



**Design and synthesis of components for
optically active metal-organic frameworks (MOFs)
and synthetic routes to diverse deuterium labelled
 α -diazoacetates, α -diazoacetamides, α -diazoketones,
and the antibiotic azaserine**

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A thesis submitted in part fulfilment of the requirements for the degree of Doctor of
Philosophy.

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Declaration

The research described within this thesis is, to the best of my knowledge, original and my own work, except where due reference has been made.

Dominika U. Bachera

Abstract

Metal-organic frameworks (MOFs) are porous crystalline solids that consist of metal nodes connected to organic linkers that assemble into one-, two- or three-dimensional frameworks. Among other applications they have recently found use in heterogeneous asymmetric catalysis. Since that time the demand for new optically active MOFs has increased and novel chiral non-racemic building blocks for their assembly are required.

The first part of this PhD thesis entails the synthesis of a novel linear organic linker equipped with ester functional groups for the future introduction of a chiral centre. In addition, a selection of novel axially chiral (*S*)-BINOL-derived building blocks bearing 1,2,3-triazole moieties is described. Secondary functional groups can undergo post-synthetic modification resulting in the introduction of a catalytically active site. Within this research project an effective method for purification of commercially available acetylene was developed and a reliable protocol for a [2+2+2] cycloaddition reaction of 1,6-diyne with acetylene was established. The 2,2'-bipyridine moiety was successfully installed in the axially chiral (*S*)-BINOL-based linker providing a highly effective chelating ligand.

α -Diazocarbonyl compounds are useful intermediates for various chemical transformations. Although known since the mid-1800s, they still offer an area for future studies and development of preparative methods as well as applications. With the recently growing need for labelled compounds, they appear to be ideal candidates for the introduction of deuterium. This area of research is presented in the second part of this PhD thesis. The synthesis of an array of α -diazocarbonyl acetic acid esters and α -diazoketones and their utilisation in a hydrogen / deuterium exchange reaction are described. Within this research project a quick, reliable and highly efficient protocol for a base-catalysed hydrogen / deuterium exchange reaction at the α -carbon atom of α -diazocarbonyl compounds was successfully developed furnishing products with moderate to high yields (63% to 90%) and excellent levels of deuterium incorporation ($\geq 96\%$). This protocol was also successfully utilised in the synthesis of α -deutero- α -diazoacetic acid ester-derived α -amino acids and α -diazoacetamide-derived α - and β -amino acids. The first chemical synthesis of a deuterium-labelled azaserine analogue was accomplished. Additionally, two protocols for the preparation of α -deuterated aromatic aldehydes have been established.

The third part of this PhD thesis illustrates briefly the synthesis of (*S*)-*N*-triflyl VANOL phosphoramidate and its employment as a catalyst in asymmetric aziridination reactions.

*To my Mother, Urszula, whose love,
support and encouragement have helped me
throughout this journey.*

*Dla mojej Mamy Urszuli, której miłość
i wsparcie w trudnych chwilach pomogły
mi wytrwać w dążeniu do celu.*

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Abbreviations

APCI	atmospheric pressure chemical ionization
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	[1,1'-binaphthalene]-2,2'-diol
Boc	<i>t</i> -butoxycarbonyl
Boc ₂ O	di- <i>t</i> -butyl dicarbonate
CI	chemical ionisation
<i>cis</i>	<i>cis</i> -isomer
CuAAC	copper(I)-catalysed azide alkyne cycloaddition
DBF	<i>N,N</i> -dibutylformamide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCU	<i>N,N'</i> -dicyclohexylurea
DEF	<i>N,N</i> -diethylformamide
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMEDA	<i>N,N'</i> -dimethylethylenediamine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DPEN	1,2-diphenylethylenediamine
<i>e.e.</i>	enantiomeric excess
EI	electron ionisation
Et ₂ O	diethyl ether
Et ₃ N	triethylamine
EtOH	ethanol
FT-IR	Fourier transform infrared spectroscopy
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
MALDI-TOF-MS	matrix-assisted laser desorption / ionisation-time-of-flight mass spectrometry
MeCN	acetonitrile
MEK	methyl ethyl ketone

MeOH	methanol
MOF	metal-organic framework
MOM	methoxymethyl
MS	mass spectrometry
MTBE	methyl <i>t</i> -butyl ether
<i>n</i> -BuLi	<i>n</i> -butyllithium
NIS	<i>N</i> -iodosuccinimide
NMR	nuclear magnetic resonance
NSI	nanospray ionisation
PCP	porous coordination polymer
PTFE	polytetrafluoroethylene
PXRD	powder X-ray diffraction
<i>rac</i>	racemic
Red-Al [®]	sodium bis(2-methoxyethoxy)aluminium hydride
TBTA	tris[(1-benzyl-1 <i>H</i> -1,2,3-triazol-4-yl)methyl]amine
TBTU	<i>O</i> -(benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TMSA	trimethylsilylacetylene
TMU	1,1,3,3-tetramethylurea
<i>trans</i>	<i>trans</i> -isomer
Ts	tosyl
TsNHNHTs	4-methyl- <i>N'</i> -tosylbenzenesulfonohydrazide

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Chapter 1
Introduction

1.1. Definition of metal-organic frameworks (MOFs)

Metal-organic frameworks (MOFs), also known as porous coordination polymers (PCPs), are a new class of hybrid materials built from metal ions that act as connecting nodes, and organic linkers that function as bridging ligands.¹ Those two components are connected to each other by metal-ligand coordinative bonds to assemble into one-, two- or three-dimensional (1D, 2D and 3D) open frameworks (**Figure 1.1**).²

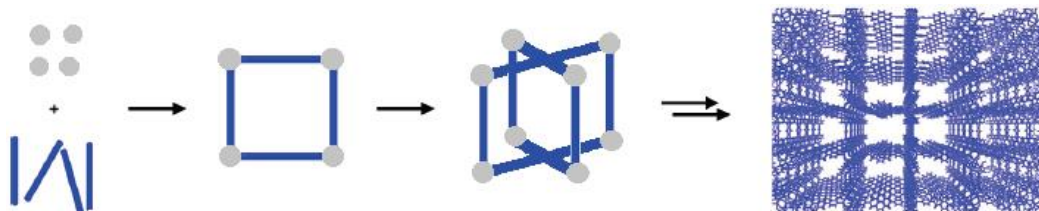


Figure 1.1 General MOF synthesis. Adapted with permission from Farha, O. K.; Hupp, J. T. *Acc. Chem. Res.* **2010**, *43*, 1166 – 1175. Copyright 2010, American Chemical Society.

For a solid formed from the components mentioned above to be considered a metal-organic framework, it must display three main characteristics: porosity, strong metal-ligand interactions to provide robustness, and geometrically well-defined structure (crystallinity).³ MOFs that fulfil these criteria have become a unique class of materials that provide surface areas of up to $5900 \text{ m}^2\text{g}^{-1}$ and pore volumes of up to $2 \text{ cm}^3\text{g}^{-1}$,⁴ and have created interest for a wide range of applications, *e.g.*, gas separation and storage,^{4,5} sensing,^{6,7} magnetism,^{8,9} catalysis,^{10,11} and drug delivery.^{12,13}

The main advantage of MOFs over the already known porous materials, such as zeolites and activated carbon, is the ability to incorporate different functional groups directly into their network and to tailor properties of these materials for potential applications.¹⁴ By choosing the preferred organic building blocks, the pore size and shape and the framework topology could be altered to provide solids with optimal host-guest interactions.¹⁴

A particularly attractive feature of MOFs is the straightforwardness of synthesis.¹⁵ The main challenge in the synthesis of MOFs is the establishment of suitable conditions under which the network assembles without the decomposition of the organic ligand. Therefore, the synthesis of MOFs typically takes place under relatively mild conditions with temperatures ranging from ambient temperature to $250 \text{ }^\circ\text{C}$.¹⁶ The conditions must be commensurate with the kinetics of assembly of a framework to ensure crystallinity of MOFs, which allows structure determination by X-ray methods.¹⁵

1.2. Historical background of metal-organic frameworks

It is widely accepted that the field of MOFs has emerged from coordination chemistry.¹⁷ Coordination compounds with infinite structures built from metal ions as connectors and ligands as linkers and known as coordination polymers have a long history.¹⁸ The term ‘coordination polymer’ came to light in the early 1960s and was reviewed four years later by Bailar¹⁹ in a comparison of organic polymers with polymeric species of inorganic compounds. The interest in porous coordination polymers and MOFs surfaced much later, only around 1990, prompted by publications by Hoskins and Robson in 1989²⁰ and 1990²¹ who reported molecules that consisted of three dimensionally linked rod-like units as illustrated (**Figure 1.2**).

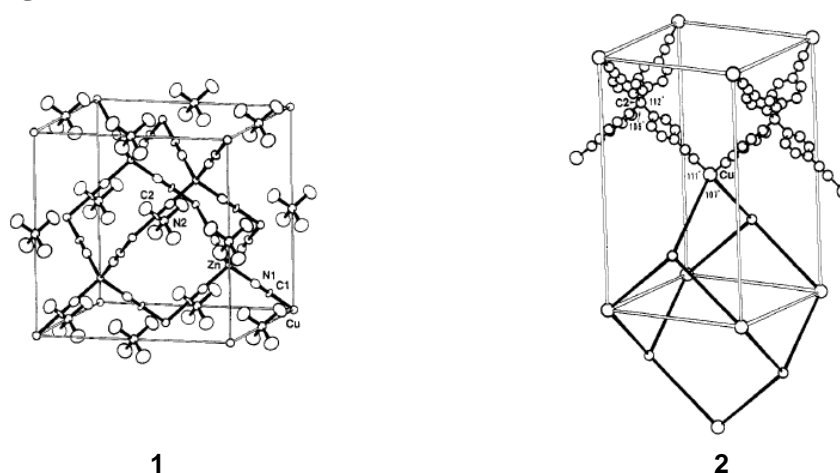


Figure 1.2 Structures of $[\text{N}(\text{CH}_3)_4][\text{CuZn}(\text{CN})_4]$ (**1**) and $\{\text{Cu}[\text{C}(\text{C}_6\text{H}_4\text{CN})_4]\}_n^{n+}$ (**2**) frameworks. Adapted with permission from Hoskins, B. F.; Robson, R. *J. Am. Chem. Soc.* **1990**, *112*, 1546 – 1554. Copyright 1990, American Chemical Society.

In addition to synthesis and characterisation of the new materials **1** and **2**, Hoskins and Robson also predicted their possible applications. These were recognised later by many scientists, building on their main features, *i.e.*, molecular sieve properties with the possibility of diffusion of a range of species, introduction of rigidity that would allow the existence of high volume pores, and functionalisation of the framework after its assembly (currently known as post-synthetic modification) including an installation of catalytic sites.²¹

It was not until 1995 that the term ‘metal-organic framework’ was introduced by Yaghi *et al.* in two publications describing the synthesis of crystalline solids $\text{CoC}_6\text{H}_3(\text{COOH}_{1/3})_3(\text{NC}_5\text{H}_5)_2 \cdot 2/3\text{NC}_5\text{H}_5$, which had the ability to bind selectively and remove guest aromatic molecules,²² and $\text{Cu}(4,4'\text{-bpy})_{1.5} \cdot \text{NO}_3(\text{H}_2\text{O})_{1.25}$ with extended channel systems.²³ Two years later Kitagawa *et al.*²⁴ reported the first synthesis of unique

three-dimensional frameworks, $\{[M_2(4,4'\text{-bpy})_3(\text{NO}_3)_4]\cdot x\text{H}_2\text{O}\}_n$, where M refers to Co, Ni, Zn, and investigated their gas adsorption properties (CH_4 , N_2 and O_2) as one of the most attractive features of microporous materials. In 1999 two metal-organic frameworks, $[\text{Cu}_3(\text{TMA})_2(\text{H}_2\text{O})_3]_n$, known as HKUST-1, where TMA refers to benzene-1,3,5-tricarboxylate,²⁵ and $\text{Zn}_4\text{O}(\text{BDC})_3\cdot(\text{DMF})_8(\text{C}_6\text{H}_5\text{Cl})$, known as MOF-5, where BDC refers to 1,4-benzenedicarboxylate,²⁶ were synthesised. These are amongst the most examined MOFs up to date.¹⁷ Since that time, the field of metal-organic frameworks became ‘popular’ among scientists around the world and has been expanding at a remarkably fast rate (**Figure 1.3**) with companies such as BASF and Sigma-Aldrich® offering nowadays industrially prepared MOFs (under the name of Basolite®) to their customers.²⁷

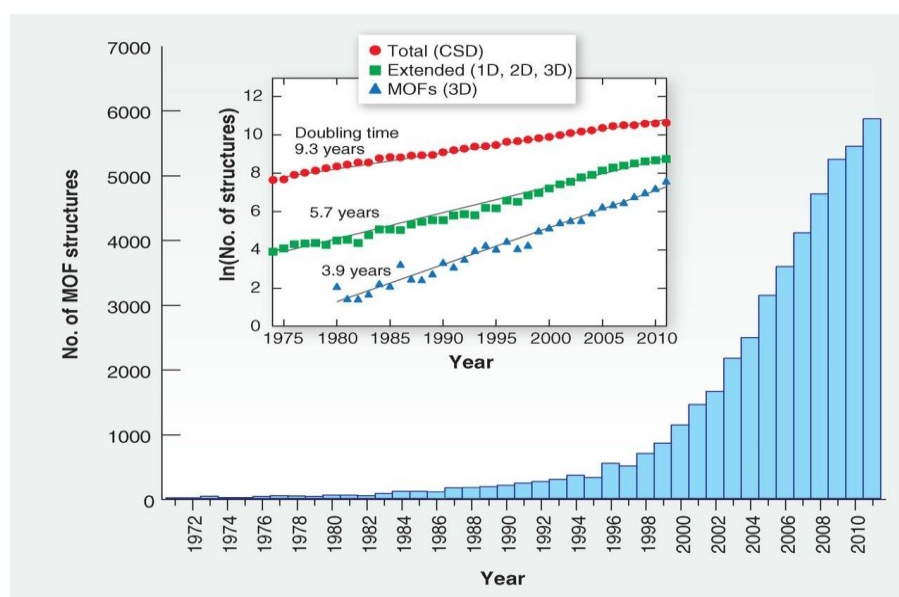
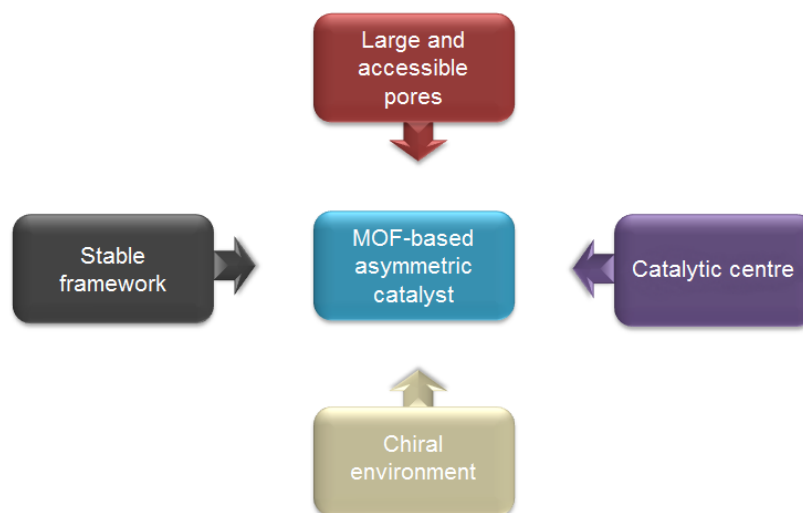


Figure 1.3 Metal-organic framework structures reported in the Cambridge Structural Database (CSD) from 1971 to 2011. From Furukawa, K.; Cordova, K. E.; O’Keeffe, M.; Yaghi, O. M. *Science* **2013**, *341*, 974 – 985. Reprinted with permission from AAAS.

1.3. Prerequisites for optically active metal-organic frameworks as catalysts for asymmetric synthesis

Since the first successful utilisation of a chiral non-racemic MOF in a catalytic asymmetric synthesis in 2000,²⁸ these materials became a promising class of porous solids for enantioselective catalysis and have been extensively studied as chiral catalysts over the past decade.²⁹ However, the number of MOFs that display high catalytic activity in asymmetric reactions is still limited due to the required features such materials should possess (**Scheme 1.1**).²⁹



Scheme 1.1 General characteristics of chiral non-racemic MOFs as catalysts for asymmetric synthesis. Adapted with permission from Yoon, M.; Srirambalaji, R.; Kim, K. *Chem. Rev.* **2012**, *112*, 1196 – 1231. Copyright 2012, American Chemical Society.

In addition to the general requirement for catalysts employed in enantioselective transformations, *i.e.*, close proximity of the catalytically active site and the chiral pocket, the MOF-derived catalysts must display two additional fundamental properties. The framework needs to be stable to remain intact after a catalytic process, and it should possess large pores accessible for the host-guest interactions thereby allowing access of reactants to the catalytic centre and departure of the product.²⁹

1.4. Synthesis of optically active metal-organic frameworks

The synthetic methods for the preparation of optically active metal-organic frameworks can be categorised into three different groups, namely direct synthesis, chiral-template synthesis, and post-synthetic modification.³⁰

1.4.1. Direct synthesis

The first method for the preparation of optically active MOFs is the direct synthesis approach whereby MOFs can be either prepared by a self-resolution of achiral building blocks into chiral non-racemic frameworks (only one enantiomorph formed) or by the employment of enantiomerically pure organic ligands and their direct instalment in the framework.

