction was stirred for 3 days until the benzyl azide was consumed as determined by TLC. The reaction mixture was loaded directly onto a silica column (Pet Ether/EtOAc) for purification to afford the title compound (15 mg,, 29%). 1H NMR (500 MHz, CDCl3) δ 7.92 (d, 1H), 7.62 (s, 1H), 7.22-7.45 (m, 13H), 4.98 (s, 4H), 2.11-2.37 (m, 2H), 2.73-2.84 (m, 3H). 13C NMR (126 MHz, CDCl3) δ 197.8, 142.3, 139.8, 133.8, 133.2, 130.5, 128.7, 128.6, 127.6, 126.6, 125.8, 125.6, 122.8, 66.2, 58.3, 37.0, 26.2. IR neat / cm^{-1} 2933, 1683, 1599, 1497, 1454, 1289, 1220, 1046, 891, 718, 694, 668, 576, 459.



bis(1-Benzyl-1H-1,2,3-triazol-4-yl)(3,4,5-trimethoxyphenyl)methanol. A sealable was tube charged with 3-(3,4,5-Trimethoxyphenyl)penta-1,4-diyn-3-ol. (25 mg, 0.1 mmol), copper(I) chloride (1 mg, 0.01 mmol) and (*R*,*R*)-Ph-PyBox (5.5 mg, 0.015 mmol), sealed, and flushed with argon. CH_2Cl_2 (1 ml) was added, and the mixture stirred for one hour or until the copper(I) salt had dissolved indicating ligation. Benzyl azide (12 mg, 0.1 mmol) was added and the reaction was stirred for 3 days until the benzyl azide was consumed as determined by TLC. The reaction mixture was loaded directly onto a silica column (Pet Ether/EtOAc) for purification to afford the title compound (17 mg, 37%). 1H NMR (500 MHz, CDCl3) δ 7.65 (s, 2H), 7.22-7.33 (m, 10H), 6.63 (s, 2H), 5.23 (s, 4H), 3.85 (s, 9H). 13C NMR (126 MHz, CDCl3) δ 152.7, 138.2, 137.0, 136.2, 130.7, 128.6, 127.5, 125.7, 122.9, 104.7, 61.8, 57.5, 56.2. IR neat / cm^{-1} 3337, 3143, 2940, 1738, 1587, 1506, 1497, 1455, 1413, 1370, 1320, 1238, 1217, 1122, 1083, 1062, 1038, 1002, 874, 894, 821, 767, 722, 710.

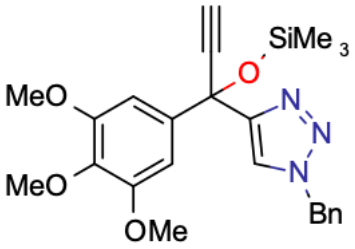


Trimethyl((3-(3,4,5-trimethoxyphenyl)penta-1,4-diyn-3-yl)oxy)silane. A solution of 3-(3,4,5-trimethoxyphenyl)penta-1,4-diyn-3-ol (0.50 g, 2.0 mmol) and triethylamine (0.43 ml, 3.1 mmol) in CH_2Cl_2 (20 ml) was cooled to 0 ºC and chlorotrimethylsilane (0.28 ml, 2.2 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight and diluted with CH_2Cl_2 (20 ml), washed with water (20 ml) and brine (20 ml). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (pet ether/EtOAc, 5:1) yielded 0.49 g (75%) of the desired silyl ether. 1H NMR (500 MHz, CDCl3) δ 7.00 (s, 2H), 3.89 (s, 7H), 3.85 (s, 3H), 2.76 (s, 2H), 0.28 (s, 8H). 13C NMR (126 MHz, CDCl3) δ 153.12, 138.47, 138.24, 103.19, 84.61, 73.79, 65.58, 61.03, 56.31, 1.76.