The first example of synthesis of optically active MOFs from achiral organic ligands *via* the self-resolution method was reported by Ezuhara *et al.*³¹ in 1999. An achiral 5-(9-anthracenyl)pyrimidine (apd) together with cadmium(II) ions formed an optically

active MOF, $\text{Cd}(\text{apd})(\text{NO}_3)_2 \cdot \text{H}_2\text{O} \cdot \text{EtOH}$ (**3**), with the chirality originating from the formation of pyrimidine-cadmium(II) helices (**Figure 1.4**). Each cadmium atom was coordinated with two 5-(9-anthracenyl)pyrimidine ligands and two nitrate ions, and one molecule of water and ethanol. Spontaneous resolution occurs apparently because primary nucleation is slow. The first nucleation event must give, in random fashion, P or M chirality but not both. Growth of the initial nucleus by secondary nucleation is apparently fast. Seeding with either one P or M helices allows propagation of the chirality.³¹

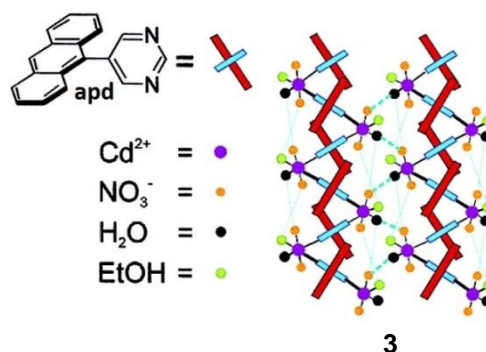
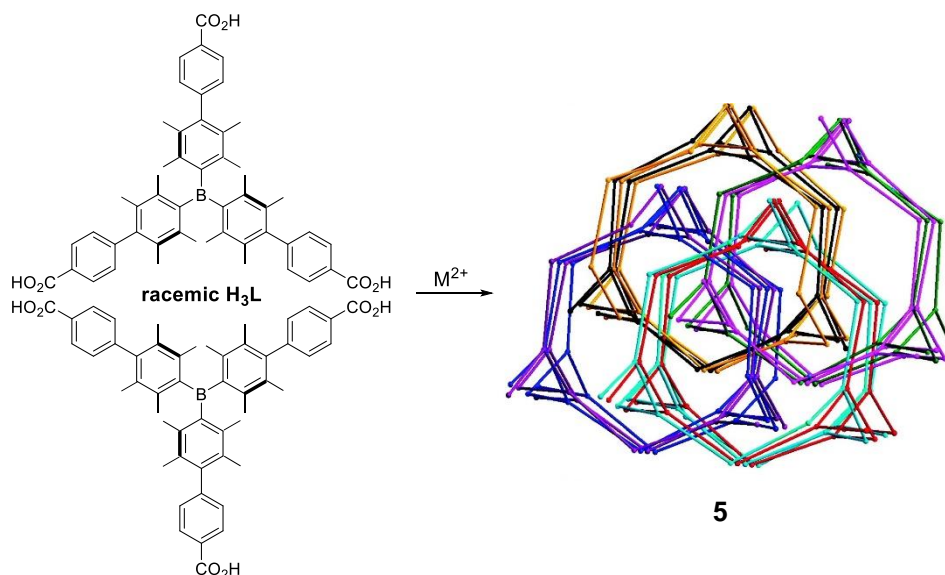


Figure 1.4 Structure of an optically active **3**. Adapted with permission from Ezuhara, T.; Endo, K.; Aoyama, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3279 – 3283. Copyright 1999, American Chemical Society.

A more recent and worthy of mention example of a direct synthesis of a chiral non-racemic MOF *via* self-resolution was reported by Wu *et al.*³² The preparation of optically active $[\{\text{Cu}(\text{succinate})(4,4'\text{-bipyridine})\}_n] \cdot (4\text{H}_2\text{O})_n$ (**4**) by altering the amount of ammonia added to the reaction mixture was described (an illustrative representation of the synthesis has not been presented within this thesis due to a copyright restrictions). This MOF is also a conglomerate. The authors observed a remarkable phenomenon. The synthesis of **4** following the previously reported procedure³³ yielded racemic $[\{\text{Cu}(\text{succinate})(4,4'\text{-bipyridine})\}_n] \cdot (4\text{H}_2\text{O})_n$ (**4**). However, after introducing ammonia into the reaction mixture as a competing ligand, the desired **4** was generated in an enantiomerically pure form. This remarkable process was explained by the formation of an ammonia complex $[\text{Cu}(\text{NH}_3)_4]^{2+}$ which competed with 4,4'-bipyridine and succinate ligands for copper ions reducing at the same time the rate of the formation of **4**. In the case of low concentration of ammonia, the crystal growth proceeded rapidly and led to the formation of a racemate or one of low enantiopurity **4**, whereas in the presence of high ammonia concentration the primary nucleation was impeded whereby secondary nucleation allowed assembly of the first primary nucleation event into **4** with a high enantiomeric excess.

In 2009, Liu *et al.*³⁴ described the preparation of six optically active metal-organoboron frameworks from a racemic building block *via* self-resolution. Chiral non-racemic three-dimensional frameworks, $[M_2L(OH)(MeOH)] \cdot 3H_2O$ (**5**), where M refers to Co, Mn, Ni, Cu, Zn, or Cd, and H_3L refers to tris((4-carboxyl)phenylduryl)borane, were assembled from racemic tris(4-benzoic acid)tridurylborane and metal ions (**Scheme 1.2**) establishing that the resolution occurs by selective crystallisation of the racemic building blocks into crystals with a chiral structure.



Scheme 1.2 Schematic demonstration of the resolution of the racemic tris((4-carboxyl)phenylduryl)borane into the optically active metal-organoboron framework **5**. Adapted with permission from Liu, Y.; Xuan, W.; Zhang, H.; Cui, Y. *Inorg. Chem.* **2009**, *48*, 10018 – 10023. Copyright 2009, American Chemical Society.

Although it is possible to synthesise optically active MOFs *via* self-resolution during crystal growth, this technique does not offer the ability to predict the enantiopurity of the final product and requires formation of a conglomerate together with the development of a method to control the relative rates of primary and secondary nucleation.³⁰ Therefore, the second approach, utilisation of a chiral non-racemic linker in the assembly of a framework, is a more effective and reliable method for the synthesis of optically active MOFs as it guarantees the chirality of produced porous material.³⁵

In 2002, Jouaiti *et al.*³⁶ reported a one-dimensional framework based on incorporation of chiral building blocks. The chiral organic linker was synthesised from 4,4'-bipyridine and two optically active oxazoline moieties. Further coordination of the chiral building block to cobalt(II) cations resulted in the assembly of the one-dimensional network, $Co(L)Cl_2 \cdot 3CHCl_3$ (**6**), where L refers to crystalline 2,6-bis(oxazolyl)-4,4'-bipyridine (**Figure 1.5**).

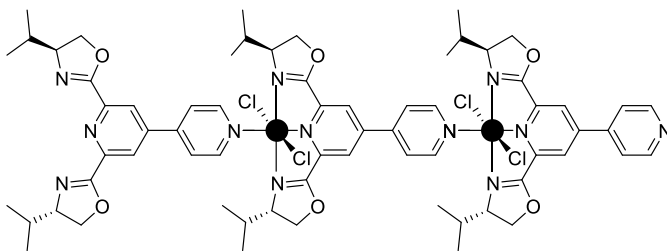


Figure 1.5 Part of the network of **6** formed between the organic building block and cobalt(II) chloride reported by Jouaiti *et al.*³⁶

In 2009, Yuan *et al.*³⁷ prepared optically active helical MOFs, $[(\text{AgL})\text{NO}_3]$ (**7**), $[\text{AgL}(\text{PF}_6)_{1/6}(\text{OH})_{5/6}]$ (**8**), and $[\text{Ag}(\text{L})\text{ClO}_4]$ (**9**), where L refers to (*R*)-3,3'-bipyridine-5,5',6,6'-tetramethyl-2,2'-dimethoxy-1,1'-biphenyl, using an axially chiral organic ligand and silver salts. The three networks formed were assembled into two-, three- and four-fold helices depending on the counteranion used in the synthesis (**Figure 1.6**). In view of the fact that 1,1'-biphenyl derivatives are an important class of compounds utilised in asymmetric synthesis, this report was a leading step towards the development of optically active MOFs.³⁷

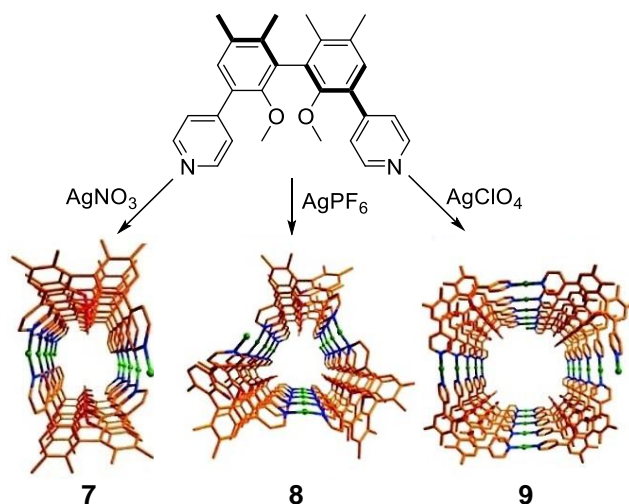


Figure 1.6 Synthesis of optically active **7**, **8**, and **9**, and the perspective view of their helices. Adapted with permission from Yuan, G.; Zhu, C.; Liu, Y.; Xuan, W.; Cui, Y. *J. Am. Chem. Soc.* **2009**, *131*, 10452 – 10460. Copyright 2009, American Chemical Society.

The area of synthesis of optically active MOFs from chiral non-racemic linkers has been extensively investigated by Lin *et al.* His research focused mainly on the utilisation of axially chiral [1,1'-binaphthalene]-2,2'-diol (BINOL) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) derived organic ligands. These molecules are of particular interest as they can be functionalised with different groups such as pyridyl, carboxyl, or phosphonic acid installed *via* linkers that may vary in length. This allows tailoring of the framework and therefore the size of cavities and channels for the substrates of a specific asymmetric

synthesis.³⁸ An additional feature of these ligands is the presence of primary and secondary functional groups. Whereas the former take part in the assembly of the framework, the latter play an important role in the generation of active sites in chiral environment.³⁰

In recent years, Lin *et al.* successfully synthesised optically active hybrid solids based on the axially chiral BINOL and BINAP. A report from 2003 is noteworthy as it described the preparation of two chiral porous zirconium phosphonates, $\text{Zr}[\text{Ru}(\text{L}_1)(\text{DPEN})\text{Cl}_2] \cdot 4\text{H}_2\text{O}$ (**10**) and $\text{Zr}[\text{Ru}(\text{L}_2)(\text{DPEN})\text{Cl}_2] \cdot 4\text{H}_2\text{O}$ (**11**) (**Figure 1.7**), where L_1 refers to (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl-4,4'-bis(phosphonic acid), L_2 to (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl-6,6'-bis(phosphonic acid) and DPEN to 1,2-diphenylethylenediamine, and their utilisation in a heterogeneous asymmetric hydrogenation of aromatic ketones (these results will be presented further on in this chapter; section 1.5.9).³⁹ Besides their high activity and enantioselectivity, these chiral catalysts were successfully recycled without the loss of the aforementioned properties, which made them promising ligands for employment in asymmetric catalysis.³⁹

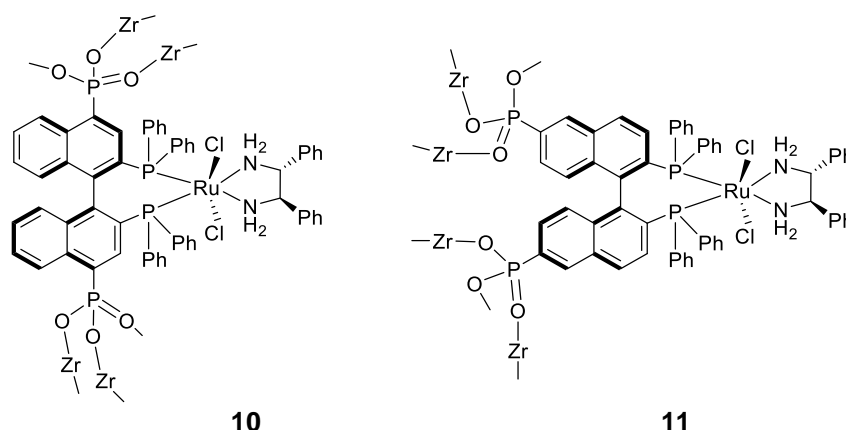
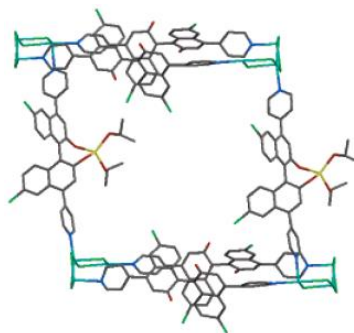


Figure 1.7 The structures of **10** and **11** reported by Lin *et al.*³⁹

In 2005, Lin *et al.*⁴⁰ reported the preparation of an optically active MOF built from an axially chiral BINOL-derived building block and cadmium ions. The framework of the chiral $[\text{Cd}_3\text{Cl}_6\text{L}_3] \cdot 4\text{DMF} \cdot 6\text{MeOH} \cdot 3\text{H}_2\text{O}$ (**12**) (**Figure 1.8**), where L refers to (*R*)-6,6'-dichloro-2,2'-dihydroxy-1,1'-binaphthyl-4,4'-bipyridine, was assembled by coordination of the primary functional groups (pyridyl groups) to cadmium atoms without the involvement of secondary functional groups (hydroxyl groups). Due to this characteristic, the hydroxyl groups were readily accessible and upon treatment of the MOF with excess of titanium isopropoxide catalytically active sites were introduced into the framework. This porous solid was subsequently utilised in an asymmetric addition of diethylzinc to aromatic aldehydes with the generation of corresponding secondary alcohols (these results will be presented further on in this chapter; section 1.5.10).⁴⁰



12

Figure 1.8 Representation of the active (BINOLate)Ti(OⁱPr)₂ catalytic sites in the open channels of **12**. Adapted with permission from Wu, C.; Hu, A.; Zhang, L.; Lin, W. *J. Am. Chem. Soc.* **2005**, *127*, 8940 – 8941. Copyright 2005, American Chemical Society.

1.4.2. Chiral-template synthesis

The second method for the preparation of optically active MOFs relies on the utilisation of achiral building blocks and chiral non-racemic co-ligands (templates). The co-ligands used do not participate in the framework assembly process as the components of MOFs but they direct all other building units into a specific topology that effects in the chirality of the final product.³⁰

The first example of chirality control in a framework by a co-ligand was reported by Kepert *et al.*⁴¹ in 2000. The authors demonstrated the synthesis of an optically active MOF [Ni₃(btc)₂(py)₆(1,2-pd)₃], where btc refers to benzene-1,3,5-tricarboxylate, py to pyridine and 1,2-pd to 1,2-propanediol, by employment of enantiomerically pure 1,2-propanediol in the synthesis. In this example, the chirality of the growing crystal was directed by the stereochemistry of the metal centre which was coordinated by the chiral non-racemic diol.³⁸

In 2007 Lin *et al.*⁴² described the employment of a chiral ionic liquid 1-butyl 3-methylimidazolium L-aspartate (BMIm) for the preparation of an optically active (BMIm)₂[Ni(TMA-H)₂(H₂O)₂] (**13**) (**Figure 1.9**), known as SIMOF-1, where TMA refers to trimesate. The chirality of the final product was determined by single-crystal X-ray diffraction of ten single samples taken from the same bulk material. To substantiate further the claim that the enantiomeric purity of the framework was induced by the utilisation of a chiral non-racemic co-ligand, achiral (BMIm)₂[Ni₃(TMA-H)₄(H₂O)₂] (**14**) (**Figure 1.9**), known as SIMOF-2, was synthesised by replacing the chiral ionic liquid with 1-butyl 3-methylimidazolium bromide. Furthermore, the use of D-aspartate instead of L-aspartate in the chiral non-racemic ionic liquid afforded the optically active MOF, known as SIMOF-1a, with the opposite chirality.

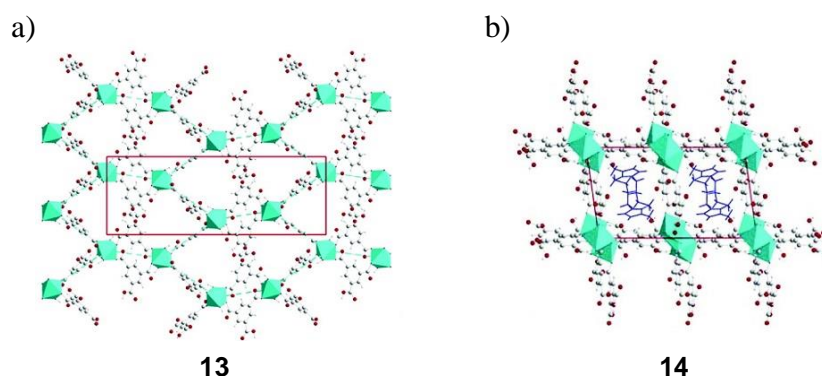
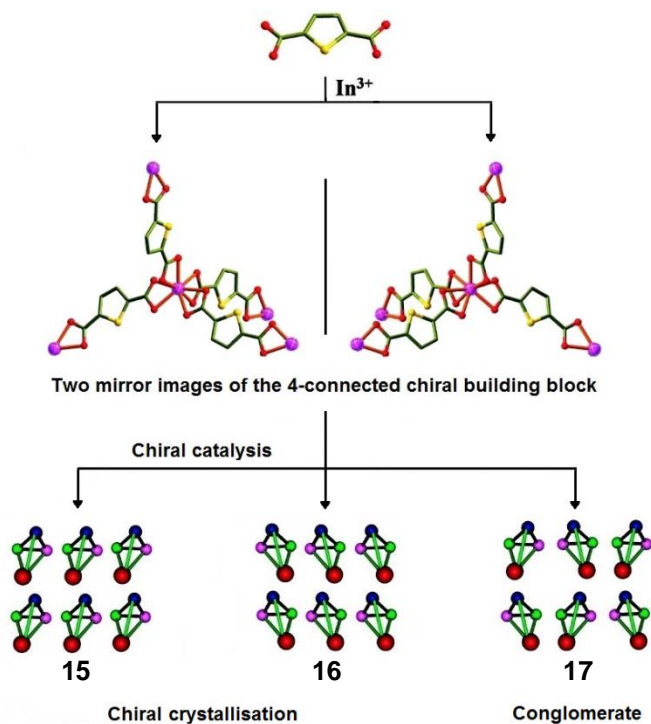


Figure 1.9 The structures of a) optically active **13** and b) achiral **14**. Adapted with permission from Lin, Z.; Slawin, A. M. Z.; Morris, R. E. *J. Am. Chem. Soc.* **2007**, *129*, 4880 – 4881. Copyright 2007, American Chemical Society.

In 2008, Zhang *et al.*⁴³ reported a synthesis of a chiral non-racemic $(\text{Me}_2\text{NH}_2)[\text{In}(\text{thb})_2] \cdot x(\text{DMF})$ (**15**), known as ATF-1P, where H_2thb refers to thiophene-2,5-dicarboxylic acid, from achiral building blocks *via* chiral catalysis. This material forms a conglomerate but without spontaneous resolution. Instead of chiral solvent, a chiral additive, (–)-cinchonidine, was employed for the induction of chirality into the framework. This afforded optically active **15**. When (+)-cinchonine instead of (–)-cinchonidine was utilised, the obtained ATF-1M (**16**) showed an opposite handedness. In comparison, the formation of a chiral conglomerate ATF-1 (**17**) was observed when no alkaloid was used (**Scheme 1.3**).

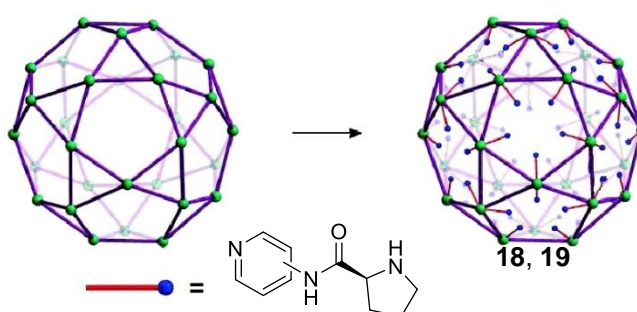


Scheme 1.3 Schematic representation of the synthesis of **15**, **16** and **17**. Adapted with permission from Zhang, J.; Chen, S.; Wu, T.; Feng, P.; Bu, X. *J. Am. Chem. Soc.* **2008**, *130*, 12882 – 12883. Copyright 2008, American Chemical Society.

1.4.3. Post-synthetic modification (PSM)

The third approach to the synthesis of optically active MOFs is the post-synthetic modification of a framework after its assembly. This area has gained much interest in recent years as it creates a valuable option not only for the introduction of different functionalities into the network but also for the preparation of catalytically active chiral non-racemic MOFs from achiral frameworks by attachment of suitable chiral catalytic units.

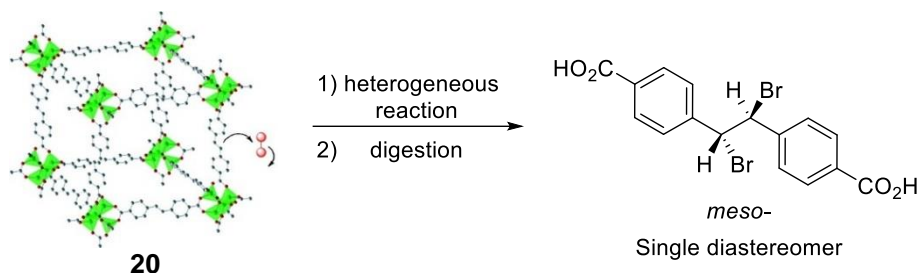
The first post-synthetic modification of an achiral MOF with the introduction of a chiral centre was reported by Banerjee *et al.*⁴⁴ in 2009. The MOF of interest was the previously prepared MIL-1017 as it displayed a robust framework, large size pores and channels, accessible metal coordination sites to which a chiral organic linker could be attached, and insolubility in most of the organic solvents and water.⁴⁴ The chiral unit chosen was L-proline as it is a well-established asymmetric organocatalyst.⁴⁴ The installation of the chiral moiety was achieved by coordination of designed chiral ligands L₁ and L₂, [(*S*)-*N*-(pyridin-3-yl)-pyrrolidine-2-carboxamide] and [(*S*)-*N*-(pyridin-4-yl)-pyrrolidine-2-carboxamide] respectively, to the open metal centres. This afforded two new chiral non-racemic MOFs [Cr₃O(L₁)_{1.8}(H₂O)_{0.2}F(bdc)₃] \cdot 0.15(H₂bdc) \cdot H₂O (CMIL-1) (**18**) and [Cr₃O(L₂)_{1.75}(H₂O)_{0.25}F(bdc)₃] \cdot 0.15(H₂bdc) \cdot H₂O (CMIL-2) (**19**), where bdc refers to 1,4-benzenedicarboxylate (**Scheme 1.4**).⁴⁴ These MOFs were consecutively utilised in asymmetric aldol reactions of various aromatic aldehydes with ketones to evaluate their catalytic activity (these results will be presented further on in this chapter; section **1.5.3**).



Scheme 1.4 Synthesis of **18** and **19**. Adapted with permission from Banerjee, M.; Das, S.; Yoon, M.; Choi, H. J.; Hyun, M. H.; Park, S. M.; Seo, G.; Kim, K. *J. Am. Chem. Soc.* **2009**, *131*, 7524 – 7525. Copyright 2009, American Chemical Society.

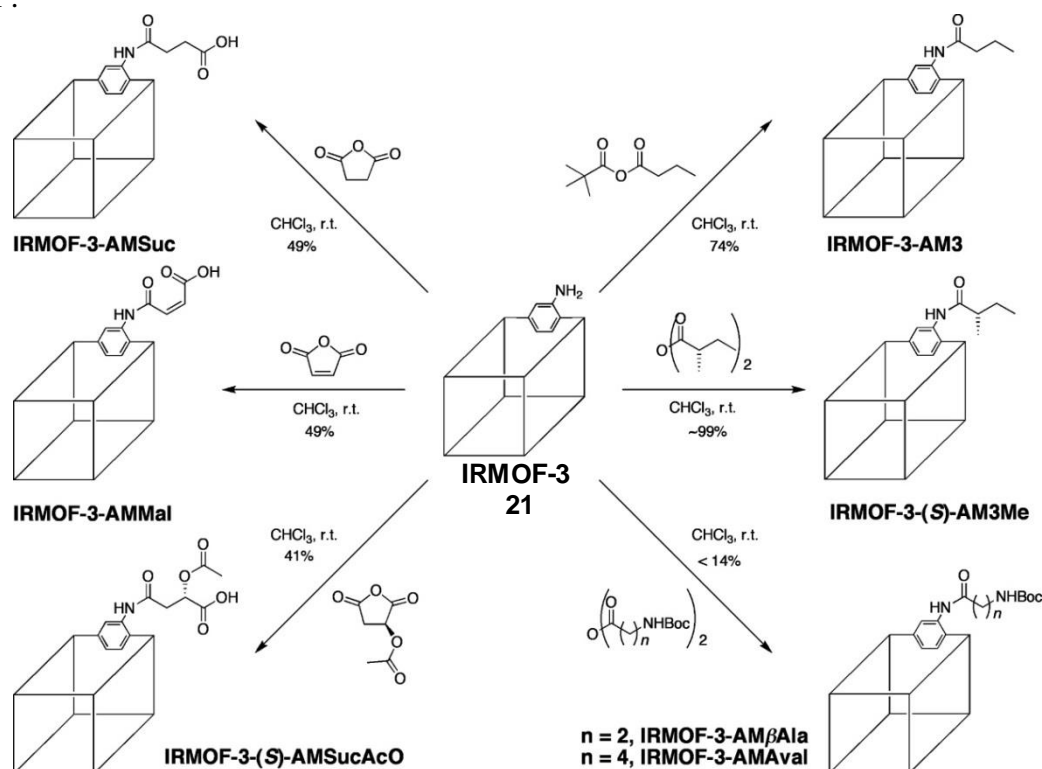
An interesting example of PSM was reported by Jones and Bauer.⁴⁵ A three-dimensional framework, Zn₄O(SDC)₃ (**20**), where SDC refers to *trans*-4,4'-stilbene dicarboxylate, was subjected to an electrophilic addition of bromine which resulted in a diastereoselective bromination of the stilbene units present in the MOF (**Scheme 1.5**). It is believed that the

stereocontrol arises from the rigidity of the organic linker and the porous nature of the framework.⁴⁵



Scheme 1.5 Post-synthetic modification of $\text{Zn}_4\text{O}(\text{SDC})_3$ (**20**). Adapted with permission from Jones, S. C.; Bauer C. A. *J. Am. Chem. Soc.* **2009**, *131*, 12516 – 12517. Copyright 2009, American Chemical Society.

In the same year, Garibay *et al.*⁴⁶ described a post-synthetic modification of IRMOF-3 (**21**) and the preparation of a range of novel MOFs, including novel chiral non-racemic MOFs from achiral frameworks. A few aspects of the PSM of IRMOF-3 (**21**) were presented within this report. The post-synthetic modification was performed with the use of simple reagents such as alkyl and cyclic anhydrides, and allowed an instalment of a broad range of functional groups within the framework of **21** (**Scheme 1.6**). Furthermore, sequential modifications permitted different functionalities (up to five) to be introduced within one MOF.⁴⁶



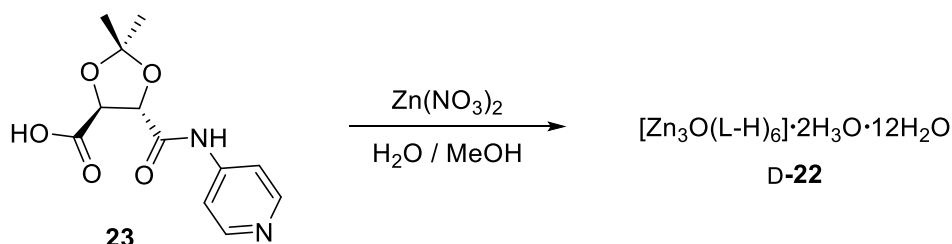
Scheme 1.6 Post-synthetic modifications of **21**. The cubes are schematic representation of the framework common to all structures. Adapted with permission from Garibay, S. J.; Wang, Z.; Tanabe, K. K.; Cohen, S. M. *Inorg. Chem.* **2009**, *48*, 7341 – 7349. Copyright 2009, American Chemical Society.

1.5. Examples of optically active metal-organic frameworks in heterogeneous asymmetric catalysis.

Since the first example of a catalytically active MOF in heterogeneous enantioselective synthesis, only a limited number of these materials have been successfully applied for the preparation of enantiomerically enriched compounds. Catalytic activities of various MOFs classified according to the asymmetric transformation they have been utilised in will be presented in more detail.

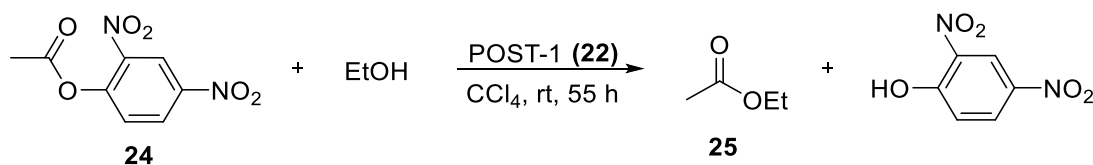
1.5.1. Transesterification

The preparation of the first chiral non-racemic MOF that displayed catalytic activity in asymmetric synthesis was reported by Seo *et al.*²⁸ in 2000. The MOF $[\text{Zn}_3\text{O}(\text{L-H})_6]\cdot 2\text{H}_3\text{O}\cdot 12\text{H}_2\text{O}$ (**22**), known as D-POST-1 (**D-22**) and L-POST-1 (**L-22**) depending on the absolute configuration of the building block used, was afforded in the reaction of a chiral non-racemic organic linker (**23**) prepared from D- or L-tartaric acid, and zinc(II) nitrate hexahydrate in a mixture of water and methanol (**Scheme 1.7**).



Scheme 1.7 Synthesis of D-POST-1 (**D-22**) reported by Seo *et al.*²⁸

The pyridyl groups are accessible through the pores, which allows **22** to be employed in transesterification of the ester **24** with ethanol for investigation of its catalytic activity (**Scheme 1.8**).



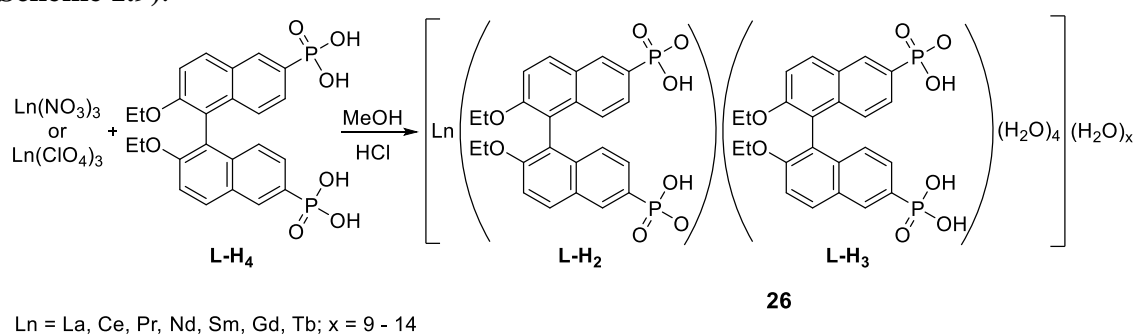
Scheme 1.8 Transesterification of **24** catalysed by POST-1 (**22**) reported by Seo *et al.*²⁸

POST-1 (**22**) (10 mol%; it is not known how the amount of the catalyst was calculated) catalysed the reaction of **24** with ethanol to afford after 55 hours ethyl acetate **25** in 77% yield. Further studies showed that no reaction occurred in the absence of **22**. When the reaction was performed with bulkier alcohols, such as isobutanol, neopentanol or 3,3,3-triphenyl-1-propanol, slower or even no conversion of the starting material was

observed suggesting that the catalysis took place inside the pores of the framework that are easily accessible for the smaller molecules. Furthermore, the reaction was repeated with a large excess of racemic 1-phenyl-2-propanol in the presence of D- or L-POST-1 (D- or L-**22**) to generate the corresponding esters, *S* or *R* respectively, with $\approx 8\%$ enantiomeric excess. Although poor, this result was significant as it was the first example of an asymmetric synthesis catalysed by porous material.²⁸

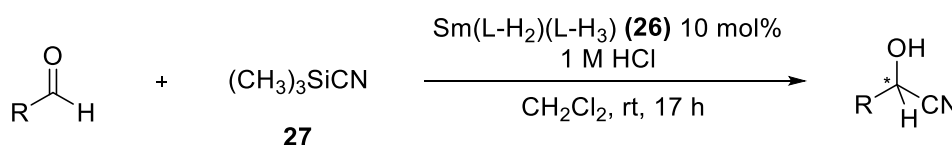
1.5.2. Cyanosilylation

Evans *et al.*⁴⁷ in 2001 prepared a chiral porous solid based on lanthanide bisphosphonates, which were subsequently utilised in an asymmetric cyanosilylation reaction. These materials, with the general formula $[\text{Ln}(\text{L-H}_2)(\text{L-H}_3)(\text{H}_2\text{O})_4] \cdot x\text{H}_2\text{O}$ (**26**), where Ln refers to either La, Ce, Pr, Nd, Sm, Gd, or Tb, and x equals 9 to 14, were synthesised in a reaction of acidic mixtures of nitrate or perchlorate salts of lanthanide(III) and (*R*)-2,2'-diethoxy-1,1'-binaphthalene-6,6'-bisphosphonic acid (**L-H₄**) in methanol at room temperature (**Scheme 1.9**).



Scheme 1.9 Synthesis of **26** reported by Evans *et al.*⁴⁷

The robustness of the framework (stable after removal of water molecules under reduced pressure at 50 °C for 24 hours) suggested exploration of the ability of **26** to act as catalyst in a heterogeneous asymmetric synthesis.⁴⁷ The catalytic activity of powdered and desolvated $[\text{Sm}(\text{L-H}_2)(\text{L-H}_3)(\text{H}_2\text{O})_4] \cdot x\text{H}_2\text{O}$ (**26**) (10 mol%; the authors did not indicate how the catalyst loading was determined) in cyanosilylation of different aldehydes with cyanotrimethylsilane (**27**) in dichloromethane was tested. After acidic work-up the corresponding cyanohydrins were obtained (**Scheme 1.10**, **Table 1.1**).



Scheme 1.10 Reaction of aldehydes with cyanotrimethylsilane catalysed by **26** reported by Evans *et al.*⁴⁷

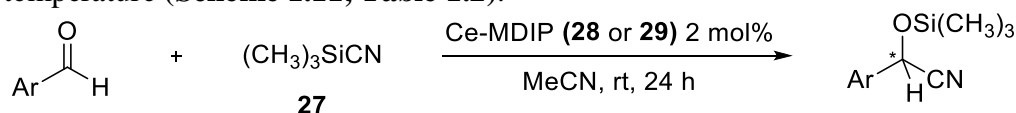
R	(CH ₃) ₃ SiCN (equiv)	Yield (%)	Enantiomeric excess (%)
Phenyl	2	69	<5
Ethyl	2	61	<5
1-Naphthyl	2	55	<5

Table 1.1 Results for the **26**-catalysed asymmetric cyanosilylation of aldehydes reported by Evans *et al.*⁴⁷

Although the enantiomeric excess of obtained products was poor, the size selectivity could have been ruled out as conversions of starting materials were similar and resulted in yields from 55% to 69%.⁴⁷ Repeating the reaction after removal of the catalyst by filtration resulted in no further conversion of the starting materials which suggested that the process was catalysed heterogeneously. Furthermore, the catalyst was recovered in high yields (>98%) without the loss of catalytic activity after several subsequent runs.⁴⁷

In 2010, Dang *et al.*⁴⁸ synthesised two optically active MOFs **28** and **29** *via* homochiral crystallisation with a chiral non-racemic compound as a chiral inductor. Reaction of methylenediisophthalic acid (H₄MDIP) and cesium(II) nitrate in the presence of L- or D-*N*-*t*-butoxy-carbonyl-2-(imidazole)-1-pyrrolidine (L- or D-BCIP) as a chiral additive in water afforded the chiral non-racemic microporous material Ce-MDIP1 (**28**) and Ce-MDIP2 (**29**) respectively.⁴⁸

Both **28** and **29** were subsequently utilised as catalysts in an enantioselective cyanosilylation of aromatic aldehydes with cyanotrimethylsilane (**27**) in acetonitrile at room temperature (**Scheme 1.11**, **Table 1.2**).