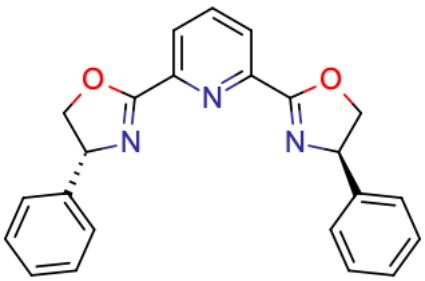


3-(2-Methoxy-phenyl)-penta-1,4-diyn-3-ol[89] A solution of trimethylsilylacetylene (3.6 ml, 25 mmol) in THF (50 ml) was cooled to 0 ºC. ^{n}Buli 2.5 M solution in hexanes (10 ml, 25 mmol) was added dropwise and the reaction was stirred for 30 minutes at 0 ºC. Methyl 2-methoxybenzoate (2.0 g, 12 mmol) was added and the reaction mixture was heated to near reflux with a heat gun for 5 minutes. The mixture was allowed to cool and added to a mixture of sat. aqueous NH_4Cl (50 ml) and EtOAc (50 ml). The phases were separated and the organic washed with water (50 ml) and brine (50 ml), dried over $MgSO_4$ and

concentrated under reduced pressure. The resulting red oil was dissolved in methanol (50 ml) and K_2CO_3 (0.14 g, 1.0 mmol) was added. After stirring for 5 hours the reaction mixture was diluted with EtOAc (100 ml) and washed with water (2 x 30 ml) and brine (30 ml). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (pet ether/EtOAc, 5:1) afforded the title compound as a white solid (1.6 g, 76%). The spectra obtained was consistent with the title compound and spectra reported in the literature.[89] 1H NMR (500 MHz, CDCl3) δ 7.83 (d, *J* = 7.9 Hz, 1H), 7.34 – 7.35 (m, 1H), 7.0 – 7.05 (m, 2H), 3.90 (s, 3H), 3.05 (s, 1H), 2.78 (s, 2H). 13C NMR (126 MHz, CDCl3) δ 138.01, 136.04, 132.56, 128.97, 127.18, 126.01, 80.59, 75.77, 71.24, 66.84, 61.36, 21.13.

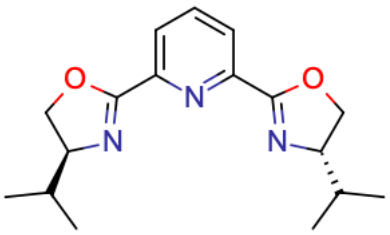


1-benzyl-4-(1-(3,4,5-trimethoxyphenyl)-1-((trimethylsilyl)oxy)prop-2-yn-1-yl)-1H-1,2,3-triazole. A sealable was tube charged with trimethyl((3-(3,4,5-trimethoxyphenyl)penta-1,4-diyn-3-yl)oxy)silane (32 mg, 0.1 mmol) copper(I) chloride (1 mg, 0.01 mmol) and (*R*,*R*)-Ph-PyBox (1.5 gm, 0.015 mmol), sealed, and flushed with argon. CH_2Cl_2 (1 ml) was added, and the mixture stirred for one hour, at which point the CuCl had dissolved indicating ligation. Benzyl azide (12 mg, 1.0 mmol) was added and the reaction was stirred for 3 days until the benzyl azide was consumed as determined by TLC. The reaction mixture was loaded directly onto a silica column (Pet Ether/EtOAc) for purification, affording the title compound as a yellow solid (23 mg, 50%). The obtained spectra was consistent with the title compound. And compared favourably with disilylated analogue, 1-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-ol. 1H NMR (500 MHz, CDCl3) δ 7.39 – 7.35 (m, 3H), 7.34 (s, 1H), 7.28 – 7.23 (m, 3H), 6.89 (s, 2H), 5.51 (d, J = 15.0 Hz, 1H), 5.47 (d, J = 15.0 Hz, 1H), 3.82 (s, 5H), 3.81 (s, 6H), 2.87 (s, 1H), 0.12 (s, 9H). 13C NMR (126 MHz, CDCl3) δ 153.31, 138.62, 136.30, 103.26, 83.51, 73.85, 64.84, 61.00, 56.36, 1.33.



(*R*,*R*)-Ph-PyBox[90] To a suspension of pyridine-2,6-dicarboxylic acid (1.3 g, 10 mmol) in CH_2Cl_2 (50 ml) was added oxalyl chloride (2.6 ml, 30 mmol) and DMF (1 drop). The reaction was stirred overnight until the suspension had dissolved to form a yellow solution. Volatiles were removed in vacuo and the resulting residue

was redissolved in CH_2Cl_2 (25 ml) and added at 0 °C to a flask charged with (*R*)-phenylethanolamine (4.1 g, 30 mmol), triethylamine (8.4 ml, 60 mmol) and CH_2Cl_2 (25 ml). The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with sat. sodium bicarbonate (100 ml) and extracted with CH_2Cl_2 (3 x 100 ml). The combined organics were dried over magnesium sulphate and concentrated under reduced pressure. The resulting yellow solid was taken up in CH_2Cl_2 (50 ml) and cooled to 0 °C. Triethylamine (14 ml, 100 mmol) was added, followed by dropwise addition of MsCl (1.7 ml, 22 mmol). The mixture was allowed to warm and stirred at room temperature for 16 hours followed by reflux for 16 hours. The reaction mixture was diluted with CH_2Cl_2 and washed with 5% aqueous NaOH, water, and brine. Dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (pet ether/EtOAc) to afford the title compound as a white solid (1.7g, 45%). Spectra obtained is consistent with the title compound and spectra reported in the literature.[90] 1H NMR (500 MHz, CDCl3) δ 8.34 (d, J = 7.8 Hz, 2H), 7.91 (t, J = 7.9 Hz, 1H), 7.39 – 7.27 (m, 11H), 5.46 (dd, J = 10.3, 8.6 Hz, 2H), 4.92 (dd, J = 10.4, 8.6 Hz, 2H), 4.42 (t, J = 8.6 Hz, 2H). 13C NMR (126 MHz, CDCl3) δ 163.60 , 146.88 , 141.81 , 137.59 , 128.96 , 127.94 , 126.96 , 126.45 , 75.66 , 70.47. m.p. 171-175 °C. IR neat / cm^{-1} 3083, 3027, 2894, 1652, 1568, 1495, 1469, 1440, 1353, 1308, 1239, 1163, 981, 971, 846, 753, 748.



(*S*,*S*)-*i*Pr-PyBox[90] To a suspension of pyridine-2,6-dicarboxylic acid (1.3 g, 10 mmol) in CH_2Cl_2 (50 ml) was added oxalyl chloride (2.6 ml, 30 mmol) and DMF (1 drop). The reaction was stirred overnight until the suspension had dissolved to form a yellow solution. Volatiles were removed in vacuo and the resulting residue was redissolved in CH_2Cl_2 (25 ml) and added at 0 °C to a flask charged with L-valinol (3.1 g, 30 mmol), triethylamine (8.4 ml, 60 mmol) and CH_2Cl_2 (25 ml). The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with sat. sodium bicarbonate (100 ml) and extracted with CH_2Cl_2 (3 x 100 ml). The combined organics were dried over magnesium sulphate and concentrated under reduced pressure. The resulting yellow solid was taken up in CH_2Cl_2 (50 ml) and cooled to 0 °C. Triethylamine (14 ml, 100 mmol) was added, followed by dropwise addition of MsCl (1.7 ml, 22 mmol). The mixture was allowed to warm and stirred at room temperature for 16 hours followed by reflux for 16 hours. The reaction mixture was diluted with CH_2Cl_2 and washed with 5% aqueous NaOH, water, and brine. Dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (pet ether/EtOAc) to afford the title compound as a white solid (1.7g, 56%). Spectra obtained is consistent with the title compound and spectra reported in the literature.[90] 1H NMR (500 MHz, CDCl3) δ 8.22 (d, J = 7.8 Hz, 2H), 7.85 (t, J = 7.9 Hz, 1H), 4.53 (dd, J = 9.8, 8.4 Hz, 2H), 4.23 (t, J = 8.5 Hz, 2H), 4.14 (ddd, J = 9.8, 8.4, 6.5 Hz, 2H), 1.87 (h, J = 6.7 Hz, 2H), 1.05 (d, J = 6.7 Hz, 6H), 0.94 (d, J = 6.7 Hz, 6H). m.p. 154-157 °C. IR neat / cm^{-1} 2958, 2891, 2869, 1634, 1568, 1470, 1459, 1378, 1359, 1266, 1098, 1071, 963, 940, 840, 760, 739.

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