Scheme 1.11 Cyanosilylation of aromatic aldehydes catalysed by **28** or **29** reported by Dang *et al.*⁴⁸

Ar	Aldehyde (equiv)	(CH ₃) ₃ SiCN (equiv)	Enantiomeric excess (%) ^a	
			Ce-MDIP1 (28)	Ce-MDIP2 (29)
Phenyl	1	2.4	93	94
4-Methoxyphenyl	1	2.4	91	97
1-Naphthyl	1	2.4	98	>98
2-Naphthyl	1	2.4	>98	>98

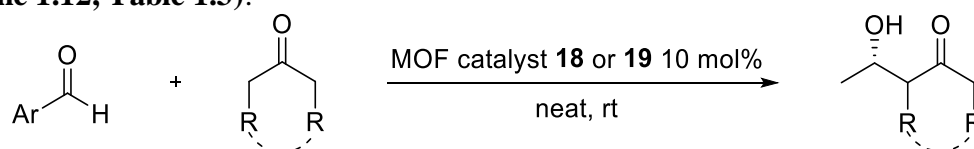
^a The enantiomeric excess was determined by chiral HPLC analysis.

Table 1.2 Results for the catalytic asymmetric cyanosilylation of aldehydes in the presence of Ce-MDIP1 (**28**) and Ce-MDIP2 (**29**) reported by Dang *et al.*⁴⁸

The Ce-MDIP1 (**28**) and Ce-MDIP2 (**29**) catalysed the enantioselective cyanosilylation of aldehydes with excellent enantiomeric excess values ranging from 91% to >98%. It is not clear how the amounts of **28** and **29** used in the reactions were calculated. Size selectivity experiments with more bulky aldehydes revealed no dependency of the asymmetric induction on the size of pores as all of the products were obtained with high enantiopurity. In an additional experiment, **28** was removed from the reaction medium after 4 hours by simple filtration, drastically slowing the conversion of starting materials. Only 10% of an additional conversion was observed after 7 hours of extra stirring, and therefore it was established that Ce-MDIP1 (**28**) is a heterogeneous asymmetric catalyst.⁴⁸

1.5.3. Aldol reaction

Banerjee *et al.*⁴⁴ utilised optically active MOFs, CMIL-1 (**18**) and CMIL-2 (**19**) (these materials have been described in more detail earlier on in this chapter; section 1.4.3), as catalysts in an asymmetric aldol reaction between aldehydes and ketones. Stirring a neat mixture of an aldehyde (1 equivalent), ketone (10 equivalents), and the catalyst **18** or **19** (10 mol%; the authors did not specify how the amount of the catalyst was determined) at room temperature for several hours afforded the desired product in a good to high yield (59% to 91%) and with a fair to good enantioselectivity for the *R*-isomer (52% to 76% *e.e.*) (Scheme 1.12, Table 1.3).⁴⁴



Scheme 1.12 Asymmetric aldol reaction catalysed by **18** or **19** reported by Banerjee *et al.*⁴⁴

Ar	R	Catalyst	Time (h)	Yield (%)	Enantiomeric excess (%) ^a
4-Nitrophenyl	H	18	24	66	69
4-Nitrophenyl	H	19	24	59	63
4-Pyridyl	H	18	16	91	76
4-Pyridyl	H	19	16	87	58
4-Chlorophenyl	H	18	40	74	70
4-Chlorophenyl	H	19	48	69	52
4-Naphthyl	H	18	60	80	63
4-Nitrophenyl	-(CH ₂) ₃ -	18	24	81	66
4-Nitrophenyl	-CH ₂ -CH(<i>t</i> -Bu)-CH ₂ -	18	36	86 ^b	68

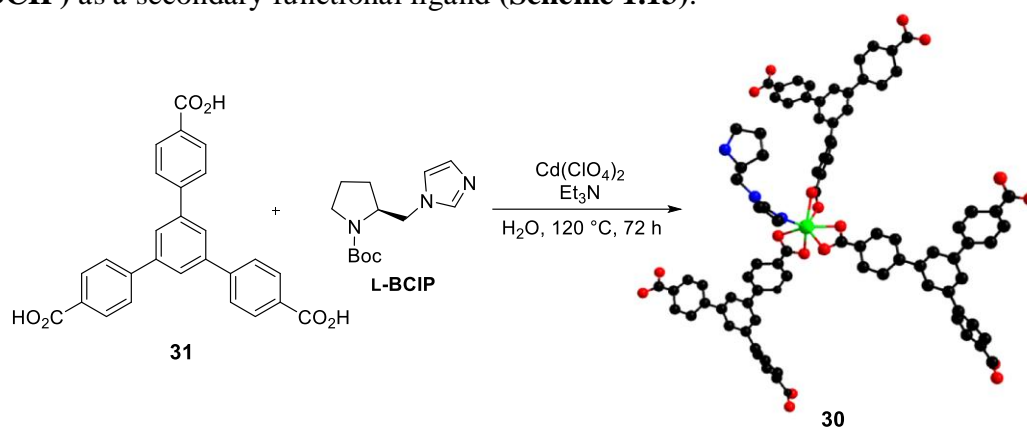
^a The enantiomeric excess was determined by chiral HPLC analysis.

^b Reaction carried out in 100 μ L of DMF.

Table 1.3 Results for the asymmetric aldol reaction catalysed by CMIL-1 (**18**) or CMIL-2 (**19**) reported by Banerjee *et al.*⁴⁴

Although the yields of the reactions were comparable for CMIL-1 (**18**) and CMIL-2 (**19**), the enantiomeric excess was noticeably higher in the case of **18**. It is postulated that this difference resulted from steric hindrance imposed upon the aldehyde during the reaction as **18** is assembled from a bent ligand.⁴⁴ A high yield (81%) of the reaction between 4-nitrobenzaldehyde and *t*-butylcyclohexanone indicated that the pores of CMIL-1 (**18**) and CMIL-2 (**19**) were large enough to be accessed by bulky substrates.⁴⁴ Furthermore, **18** was re-used up to three times in a reaction of 4-nitrobenzaldehyde with acetone without a significant loss of the catalytic activity and enantioselectivity.⁴⁴

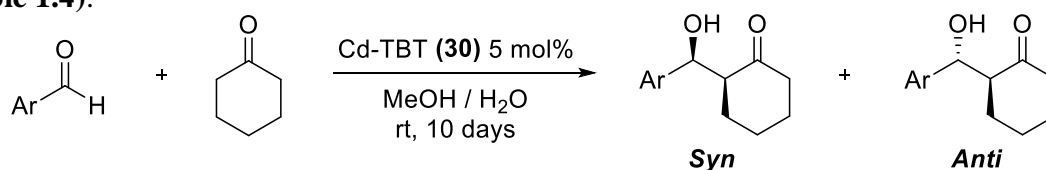
In 2010, Dang *et al.*⁴⁸ prepared an optically active MOF, Cd-TBT (**30**), in a reaction of cadmium(II) perchlorate hexahydrate, 1,3,5-tris(4-carboxyphenyl)benzene (**31**) as a primary functional ligand, and *L*-*N*-*t*-butoxy-carbonyl-2-(imidazole)-1-pyrrolidine (**L-BCIP**) as a secondary functional ligand (**Scheme 1.13**).



Scheme 1.13 Synthesis of the chiral non-racemic **30**. Adapted with permission from Dang, D.; Wu, P.; He, C.; Xie, Z.; Duan, C. *J. Am. Chem. Soc.* **2010**, *132*, 14321 – 14323.

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Owing to the catalytically active sites (N-H of pyrrolidine) being exposed and thus easily accessible through the channels, **30** was investigated as a catalyst for the enantioselective aldol reaction of various aromatic aldehydes and cyclohexanone.⁴⁸ Cd-TBT (**30**) (5 mol%; it is not evident how the amount of the catalyst was calculated) catalysed the reaction of an aldehyde (1 equivalent) with cyclohexanone (10 equivalents) in a mixture of methanol and water at room temperature to afford after 10 days the final product in a low to high yield (8% to 97%) and with moderate enantioselectivity (58% to 61% *e.e.*) (**Scheme 1.14**, **Table 1.4**).



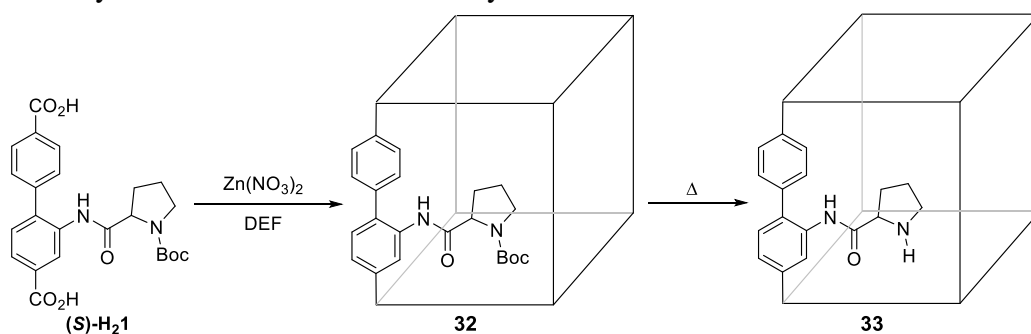
Scheme 1.14 Asymmetric aldol reaction catalysed by an optically active **30** reported by Dang *et al.*⁴⁸

Ar	Aldehyde (equiv)	Cyclohexanone (equiv)	Yield (%)	Diastereomeric ratio (<i>syn</i> : <i>anti</i>) (%)	Enantiomeric excess (%)
2-Nitrophenyl	1	10	42	>50 : 1	60
3-Nitrophenyl	1	10	77	1 : 1	61
4-Nitrophenyl	1	10	97	1 : 1	58
1-Naphthyl	1	10	8	2 : 1	Not determined

Table 1.4 Results of **30**-catalysed enantioselective aldol reaction reported by Dang *et al.*⁴⁸

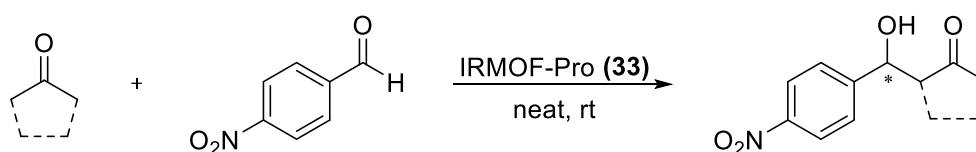
The absolute configuration at the chiral centre for the above products was not determined by the authors. The low yield (8%) of the reaction utilising 1-naphthaldehyde could imply that the catalytic centre was only accessible for the less bulky molecules. However, structural simulations of the starting materials indicated that the size of channels of the framework was not large enough to enclose both the substrates and the L-pyrrolidine-2-yl-imidazole molecules.⁴⁸ Building on the above observation, it could be hypothesised that during the reaction only L-*N*-*t*-butoxy-carbonyl-2-(imidazole)-1-pyrrolidine (L-BCIP) located on the surface of the MOF induces the chirality without the involvement of the structural motif of **30**.⁴⁸

A year later, in 2011, Lun *et al.*⁴⁹ presented a new strategy for the synthesis of optically active MOFs containing organocatalytic moieties. A preparation of a chiral non-racemic MOF **32** formed from zinc(II) nitrate tetrahydrate and a building block equipped with *N*-Boc-L-proline had been described. The organic linker ((*S*)-**H21**) was synthesised from *N*-Boc-L-proline and dimethyl 2-aminobiphenyl-4,4'-dicarboxylate having 94% enantiomeric excess and subsequently used in a reaction with zinc(II) nitrate tetrahydrate in *N,N*-diethylformamide (DEF) to afford the porous material [Zn₄O((*S*)-1)₃] (**32**), known as IRMOF-Pro-Boc (**Scheme 1.15**). Interestingly, repeating the procedure but utilising *N*-Boc deprotected L-proline instead of *N*-Boc-L-proline did not result in MOF formation. It is postulated that the free nitrogen atom coordinates to zinc(II) ions thus stopping the assembly process of the framework. Also replacing *N,N*-diethylformamide with *N,N*-dimethylformamide led to failure of synthesis of **32**.



Scheme 1.15 Synthesis of IRMOF-Pro-Boc (**32**) and IRMOF-Pro (**33**) reported by Lun *et al.*⁴⁹

Because of the bulky nature of the *N*-Boc protecting group the framework of **32** was equipped with open channels that could be easily accessible by large substrates.⁴⁹ Furthermore, the presence of the *N*-Boc protecting group prohibited the framework interpenetration making this porous solid a promising catalyst for asymmetric synthesis.⁴⁹ The enantioselective aldol reaction was chosen for the exploration of the catalytic activity of **32**, but before initiating any studies the *N*-Boc protecting group needed to be removed. This process was achieved by heating IRMOF-Pro-Boc (**32**) at 165 °C in *N,N*-dimethylformamide for 4 hours under microwave irradiations. The thus obtained **33** was further employed as a catalyst in an asymmetric aldol reaction (**Scheme 1.16**, **Table 1.5**).



Scheme 1.16 Asymmetric aldol reaction catalysed by **33** reported by Lun *et al.*⁴⁹

Ketone	Catalyst (mol%) ^a	Time (h)	Diastereomeric ratio (<i>syn</i> : <i>anti</i>) (%)	Enantiomeric excess (%)
Acetone	100	40	-	29
Cyclopentanone	100	30	1 : 3	3 (<i>syn</i>), 14 (<i>anti</i>)

^a Approximate molar ratio of the number of proline units with respect to an aldehyde.

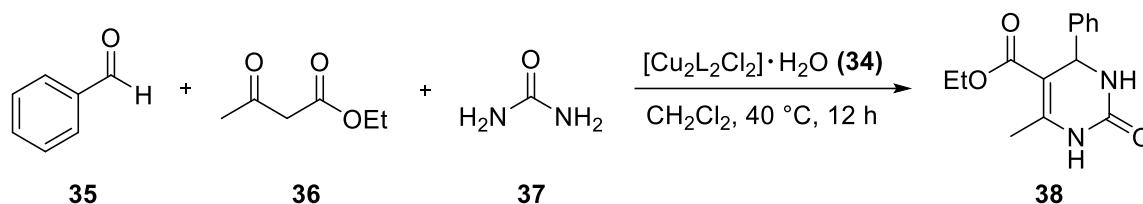
Table 1.5 Results of **33**-catalysed enantioselective aldol reaction reported by Lun *et al.*⁴⁹

Although IRMOF-Pro (**33**) catalysed the aldol reaction of 4-nitrobenzaldehyde with acetone or cyclopentanone, the enantiomeric excess in both examples remained low and did not exceed 29%. To demonstrate fully that the reaction was catalysed by **33**, the catalyst was removed from the reaction mixture by filtration stopping any further consumption of the aldehyde. Furthermore, upon the utilisation of IRMOF-Pro-Boc (**32**) instead of IRMOF-Pro (**33**) in a reaction, no conversion of starting materials was observed. The IRMOF-Pro (**33**) proved to be reusable up to three times with each reaction being completed but in a longer period of time.⁴⁹

1.5.4. 1,2-Addition of a Grignard reagent to α,β -unsaturated ketones

Wang *et al.*⁵⁰ in 2009 reported a preparation of a three-dimensional optically active MOF **34** from a serine-based ligand and copper salt. $[\text{Cu}_2\text{L}_2\text{Cl}_2]\cdot\text{H}_2\text{O}$ (**34**) was synthesised in a reaction of (*S*)-3-hydroxy-2-(pyridin-4-ylmethylamino)propanoic acid (L) with copper(II) chloride in a mixture of water and ethanol and displayed high potential as a catalyst in heterogeneous asymmetric synthesis.

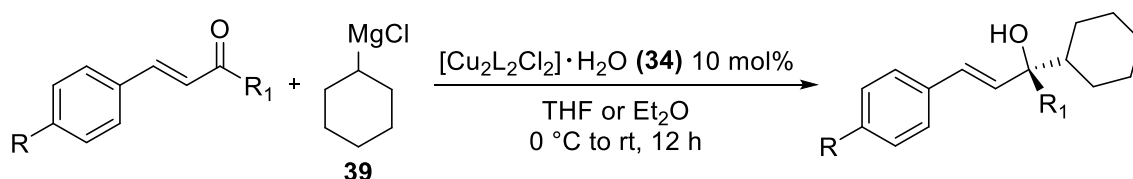
The porous material **34** was first utilised in the Biginelli reaction of benzaldehyde (**35**) with ethyl acetoacetate (**36**) and urea (**37**) in dichloromethane at 40 °C to afford after 12 hours the corresponding dihydropyrimidinone **38** in 90% yield (**Scheme 1.17**).



Scheme 1.17 The Biginelli reaction catalysed by **34** reported by Wang *et al.*⁵⁰

Despite the high yield of the reaction, the product was obtained as a racemate as no enantioenriched isomer was observed.⁵⁰

To investigate further the catalytic activity, **34** was used in 1,2-addition of a Grignard reagent to α,β -unsaturated ketones. $[\text{Cu}_2\text{L}_2\text{Cl}_2] \cdot \text{H}_2\text{O}$ (**34**) (10 mol%; the authors failed to define how the amount of the catalyst was calculated) catalysed the reaction of ketones (1 equivalent) with cyclohexylmagnesium chloride (**39**) (1.2 equivalents) in tetrahydrofuran or diethyl ether at 0 °C followed by warming to room temperature to afford the 1,2-addition products after 12 hours (**Scheme 1.18**, **Table 1.6**).



Scheme 1.18 1,2-Addition of a Grignard reagent to α,β -unsaturated ketones catalysed by $[\text{Cu}_2\text{L}_2\text{Cl}_2] \cdot \text{H}_2\text{O}$ (**34**) reported by Wang *et al.*⁵⁰

R	R ₁	Catalyst (mol%)	Solvent	Conversion (%) ^a	Enantiomeric excess (%) ^a
H	Me	10	THF	97	65
H	Me	10	Et ₂ O	98	67
H	Me	10	THF	48	88 ^b
H	Me	10	THF	84	51
Me	Me	10	THF	93	>99
Cl	Me	10	THF	94	97

^a The conversion and enantiomeric excess were determined by GC.

^b The reaction was performed at -80 °C.

Table 1.6 Results for **34**-catalysed 1,2-addition of a Grignard reagent to α,β -unsaturated ketones reported by Wang *et al.*⁵⁰

$[\text{Cu}_2\text{L}_2\text{Cl}_2] \cdot \text{H}_2\text{O}$ (**34**) catalysed the reaction with average to high conversions (48% to 98%) and fair to high enantiomeric excess levels (51% to >99%). Using diethyl ether as the

reaction solvent only slightly changed the conversion and enantiomeric excess values, whereas performing the reaction at lower temperature had a positive effect on the enantiomeric excess level but suppressed the conversion of starting materials.⁵⁰ Additional experiments displayed the heterogeneous nature of the catalysis as no conversion was observed after removal of **34** from the reaction mixture. On utilisation of copper(II) chloride instead of **34** no reaction occurred, confirming that the process was initiated by an organic functionality.⁵⁰ Furthermore, structural analysis of the framework of **34** revealed small size pores and displayed the existence of active sites predominantly on the surface indicating that the catalysis occurred on the exterior rather than interior of **34**.⁵⁰

1.5.5. Mukaiyama aldol reaction

A new strategy for synthesising optically active MOFs was developed by Gedrich *et al.*⁵¹ in 2011. An appropriate organic linker was first designed and subsequently used in a chiral non-racemic MOF preparation. The synthetic approach involved synthesis of rigid organic ligands with chiral auxiliaries attached to them. Interestingly, the design did not involve an organocatalyst but relied on the metal centres that could be used in Lewis acid or metal-catalysed reactions.⁵¹ Instalment of the chiral units in close vicinity to the active metal centres was of significance as it could induce enantioselectivity in asymmetric catalysis.

Considering all the above aspects two organic linkers, H₃ChirBTB-1 (1,3,5-tri{4-[2-(4-isopropyl-2-oxooxazolidin-3-yl)]benzoate}benzene) (**40**) and H₃ChirBTB-2 (1,3,5-tri{4-[2-(4-benzyl-2-oxooxazolidin-3-yl)]benzoate}benzene) (**41**), consisting of chiral non-racemic oxazolidinones were prepared (**Figure 1.10**).

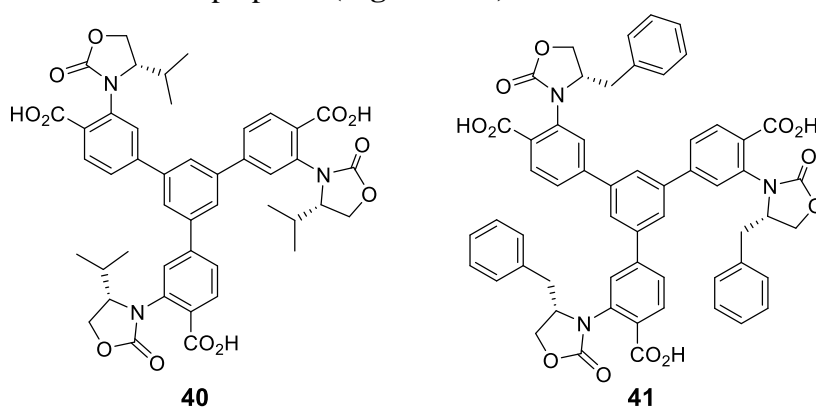


Figure 1.10 Structures of **40** and **41** reported by Gedrich *et al.*⁵¹

Employment of H₃ChirBTB-1 (**40**) or H₃ChirBTB-2 (**41**) in a reaction with zinc(II) nitrate in *N,N*-diethylformamide at 100 °C afforded after 20 hours the optically active MOFs, [Zn₃(ChirBTB-1)₂] (**42**) and [Zn₃(ChirBTB-2)₂] (**43**) respectively (**Figure 1.11**). Although

synthesised in the same manner, the frameworks of **42** and **43** were significantly different.²⁹ While **42** displayed three different types of pores with the largest reaching ≈ 33.7 Å in diameter and having accessible metal centres, **43** exhibited two different types of channels partly occupied by the benzyl groups present in the chiral moieties with the largest channel being 18×18 Å².

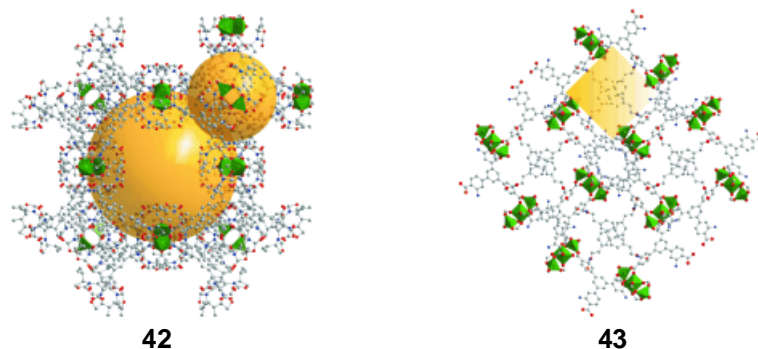
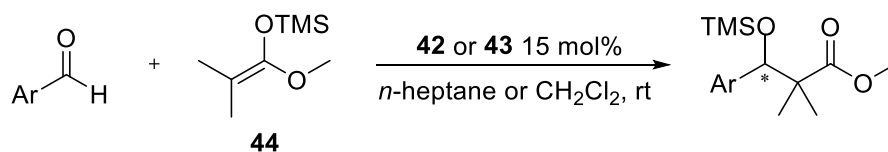


Figure 1.11 The frameworks of **42** and **43**. Adapted with permission from Gedrich, K.; Heitbaum, M.; Notzon, A.; Senkovska, I.; Fröhlich, R.; Getzschmann, J.; Mueller, U.; Glorius, F.; Kaskel, S. *Chem. Eur. J.* **2011**, *17*, 2099 – 2106. Copyright 2011, Wiley-VCH.

Owing to the large size of pores, **42** and **43** were potential candidates as catalysts in asymmetric transformations and were explored in the Mukaiyama aldol reaction. Benzaldehyde (**35**) or 1-naphthaldehyde (1 equivalent) was allowed to react with silyl enol ether **44** (2 equivalents) in the presence of $[\text{Zn}_3(\text{ChirBTB-1})_2]$ (**42**) or $[\text{Zn}_3(\text{ChirBTB-2})_2]$ (**43**) (15 mol%; this value represents the percentage of accessible metal centres in reference to the amount of an aldehyde used) as the reaction catalyst in *n*-heptane or dichloromethane at room temperature to afford the anticipated products in yields up to 83% and with enantiomeric excess values up to 40% (**Scheme 1.19**, **Table 1.7**).



Scheme 1.19 The Mukaiyama aldol reaction catalysed by $[\text{Zn}_3(\text{ChirBTB-1})_2]$ (**42**) or $[\text{Zn}_3(\text{ChirBTB-2})_2]$ (**43**) reported by Gedrich *et al.*⁵¹

Ar	Catalyst (15 mol%)	Solvent	Time (days)	Yield (%)	Enantiomeric excess (%)
Phenyl	42	CH ₂ Cl ₂	2	83	0
1-Naphthyl	42	CH ₂ Cl ₂	17	31	40
Phenyl	43	CH ₂ Cl ₂	13	66	8
1-Naphthyl	43	CH ₂ Cl ₂	14	0	-
Phenyl	42	<i>n</i> -Heptane	2	77	9
1-Naphthyl	42	<i>n</i> -Heptane	2	77	16
Phenyl	43	<i>n</i> -Heptane	2	43	6

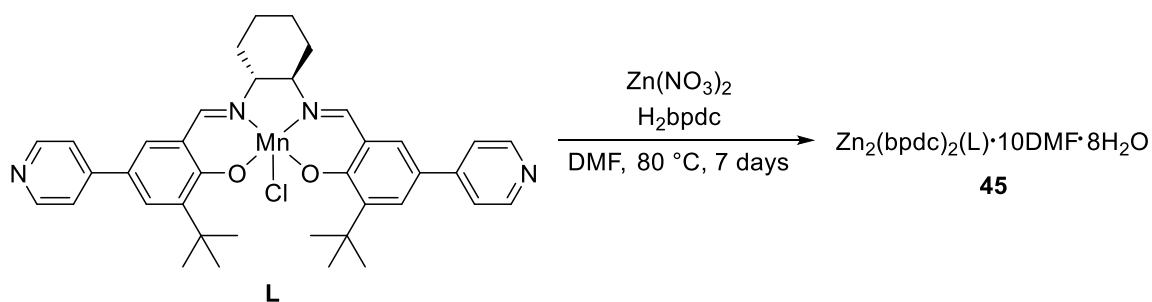
Table 1.7 Results for the [Zn₃(ChirBTB-1)₂] (**42**) or [Zn₃(ChirBTB-2)₂] (**43**)-catalysed Mukaiyama aldol reaction reported by Gedrich *et al.*⁵¹

Interestingly, when benzaldehyde (**35**) and [Zn₃(ChirBTB-1)₂] (**42**) were employed in the reaction, the enantioselectivity of MOF was solvent dependent. Performing the reaction in dichloromethane resulted in a racemic mixture whereas on use of *n*-heptane a product with 9% enantiomeric excess was obtained.⁵¹ However, utilising benzaldehyde (**35**) and [Zn₃(ChirBTB-2)₂] (**43**) in dichloromethane or *n*-heptane returned similar enantiomeric excess values, 8% and 6% respectively. The highest enantiomeric excess (40%) was detected for a reaction when 1-naphthaldehyde and [Zn₃(ChirBTB-1)₂] (**42**) were used in dichloromethane. In comparison, the same reaction performed in *n*-heptane gave lower enantiomeric excess of 16%. Removal of **42** from the reaction mixture resulted in no further conversion of starting materials confirming heterogeneous nature of the catalytic process. Although both MOFs displayed large size pores, the enantiomeric excess values remained low. Further investigations of the host-guest interactions are required to fully understand the nature of this process.⁵¹

1.5.6. Epoxidation

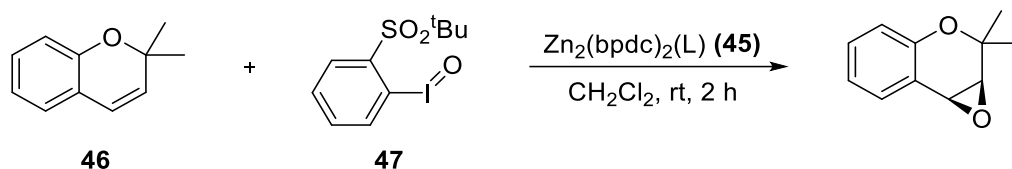
In 2006, Cho *et al.*⁵² reported a synthesis of a chiral non-racemic MOF **45** assembled from a chiral non-racemic salen-manganese complex, secondary building units and zinc(II) ions, which exhibited high enantioselectivity in olefin epoxidation.

This porous solid, Zn₂(bpdc)₂(L)·10DMF·8H₂O (**45**), which displays an interpenetrating framework, was prepared in a reaction of (*R,R*)-(2)-1,2-cyclohexanediamino-*N,N'*-bis(3-*t*-butyl-5-(4-pyridyl)salicylidene)Mn(III) chloride (**L**), biphenyl-4,4'-dicarboxylic acid (H₂bpdc) and zinc(II) nitrate hexahydrate in *N,N*-dimethylformamide at 80 °C within 7 days (**Scheme 1.20**). Despite the interpenetration of the network, the solvent molecules still occupied 57% of the volume of **45** indicating the possibility of catalytic activity.



Scheme 1.20 Synthesis of $\text{Zn}_2(\text{bpdc})_2(\text{L}) \cdot 10\text{DMF} \cdot 8\text{H}_2\text{O}$ (**45**) reported by Cho *et al.*⁵²

The catalytic activity of $\text{Zn}_2(\text{bpdc})_2(\text{L}) \cdot 10\text{DMF} \cdot 8\text{H}_2\text{O}$ (**45**) was subsequently investigated in an asymmetric epoxidation of olefins. Reaction of 2,2-dimethyl-2*H*-chromene (**46**) and 2-(*t*-butylsulfonyl)iodosylbenzene (**47**) in the presence of **45** in a molar ratio 4000 : 2000 : 1 respectively, in dichloromethane at room temperature afforded after 2 hours the desired epoxidation product in 71% yield and with high 82% enantiomeric excess (**Scheme 1.21**).



Scheme 1.21 Enantioselective epoxidation catalysed by **45** reported by Cho *et al.*⁵²

As the flexibility of the salen complex is believed to be crucial in enantioselective transformations, the reaction was repeated under the same conditions utilising the salen-manganese complex (**L**) as the reaction catalyst instead of the less-flexible **45**.⁵² However, the enantiomeric excess obtained (88%) was only a little higher. The MOF catalyst **45** proved to be reusable up to three times with no significant change in the catalytic activity and enantioselectivity. Additional experiments performed with different size substrates indicated that the catalytic process occurred predominantly inside the channels.²⁹

The chiral non-racemic salen-manganese unit was also utilised by Song *et al.*⁵³ in 2010 in the preparation of a series of optically active MOFs **48** – **52** that were consecutively employed as catalysts in an enantioselective olefin epoxidation. The synthetic approach used in this report involved the preparation of chiral non-racemic salen-manganese-derived linkers **L1-H₂**, **L2-H₂**, and **L3-H₂** (**Figure 1.12**) that vary in length, which should furnish MOFs with different size pores and channels.

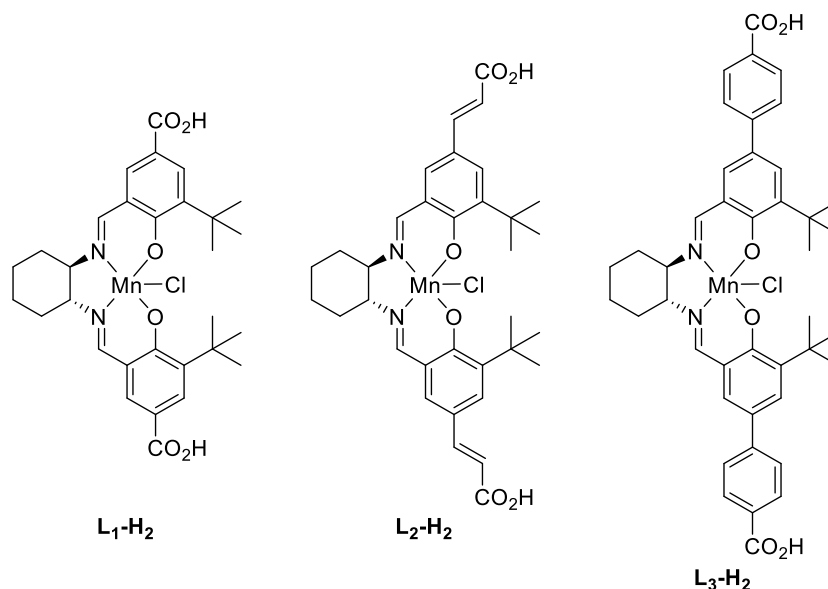
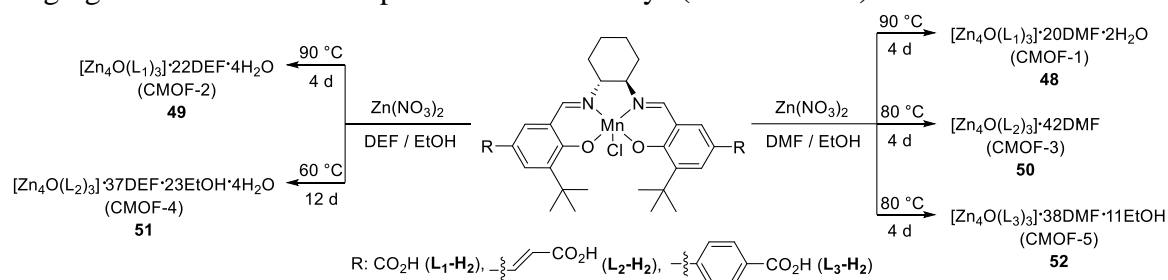


Figure 1.12 Chiral linkers L_1-H_2 , L_2-H_2 , and L_3-H_2 reported by Song *et al.*⁵³

Five different porous solids were prepared in reactions of zinc(II) nitrate hexahydrate with the salen-manganese-derived ligands L_1-H_2 , L_2-H_2 , and L_3-H_2 in a mixture of *N,N*-dimethylformamide and ethanol or *N,N*-diethylformamide and ethanol at temperatures ranging from 60 to 90 °C for periods of 4 to 12 days (**Scheme 1.22**).



Scheme 1.22 Synthesis of chiral non-racemic MOFs **48** – **52** reported by Song *et al.*⁵³

Depending on the solvent utilised the assembled frameworks were interpenetrated or non-interpenetrated. Smaller in size *N,N*-dimethylformamide favoured formation of the interpenetrated structure (CMOF-1 (**48**), CMOF-3 (**50**), and CMOF-5 (**52**)) whereas the larger *N,N*-diethylformamide provided non-interpenetrated MOFs (CMOF-2 (**49**) and CMOF-4 (**51**)) (**Figure 1.13**).

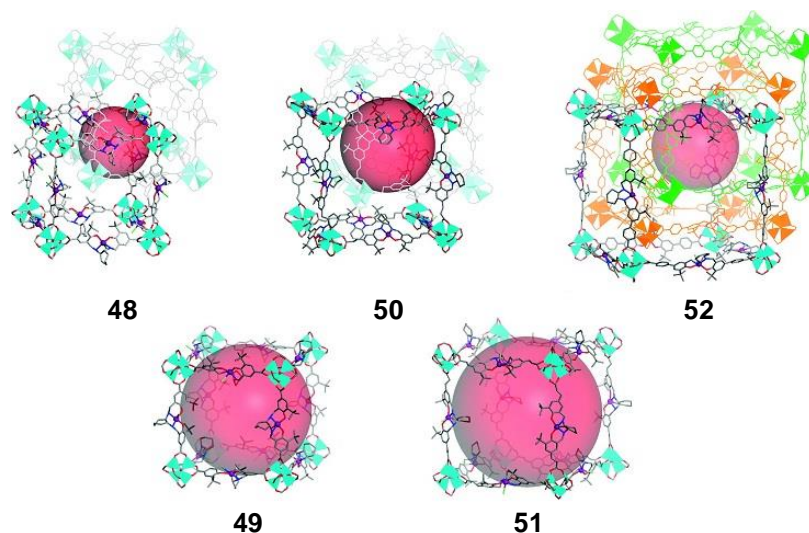
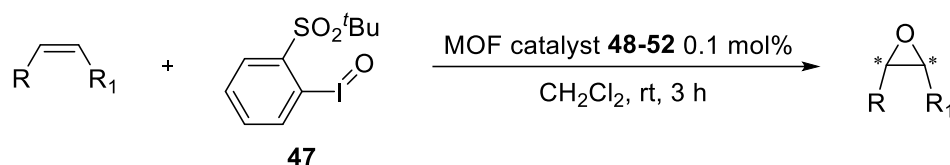
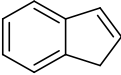
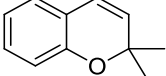
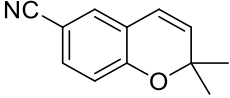
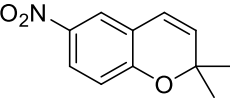
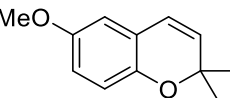
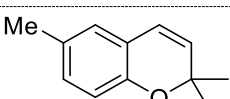
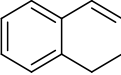


Figure 1.13 Structures of the optically active MOFs **48** – **52** with the representation of pore sizes reported by Song *et al.*⁵³ Adapted with permission from Song, F.; Wang, C.; Falkowski, J. M.; Ma, L.; Lin, W. *J. Am. Chem. Soc.* **2010**, *132*, 15390 – 15398. Copyright 2010, American Chemical Society.

The optically active MOFs **48** – **52** were next used in an asymmetric epoxidation of olefins. The MOF **48** – **52** (0.1 mol%; it is not clear how the amount of the catalyst was calculated) catalysed the reaction of an olefin (1 equivalent) and 2-(*t*-butylsulfonyl)iodosylbenzene (**47**) (0.5 equivalent) in dichloromethane at room temperature to afford after 3 hours the desired epoxides with conversions up to 99% and enantiomeric excess values as high as 92% (**Scheme 1.23**, **Table 1.8**).



Scheme 1.23 Enantioselective olefin epoxidation catalysed by chiral non-racemic MOF **48** – **52** reported by Song *et al.*⁵³

Olefin	Catalyst (0.1 mol%)	Conversion (%) ^a	Enantiomeric excess (%) ^b
	48	63	47
	50	80	64
	52	54	61
	51	87	85
	52	82	92
	51	79	83
	52	60	79
	51	93	81
	51	89	77
	51	79	75
	51	>99	39
	52	>99	42

^a Determined by GC.

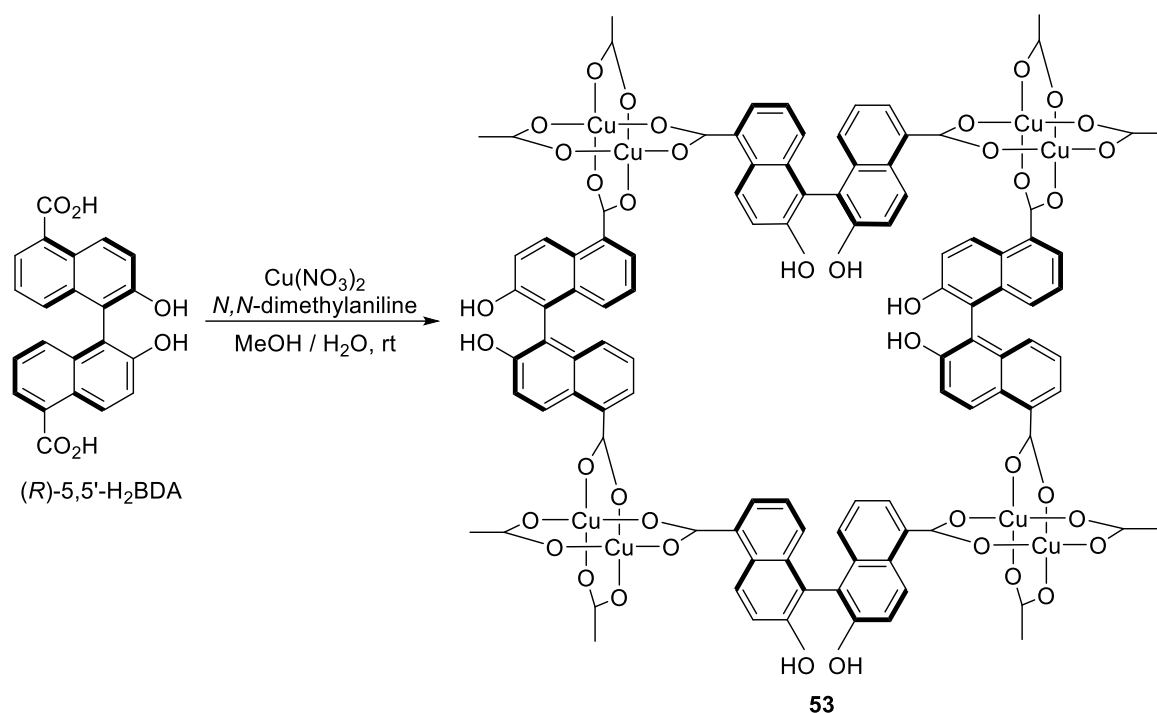
^b Determined by chiral GC or HPLC.

Table 1.8 Enantioselective epoxidation of olefins catalysed by a series of MOFs
48 – 52 reported by Song *et al.*⁵³

The optically active MOFs **48 – 52** catalysed the asymmetric epoxidation of olefins with average to high conversions (54% to >99%) and moderate to high enantiomeric excess values (39% to 92%). Interpenetrated MOFs, CMOF-1 (**48**), CMOF-3 (**50**), and CMOF-5 (**52**), resulted generally in lower conversions and enantiomeric excess levels in comparison to the non-interpenetrated CMOF-2 (**49**) and CMOF-4 (**51**). This could imply that the catalytic process takes place mainly inside the pores and not on the surface of MOFs as the catalysts with bigger size pores provided higher conversions and enantiomeric excess values. Additional experiments confirmed that the process was heterogeneous (no conversion was observed after removing the catalyst from the reaction mixture) and that the MOF catalysts **48 – 52** displayed stable frameworks. They could be recycled at least three times with no significant change in conversions and enantiomeric excess values.

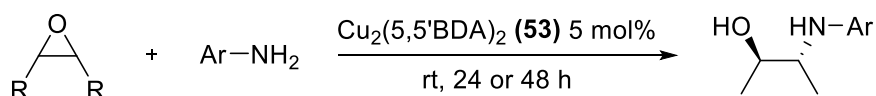
1.5.7. Ring-opening reaction of epoxides

In 2008, Tanaka *et al.*⁵⁴ prepared optically active MOF **53** that was utilised in an enantioselective ring-opening reaction of epoxides with amines under solvent-free conditions. The porous material **53** was synthesised from chiral non-racemic BINOL-derived linkers and copper ions. Reaction of (*R*)-2,2'-dihydroxy-1,10-binaphthalene-5,5'-dicarboxylic acid ((*R*)-5,5'-H₂BDA), *N,N*-dimethylaniline and copper(II) nitrate hexahydrate in a mixture of methanol and water at room temperature afforded after several days [Cu₂(5,5'BDA)₂(H₂O)₂] \cdot MeOH \cdot 2H₂O (**53**) as green needle-like crystals (**Scheme 1.24**).



Scheme 1.24 Synthesis of an optically active **53** reported by Tanaka *et al.*⁵⁴

The BINOL-based **53** was employed in an asymmetric ring-opening reaction of epoxides with aromatic amines. Cu₂(5,5'BDA)₂ (**53**) (5 mol%; the authors did not indicate how the amount of the catalyst was determined) catalysed the reaction of an epoxide (1 equivalent) with an amine (1 equivalent) in toluene or under solvent-free conditions at room temperature to afford after 24 hours β -amino alcohols in low to moderate yields (1% to 54%) and enantiomeric excess values of up to 51% (**Scheme 1.25**, **Table 1.9**).



Scheme 1.25 Enantioselective ring-opening reaction of epoxides catalysed by optically active BINOL-derived **53** reported by Tanaka *et al.*⁵⁴

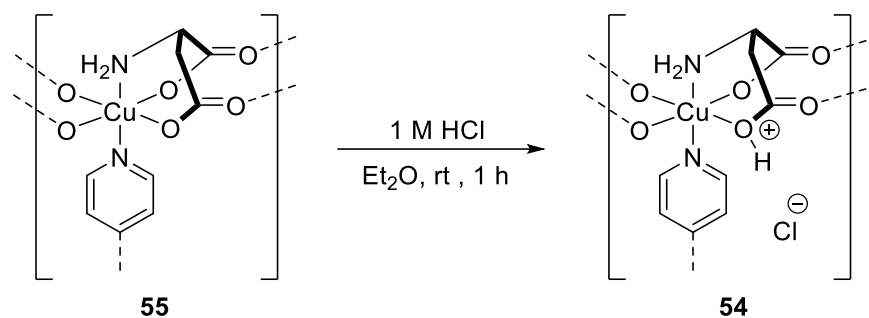
R	Ar	Solvent	Time (h)	Yield (%)	Enantiomeric excess (%) ^a
-(CH ₂) ₄ -	Ph	Toluene	48	54	45
-(CH ₂) ₃ -	Ph	Toluene	48	15	43
-(CH ₂) ₄ -	Ph	Neat	24	51	51
-(CH ₂) ₃ -	Ph	Neat	24	30	50
-(CH ₂) ₄ -	2-MeC ₆ H ₄	Neat	24	3	2
-(CH ₂) ₄ -	4-MeC ₆ H ₄	Neat	24	13	0

^a Determined by chiral HPLC.

Table 1.9 Enantioselective ring-opening reaction of epoxides with an amine catalysed by **53** reported by Tanaka *et al.*⁵⁴

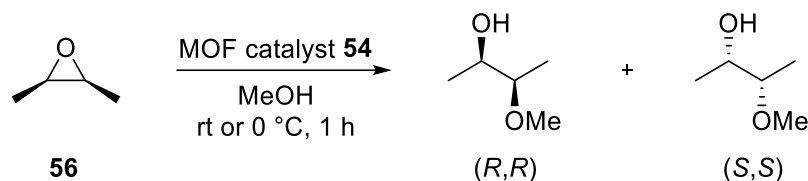
Although Cu₂(5,5'BDA)₂ (**53**) catalysed the asymmetric ring-opening reaction of epoxides, the observed yields and enantiomeric excess values were low to average. Interestingly, when aniline was used, the reaction also proceeded under solvent-free conditions providing higher enantiomeric excess levels compared to those observed when the reaction was performed in toluene. When amines larger in size (2- and 4-methylaniline) were employed in the reaction a significant drop in the yield and enantiopurity of the products was observed. It could be postulated that the pores were only accessible to smaller molecules and therefore the catalytic process predominantly occurred inside the pores and channels and not on the surface of **53**. Furthermore, the catalyst **53** was reused in an additional cycle without the loss of catalytic activity or enantioselectivity.

In 2008, Ingleson *et al.*⁵⁵ synthesised a chiral non-racemic amino acid-derived MOF **54** with a Brønsted acid centre introduced into the framework *via* post-synthetic modification, and utilised it for the methanolysis of *cis*-2,3-epoxybutane. First, [Cu(L-asp)(bpe)_{0.5}]_{0.5}H₂O_{0.5}MeOH (**55**) was synthesised in a reaction of copper(II) nitrate, 1,2-bis(4-pyridyl)ethylene (bpe) and L-aspartic acid (L-asp) in a mixture of water and methanol at 100 °C for 18 hours. Further treatment of the three-dimensional **55** with 1 M hydrochloric acid (0.95 equivalents) in diethyl ether at room temperature generated after 1 hour the protonated material Cu(L-asp)bpe_{0.5}(HCl)(H₂O) **54** (Scheme 1.26).⁵⁵ Although the reaction was performed under anhydrous conditions the porous solid adsorbed water from the atmosphere.⁵⁵ Comparison of the non-protonated **55** and protonated **54** by powder X-ray diffraction (PXRD) did not reveal any significant changes in the structure of framework upon treatment with hydrochloric acid.



Scheme 1.26 Generation of a Brønsted acid centre in a porous optically active MOF **54** via post-synthetic modification of **55** reported by Ingleson *et al.*⁵⁵

The Cu(L-asp)bpe_{0.5}(HCl)(H₂O) (**54**) was investigated for catalytic activity in an asymmetric methanolysis of *cis*-2,3-epoxybutane. Reaction of *cis*-2,3-epoxybutane (**56**) in the presence of **54** (the authors failed to indicate the mol% of the catalyst used) in methanol at room temperature or 0 °C afforded after 48 hours the ring-opened products in moderate yields but with low enantiomeric excess values (**Scheme 1.27**, **Table 1.10**).



Scheme 1.27 Methanolysis of *cis*-2,3-epoxybutane (**56**) catalysed by an optically active **54** reported by Ingleson *et al.*⁵⁵

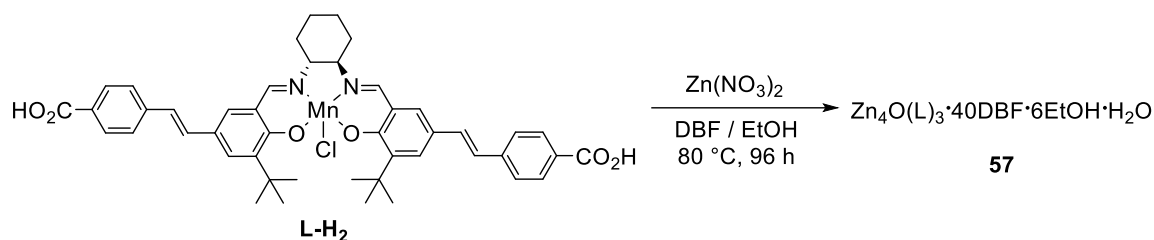
Temperature (°C)	Yield (%)	Enantiomeric excess (%)
25	59	10
0	30	17

Table 1.10 The Cu(L-asp)bpe_{0.5}(HCl) (**54**)-catalysed methanolysis of *cis*-2,3-epoxybutane (**56**) reported by Ingleson *et al.*⁵⁵

The post-synthetically modified **54** catalysed the methanolysis of *cis*-2,3-epoxybutane (**56**) in modest 59% yield and with low 10% enantiomeric excess. Interestingly, the enantiopurity of the product increased to 17% when the reaction was performed at lower temperature. The catalytic system proved to be heterogeneous as no conversion of the starting material was observed after removal of the MOF catalyst from the reaction mixture. In an additional experiment with bulkier (2,3-epoxypropyl)-benzene as a starting material, the catalytic activity of Cu(L-asp)bpe_{0.5}(HCl) (**54**) was suppressed indicating that the catalysis took place inside the pores and not on the surface of **54**.

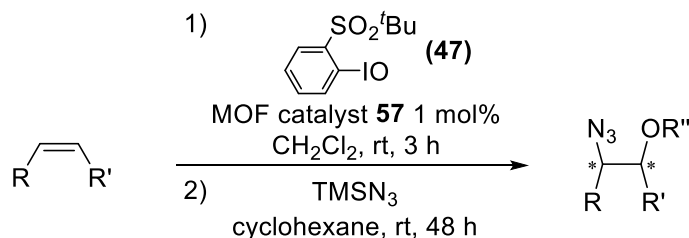
Song *et al.*⁵⁶ in 2011 once more reported a chiral non-racemic MOF **57** built from an enantiopure salen-manganese unit and utilised it in a one-pot asymmetric

epoxidation / ring-opening reaction. This hybrid solid, $\text{Zn}_4\text{O}(\text{L})_3 \cdot 40\text{DBF} \cdot 6\text{EtOH} \cdot \text{H}_2\text{O}$ (**57**), was prepared in a reaction of zinc(II) nitrate hexahydrate, salen-manganese derived dicarboxylate linker (**L-H₂**) in a mixture of *N,N*-dibutylformamide (DBF) and ethanol at 80 °C within 96 hours (**Scheme 1.28**).



Scheme 1.28 Synthesis of $\text{Zn}_4\text{O}(\text{L})_3 \cdot 40\text{DBF} \cdot 6\text{EtOH} \cdot \text{H}_2\text{O}$ (**57**) reported by Song *et al.*⁵⁶

Song *et al.* extended their study of MOF-catalysed asymmetric transformations by utilisation of **57** in a one-pot enantioselective epoxidation / ring-opening reaction. The prepared **57** (1 mol%; it is not evident how the amount of the catalyst used was calculated) catalysed the reaction of an olefin (1 equivalent) and 2-(*t*-butylsulfonyl)iodosylbenzene (**47**) (1 equivalent) in dichloromethane at room temperature to afford after 3 hours the desired epoxide. The solvent was changed to cyclohexane and the thus prepared epoxide was treated with azidotrimethylsilane (1.5 equivalents) at room temperature to afford after 48 hours the epoxide ring-opened product (**Scheme 1.29**, **Table 1.11**).



Scheme 1.29 One-pot asymmetric epoxidation / ring-opening reaction catalysed by **57** reported by Song *et al.*⁵⁶

Olefin	Product	Yield (%)	Enantiomeric excess (%) ^a
		60	50 (48)
		57	81 (82)

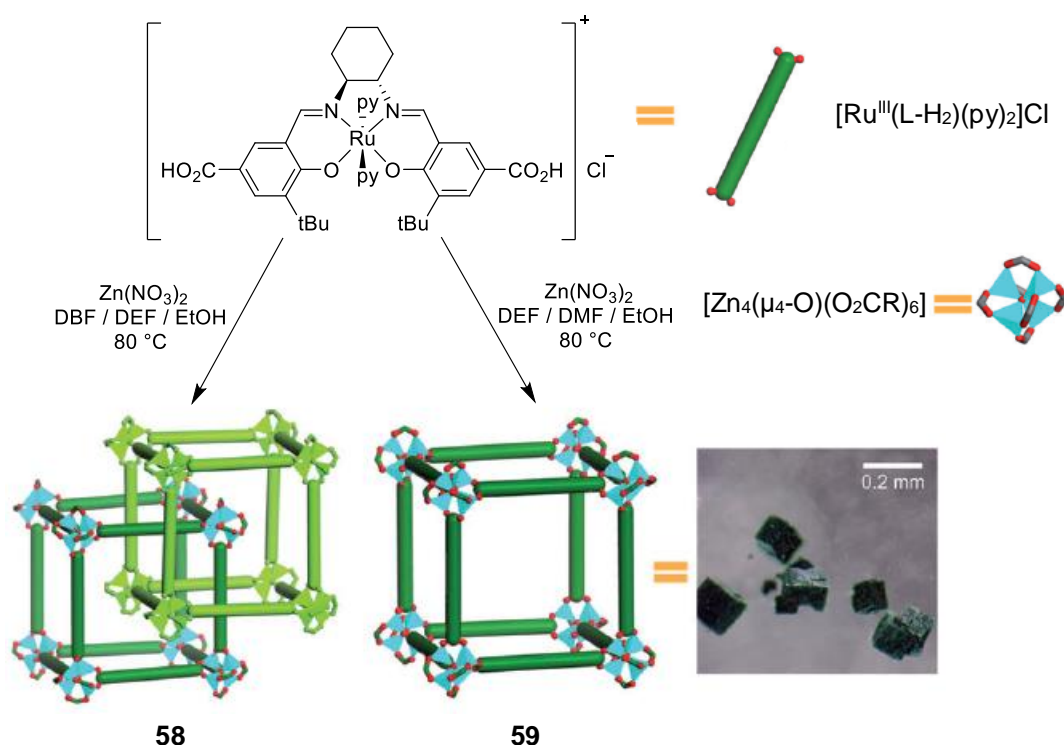
^a Determined by chiral GC or chiral HPLC; value in parenthesis displays the enantiomeric excess of the corresponding epoxide.

Table 1.11 The **57**-catalysed one-pot enantioselective epoxidation / ring-opening reaction reported by Song *et al.*⁵⁶

The $\text{Zn}_4\text{O}(\text{L})_3$ (**57**) catalysed the one-pot epoxidation / ring-opening reaction in good yield (57% and 60%). The enantiomeric excess values of the epoxidation and ring-opening reaction were almost identical. Although the enantiomeric excess levels were moderate, it was the first one-pot epoxidation / ring-opening reaction catalysed by an optically active MOF.

1.5.8. Cyclopropanation

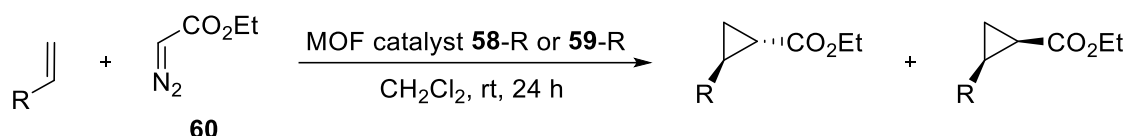
In 2011 chiral non-racemic MOFs **58-R** and **59-R** assembled from metal-salen building blocks were synthesised.⁵⁷ These porous materials exhibited catalytic activity in an asymmetric cyclopropanation and were the first to display a reversible reduction / reoxidation nature.⁵⁷ First, interpenetrated $\{\text{Zn}_4\text{O}[(\text{Ru}(\text{L-H}_2)(\text{py})_2\text{Cl})_3] \cdot 7\text{DBF} \cdot 7\text{DEF}\}$ (CMOF 1) (**58**) and non-interpenetrated $\{\text{Zn}_4\text{O}[(\text{Ru}(\text{L-H}_2)(\text{py})_2\text{Cl})_3] \cdot 19\text{DEF} \cdot 5\text{DMF} \cdot 17\text{H}_2\text{O}\}$ (CMOF 2) (**59**) were prepared in a reaction of a building block $[\text{Ru}(\text{L-H}_2)(\text{py})_2]\text{Cl}$ and zinc(II) nitrate hexahydrate in a mixture of *N,N*-dibutylformamide, *N,N*-diethylformamide and ethanol, or *N,N*-diethylformamide, *N,N*-dimethylformamide and ethanol at 80 °C for 36 hours (Scheme 1.30).



Scheme 1.30 Syntheses and crystal structures of CMOF 1 (**58**) and CMOF 2 (**59**). Adapted with permission from Falkowski, J. M.; Wang, C.; Liu, S.; Lin, W. *Angew. Chem. Int. Ed.* **2011**, *50*, 8674 – 8678. Copyright 2011, Wiley-VCH.

Treatment of **58** and **59** with reducing agents such as lithium triethylborohydride or sodium trimethoxyborohydride resulted in a colour change from green to red indicating that the ruthenium centres in the framework underwent reduction and changed their oxidation state from +3 to +2.⁵⁷ Despite the colour change, no structural changes in the frameworks of **58** and **59** were observed. Furthermore, these reduced MOFs (CMOF 1R (**58-R**) and CMOF 2R (**59-R**)) could be easily reoxidised in the air with the change of colour back to green.⁵⁷

Due to the known catalytic activity of ruthenium-salen complexes in homogeneous asymmetric cyclopropanations,⁵⁸ **58-R** and **59-R** were explored as heterogeneous catalysts for the cyclopropanation reaction of substituted olefins.⁵⁷ CMOF 1R (**58-R**) or CMOF 2R (**59-R**) catalysed the reaction of substituted olefin (5 equivalents) and ethyl α -diazoacetate (**60**) (1 equivalent) in dichloromethane at room temperature to afford after 24 hours the cyclopropanation product (**Scheme 1.31**, **Table 1.12**).



Scheme 1.31 Asymmetric cyclopropanation catalysed by **58-R** and **59-R** reported by Falkowski *et al.*⁵⁷

Catalyst	R	Catalyst loading (mol%) ^a	Yield (%)	Diastereomeric ratio (%)	Enantiomeric excess (%) (<i>cis</i>) ^b
59-R	Ph	3	8	4.2	65 (51)
59-R^c	Ph	3	54	7	91 (84)
59	Ph	3	1	-	-
58-R	Ph	3	1	1.2	33 (47)
59-R^c	OEt	2	20	2	61 (67)
59-R^c	CH ₃ (CH) ₂	2	27	1.7	25 (13)

^a The authors did not specify how the amount of the catalyst was calculated.

^b The first value represents the *trans*-isomer; value in parenthesis is for the *cis*-isomer.

^c Reaction performed with reducing agent NaB(OMe)₃H.

Table 1.12 Enantioselective cyclopropanation catalysed by **58-R** and **59-R** reported by Falkowski *et al.*⁵⁷

The first cyclopropanation of styrene performed with the use of **59-R** (reduced ruthenium centres) resulted in a low yield (8%) and moderate enantiomeric excess (65% and 51% for the *trans*- and *cis*-isomer respectively). It was suspected that the ruthenium centres in CMOF 2R (**59-R**) oxidised during the reaction preventing its catalytic activity resulting in a poor yield.⁵⁷ To substantiate this hypothesis two experiments were carried out. The first

involved utilisation of CMOF 2 (**59**) as the reaction catalyst, and the second employment of CMOF 2R (**59-R**) together with the reducing agent sodium trimethoxyborohydride. As predicted, **59** with oxidised ruthenium centres exhibited a low catalytic activity (reaction yield 1%), whereas the reaction performed in the presence of both, **59-R** with reduced ruthenium centres and a reducing agent, afforded the anticipated cyclopropanation product in a good 54% yield and with high enantiomeric excess (91% and 84% for the *trans*- and *cis*-isomer respectively). The employment of CMOF 1R (**58-R**) in the reaction of styrene with ethyl α -diazoacetate (**60**) displayed lower yield (1%) in comparison to the yield when CMOF 2R (**59-R**) was employed as catalyst (8%). This could be due to the interpenetrated framework of **58-R** and therefore smaller size of pores and channels.⁵⁷ Although the yields were poor, CMOF 2R (**59-R**) in the presence of a reducing agent also catalysed the reaction of 1,3-pentadiene with ethyl vinyl ether and with ethyl α -diazoacetate (**60**). Furthermore, the heterogeneity of the catalytic process was confirmed by the removal of catalyst from the reaction mixture what resulted in no further conversion of the starting materials.

1.5.9. Hydrogenation

In 2003 Lin *et al.* reported the synthesis of two optically active porous zirconium phosphonates **61** and **62**, which displayed good enantioselectivity for the hydrogenation of β -keto esters and aromatic ketones.^{59,39} Although both were 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP)-derived materials, they displayed different chiral environments or varied in the position of phosphonic acid in the molecule.

The $[\text{Zr}\{\text{Ru}(\text{L}_1)(\text{dmf})_2\text{Cl}_2\}]\cdot 2\text{MeOH}$ (**61**), referred to as Zr-Ru-L₁, and $[\text{Zr}\{\text{Ru}(\text{L}_2)(\text{dmf})_2\text{Cl}_2\}]\cdot 2\text{MeOH}$ (**62**), referred to as Zr-Ru-L₂, were synthesised in two steps. First, the chiral non-racemic ligand L₁-H₄ or L₂-H₄, (*R*)-2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl-6,6'-bis(phosphonic acid) or (*R*)-2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl-4,4'-bis(phosphonic acid) were treated with $[\{\text{Ru}(\text{benzene})\text{Cl}_2\}_2]$ in *N,N*-dimethylformamide at 100 °C to afford the intermediates $[\text{Ru}(\text{L}_1\text{-H}_4)(\text{dmf})_2\text{Cl}_2]$ and $[\text{Ru}(\text{L}_2\text{-H}_4)(\text{dmf})_2\text{Cl}_2]$ respectively, which were subsequently allowed to react with zirconium(IV) *t*-butoxide at reflux in methanol to yield the porous solids **61** and **62** respectively (Figure 1.14).⁵⁹

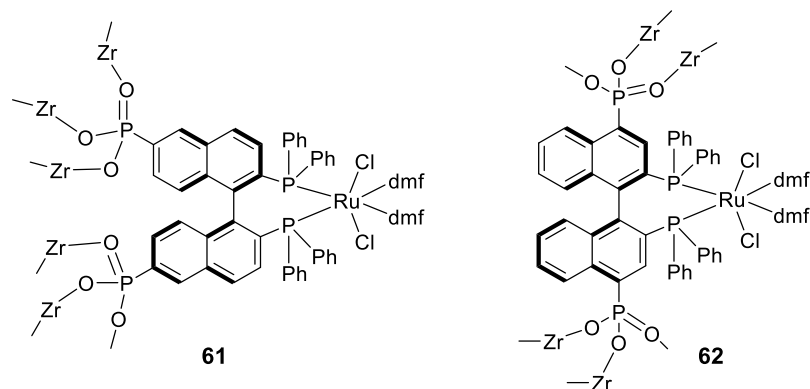
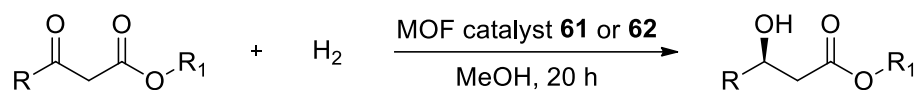


Figure 1.14 The structure of Zr-Ru-L₁ (**61**) and Zr-Ru-L₂ (**62**) reported by Lin *et al.*⁵⁹

Despite their amorphous nature, these materials displayed high porosity and were explored for an asymmetric hydrogenation of β -keto esters.²⁹ The porous Zr-Ru-L₁ (**61**) and Zr-Ru-L₂ (**62**) catalysed the reaction of β -keto esters with hydrogen (1420 or 700 psi) in methanol at room temperature or 60 °C to afford after 20 hours the desired hydrogenation product in moderate to high yields and with enantiomeric excess values (*e.e.*) of up to 95% (**Scheme 1.32**, **Table 1.13**).



Scheme 1.32 Asymmetric hydrogenation of β -keto esters catalysed by **61** or **62** reported by Lin *et al.*⁵⁹

β -Keto ester	Catalyst loading (mol%) ^a	Temperature (°C)	H ₂ pressure (psi)	Zr-Ru-L ₁ (61)		Zr-Ru-L ₂ (62)	
				Yield (%)	<i>e.e.</i> (%) ^b	Yield (%)	<i>e.e.</i> (%) ^b
	1	60	700	100	94		
	1	rt	1400	100	95	73	90
	0.1	60	700	100	93		
	1	rt	1400	100	92	65	90
	1	rt	1400	100	92	68	85
	1	rt	1400	100	70	16	50
	1	rt	1400	100	93	64	100
	1	rt	1400	100	93	79	70

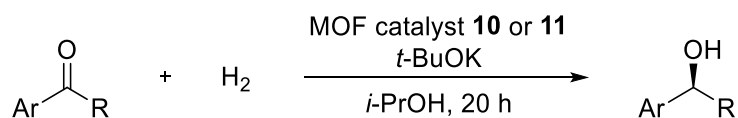
^a The authors did not indicate how the amount of the catalyst was determined.

^b Determined by chiral GC.

Table 1.13 The Zr-Ru-L₁ (**61**) and Zr-Ru-L₂ (**62**)-catalysed enantioselective hydrogenation of β -keto esters reported by Lin *et al.*⁵⁹

The authors failed to make clear if **61** and **62** returned products with the same absolute configuration at the chiral centre. Zr-Ru-L₁ (**61**) catalysed the asymmetric hydrogenation of β -alkyl-substituted β -keto esters in excellent yields and with enantiomeric excess values above 92%. However, the Zr-Ru-L₂ (**62**) catalyst provided lower yields ranging between 16% and 79%, and poorer enantiomeric excess values. Utilisation of both catalysts in the reaction of β -aryl-substituted β -keto ester resulted in only modest enantiomeric excess (70%) for **61** and significantly lower (16%) for **62**. The heterogeneous nature of this catalytic process was demonstrated by removal of **61** from the reaction mixture, which resulted in no further conversion of the starting material. Furthermore, Zr-Ru-L₁ (**61**) was successfully recycled up to six times without any significant change in the catalytic activity and enantioselectivity.

Due to the low enantiomeric excess value for the asymmetric hydrogenation of β -aryl-substituted β -keto ester with Zr-Ru-L₁ (**61**) and Zr-Ru-L₂ (**62**), Lin *et al.* further investigated a synthesis of porous material that would catalyse the asymmetric hydrogenation of aromatic ketones more effectively. Two additional chiral porous zirconium phosphonates, Zr[Ru(L₁)(DPEN)Cl₂] \cdot 4H₂O (**10**) and Zr[Ru(L₂)(DPEN)Cl₂] \cdot 4H₂O (**11**), were prepared (these solids have been described in more detail earlier on in this chapter; section 1.4.1).³⁹ Reaction of (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl-4,4'-bis(phosphonic acid) (L₁-H₄) or (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl-6,6'-bis(phosphonic acid) (L₂-H₄) with [Ru(benzene)Cl₂]₂ and 1,2-diphenylethylenediamine (DPEN) afforded Ru-BINAP-DPEN intermediates.³⁹ Treatment of the intermediates with zirconium(IV) *t*-butoxide at reflux generated the anticipated optically active **10**, referred to as Zr-Ru-L₁, or **11**, referred to as Zr-Ru-L₂, that were subsequently utilised in an asymmetric hydrogenation of aromatic ketones. The Zr-Ru-L₁ (**10**) or Zr-Ru-L₂ (**11**) catalysed the reaction of aromatic ketones with hydrogen in the presence of potassium *t*-butoxide in isopropyl alcohol at room temperature to afford, after 20 hours, the hydrogenation product with modest to high enantiomeric excess values (**Scheme 1.33**, **Table 1.14**).



Scheme 1.33 Asymmetric hydrogenation of aromatic ketones catalysed by Zr-Ru-L₁ (**10**) or Zr-Ru-L₂ (**11**) reported by Lin *et al.*⁵⁹

Ar	R	Catalyst loading (mol%) ^a	<i>t</i> -BuOK (mol%)	Zr-Ru-L ₁ (10) Enantiomeric excess (%) ^b	Zr-Ru-L ₂ (11) Enantiomeric excess (%) ^b
Ph	Me	0.1	1	96	79
2-Naphthyl	Me	0.1	1	97	82
4- <i>t</i> -BuPh	Me	0.1	1	99	92
4-MeOPh	Me	0.1	1	96	80
4-ClPh	Me	0.1	1	95	59
4-MePh	Me	0.1	1	97	80
Ph	Et	0.1	1	93	84
Ph	<i>Cyclo</i> -Pr	0.1	1	91	-
1-Naphthyl	Me	0.1	1	99	96

^a The amount of the catalyst was calculated based on ruthenium.

^b The enantiomeric excess values were determined by chiral GC.

Table 1.14 Enantioselective hydrogenation of aromatic ketones catalysed by **10** or **11** reported by Lin *et al.*⁵⁹

Zr-Ru-L₁ (**10**) catalysed the enantioselective hydrogenation of aromatic ketones with very high enantiomeric excess values (91% to 99%) using only 0.1 mol% of loading, whereas Zr-Ru-L₂ (**11**) afforded the hydrogenation products with lower enantiomeric excess values (59% to 96%). A further study of the catalyst loading revealed that the hydrogenation of 1-acetonaphthone could be performed with as low as 0.005 mol% of the catalyst and still provide the product with 99% enantiomeric excess. The Zr-Ru-L₁ (**10**) and Zr-Ru-L₂ (**11**) were recyclable up to eight and three times respectively without any decrease in enantioselectivity. However, lower catalytic activity was observed for both materials, which was most likely due to an oxidation of the ruthenium centre as the reactions were not performed under strictly air-free conditions.⁵⁹

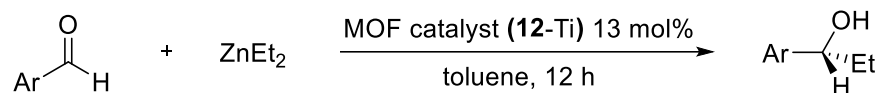
1.5.10. Diethylzinc addition to aromatic aldehydes

In recent years Lin *et al.*^{40,60,61} reported syntheses of optically active MOFs that were successfully utilised in an asymmetric diethylzinc addition to aromatic aldehydes. The synthetic approach to these porous solids relied on the employment of an axially chiral pyridyl functionalised [1,1'-binaphthalene]-2,2'-diol (BINOL) building blocks and generation of enantioselective catalytic sites *via* post-synthetic modification of the assembled frameworks.

In 2005, a crystalline solid [Cd₃Cl₆L₃]·4DMF·6MeOH·3H₂O (**12**) was prepared by the diffusion of diethyl ether into a mixture of a rigid (*R*)-6,6'-dichloro-2,2'-dihydroxy-1,1'-

binaphthyl-4,4'-bipyridine (L) and cadmium(II) chloride in a mixture of methanol and *N,N*-dimethylformamide for 3 days (this solid has been described in more detail earlier on in this chapter; section 1.4.1).⁴⁰ Although the dihydroxyl groups of two-thirds of the BINOL-derived linkers (L) built into the network were shielded from open channels by the neighbouring naphthyl rings, subsequent treatment of the MOF **12** with an excess of titanium isopropoxide led to a reaction with the remaining dihydroxyl groups and generation of the titanium-coordinated framework (**12-Ti**) with Ti(BINOL)(*O*^{*i*}Pr)₂ catalytically active metal sites. This solid was investigated for diethylzinc addition to aromatic aldehydes.²⁹

Reaction of an aromatic aldehyde (1 equivalent) and diethylzinc (3 equivalents) was catalysed by the **12-Ti** (13 mol%; the authors failed to indicate how the amount of the catalyst was determined) at room temperature to afford after 12 hours and acidic work-up the anticipated secondary alcohol (**Scheme 1.34, Table 1.15**).

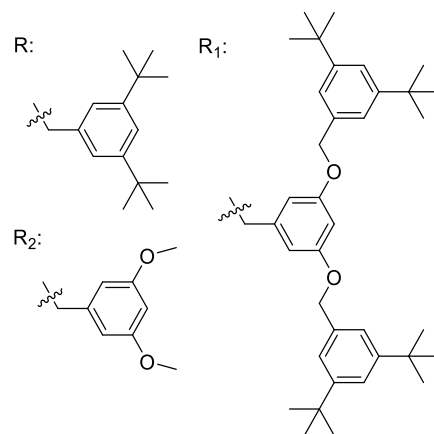


Scheme 1.34 Asymmetric diethylzinc addition to aromatic aldehydes catalysed by the titanium-coordinated [Cd₃Cl₆L₃] (**12-Ti**) reported by Lin *et al.*⁴⁰

Ar	Conversion (%)	Enantiomeric excess (%)
1-Naphthyl	>99	94
Ph	>99	88
4-ClPh	>99	86
3-BrPh	>99	84
4-MeOPh	>99	80
4-ROPh	>99	75
4-R ₂ OPh	>99	78
4-R ₁ OPh	95 ^a	67 ^a

^aThe reaction was performed with 40 mol% of BINOL.

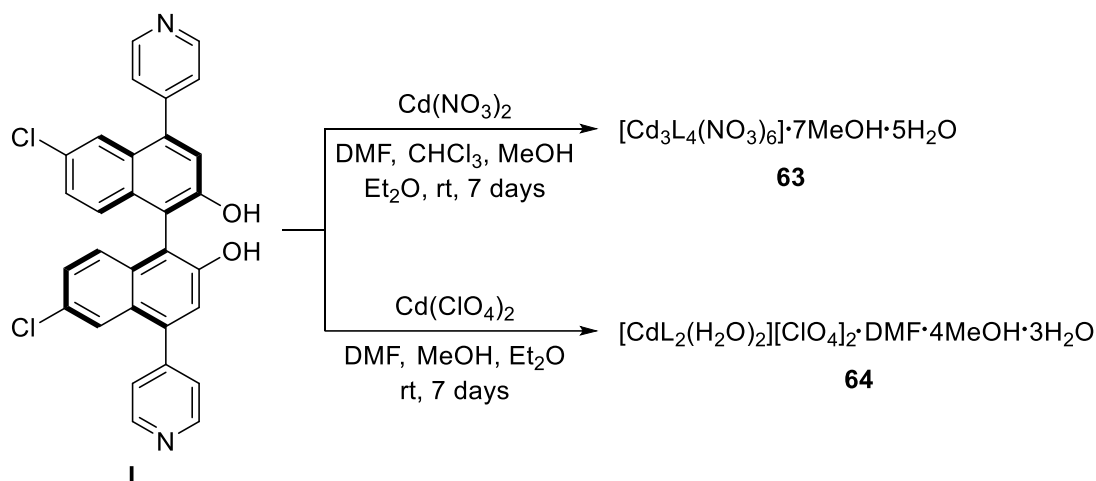
Table 1.15 Titanium-coordinated [Cd₃Cl₆L₃] (**12-Ti**)-catalysed enantioselective diethylzinc addition to aromatic aldehydes reported by Lin *et al.*⁴⁰



Titanium-coordinated [Cd₃Cl₆L₃] (**12-Ti**) catalysed the enantioselective diethylzinc addition to aromatic aldehydes in high yields and with average to high enantiomeric excess values varying from 67% to 94%. To study the size selectivity of **12-Ti**, the reaction was performed utilising different size aldehydes.⁴⁰ The enantiomeric excess values decreased

with increase of the size of aldehydes confirming that the catalytic process took place inside of pores and not on the surface of **12-Ti**.⁴⁰ Additionally, no product was observed when the catalyst was removed from the reaction mixture confirming the heterogeneous nature of the catalytic process.

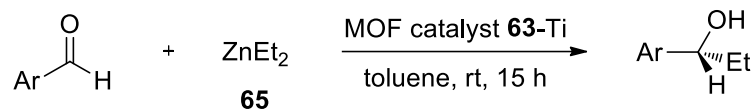
Two years later, in 2007, Lin and Wu,⁶⁰ synthesised two more chiral non-racemic MOFs **63-Ti** and **64-Ti**, built from pyridyl functionalised BINOL ligand and cadmium ions, that displayed catalytic activity towards the asymmetric diethylzinc addition to aromatic aldehydes. Diffusion of diethyl ether into a mixture of (*R*)-6,6'-dichloro-2,2'-dihydroxy-1,1'-binaphthyl-4,4'-bipyridine (**L**) and cadmium(II) nitrate tetrahydrate or cadmium(II) perchlorate hexahydrate in a mixture of *N,N*-dimethylformamide, chloroform and methanol or *N,N*-dimethylformamide and methanol at room temperature afforded after 7 days the crystalline solid $[\text{Cd}_3\text{L}_4(\text{NO}_3)_6] \cdot 7\text{MeOH} \cdot 5\text{H}_2\text{O}$ (**63**) or $[\text{CdL}_2(\text{H}_2\text{O})_2][\text{ClO}_4]_2 \cdot \text{DMF} \cdot 4\text{MeOH} \cdot 3\text{H}_2\text{O}$ (**64**) respectively (**Scheme 1.35**).



Scheme 1.35 Synthesis of chiral non-racemic MOFs **63** and **64** reported by Lin and Wu.⁶⁰

Although **63** and **64** were prepared under similar reaction conditions they displayed different properties. Both MOFs incorporated interpenetrated three-dimensional frameworks. However, **63** exhibited a surface area of $772.3 \text{ m}^2\text{g}^{-1}$ and pore volume of 0.25 mLg^{-1} , whereas **64** displayed a surface area of $370 \text{ m}^2\text{g}^{-1}$ and pore volume of 0.16 mLg^{-1} . Despite the interpenetrated frameworks, **63** and **64** were treated with an excess of titanium isopropoxide to afford asymmetric catalysts for the addition of diethylzinc to aromatic aldehydes. The titanium-coordinated **63-Ti** displayed good enantioselectivity and catalytic activity in a reaction of an aromatic aldehyde (1 equivalent) with diethylzinc (**65**) (3 equivalents) in toluene at room temperature to generate, after 15 hours and acidic work-up, the anticipated secondary alcohol (**Scheme 1.36**, **Table 1.16**). In contrast, treatment of **64** with excess of titanium isopropoxide resulted in no catalytic activity for

the titanium-coordinated **64**-Ti in an addition of diethylzinc (**65**) to aromatic aldehydes, albeit the presence of hydroxyl groups and permanent porosity.⁶⁰ It is thought that this problem arose from structural congestion around the hydroxyl groups, which did not undergo the complexation with titanium isopropoxide to form the catalytically active sites.



Scheme 1.36 Enantioselective addition of diethylzinc to aromatic aldehydes catalysed by **63**-Ti reported by Lin and Wu.⁶⁰

Ar	Catalyst loading (%) ^a	Conversion (%)	Enantiomeric excess (%) ^b
1-Naphthyl	12	>99	90
4-MePh	12	>99	84
4-MePh	25	>99	85
Ph	12	>99	82
Ph	20	>99	79
3-BrPh	12	>99	71
4-ClPh	12	>99	60
4-CF ₃ Ph	12	>99	45

^aThe authors did not indicate how the amount of the catalyst was calculated.

^bDetermined by chiral GC.

Table 1.16 Asymmetric diethylzinc addition to aromatic aldehydes catalysed by **63**-Ti reported by Lin and Wu.⁶⁰

The titanium-coordinated **63**-Ti exhibited excellent catalytic activity and good enantioselectivity resulting in conversions of the starting material above 99% and enantiomeric excess values for the generated secondary alcohols ranging from 45% to 90%. A catalyst loading study revealed that increasing the amount of **63**-Ti from 12 mol% to 25 mol% for 4-methylbenzaldehyde, and from 12 mol% to 20 mol% for benzaldehyde (**35**), only slightly changed the conversions and enantiomeric excess values. Although only one out of the two synthesised optically active MOFs was able to catalyse the asymmetric diethylzinc addition to aromatic aldehydes, the research reported by Lin and Wu⁶⁰ emphasised the influence of a framework structure on a catalytic process.²⁹

Broadening the area of synthesising optically active BINOL-derived MOFs for asymmetric catalysis, Lin *et al.*⁶¹ reported a series of chiral non-racemic porous materials CMOF-**66** to CMOF-**73** assembled from BINOL-based ligands **66** – **73** varying in length and equipped with carboxylate groups (**Figure 1.15**).

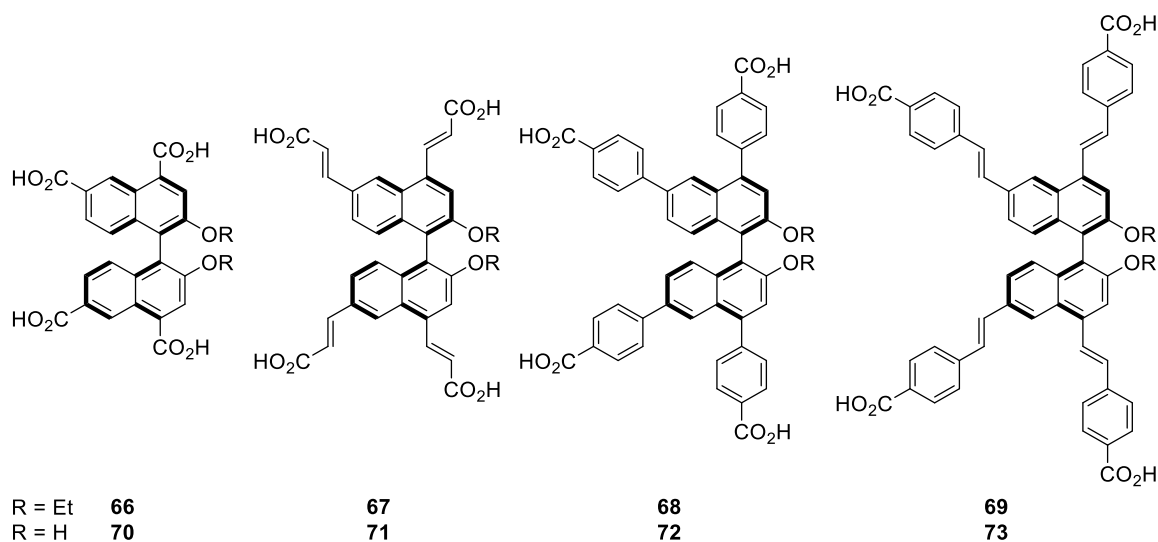
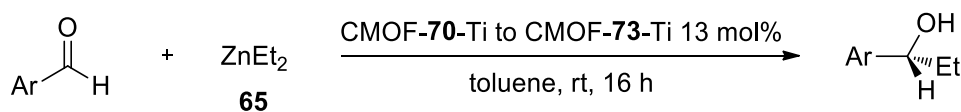


Figure 1.15 BINOL-derived organic linkers **66** – **73** reported by Lin *et al.*⁶¹

Reaction of a BINOL-derived linker **66** – **73** with copper(II) nitrate in the presence of 3 M aqueous hydrochloric acid solution in a mixture of *N,N*-diethylformamide and water at 80 °C afforded after 24 hours the optically active MOF with a general formula $[\text{L}]\text{Cu}_2(\text{solvent})_2$ (CMOF-**66** to CMOF-**73**). All of the MOFs, CMOF-**66** to CMOF-**73**, exhibited three-dimensional non-interpenetrated frameworks with high porosity and open channels that increased with the length of the linker. In addition, the ethoxy-protected CMOF-**66** to CMOF-**69** series displayed smaller open channels in comparison to CMOF-**70** to CMOF-**73** series due to a more bulky ethyl group.

The CMOF-**70** to CMOF-**73** series, which have a high porosity, open channels and free hydroxyl groups, were attractive candidates for a post-synthetic modification and introduction of catalytically active sites into the framework.⁶¹ Therefore treatment of CMOF-**70** to CMOF-**73** series with excess of titanium isopropoxide generated the titanium-coordinated CMOF-**70**-Ti to CMOF-**73**-Ti series that exhibited catalytic activity towards the diethylzinc addition to aromatic aldehydes. Reaction of an aromatic aldehyde (1 equivalent) with diethylzinc (**65**) (2.7 equivalents) in the presence of CMOF-**70**-Ti to CMOF-**73**-Ti (13 mol%; the authors failed to indicate how the amount of the catalyst was determined) in toluene at room temperature afforded, after 16 hours and acidic work-up, the anticipated secondary alcohol (**Scheme 1.37**, **Table 1.17**).



Scheme 1.37 Asymmetric addition of diethylzinc to aromatic aldehydes catalysed by CMOF-**70**-Ti to CMOF-**73**-Ti series reported by Lin *et al.*⁶¹

Ar	Catalyst	Conversion (%)	Enantiomeric excess (%)
1-Naphthyl	CMOF-72-Ti	>99	91
4-ClPh	CMOF-72-Ti	>99	80
4-BrPh	CMOF-72-Ti	96	80
4-MePh	CMOF-72-Ti	>99	78
Ph	CMOF-72-Ti	>99	82
Ph	CMOF-73-Ti	>99	84
Ph	CMOF-71-Ti	98	70
Ph	CMOF-70-Ti	98	<3
1-Naphthyl	CMOF-73-Ti	60	91
1-Naphthyl	CMOF-71-Ti	>99	86
1-Naphthyl	CMOF-70-Ti	81	9

Table 1.17 Enantioselective diethylzinc addition to aromatic aldehydes catalysed by CMOF-70-Ti to CMOF-73-Ti series reported by Lin *et al.*⁶¹

The titanium-coordinated CMOF-70-Ti to CMOF-73-Ti series catalysed the diethylzinc addition to aromatic aldehydes with conversions and enantiomeric excess values of up to >99% and 91% respectively. Having a series of CMOFs with open channels varying in size, the dependency of the asymmetric induction on the open channel sizes was investigated. Additional experiments with benzaldehyde (**35**) and 1-naphthaldehyde as starting materials revealed that the enantiomeric excess values of the corresponding secondary alcohols were highest when CMOF-73-Ti was utilised in the diethylzinc addition. Although these results did not differ significantly from those obtained for CMOF-72-Ti, it was believed that the framework of CMOF-72-Ti was the least stable and could undergo distortion resulting in a reduction of the enantioselectivity of the catalyst.⁶¹ The remaining CMOF-70-Ti and CMOF-71-Ti provided even lower enantiomeric excess values confirming the dependency of asymmetric induction on the size of open channels. Furthermore, the catalytic process was verified to be heterogeneous in nature as no conversion of the starting material was observed after filtration of CMOF-72-Ti from the reaction mixture.

1.6. Conclusion

Metal-organic frameworks, a new class of porous hybrid solids, have become attractive candidates as catalysts. Although still in their infancy, catalytic studies, some of which

have been presented in the preceding pages, show great promise of these materials for the application in heterogeneous asymmetric catalysis. The most successful optically active MOFs have been synthesised *via* direct incorporation of a chiral non-racemic organic linker or post-synthetic modification of the already assembled framework. The same approaches are those most successfully utilised for the introduction of catalytically active centres. The catalytic activity of MOFs can arise either from functional groups being directly located at the building blocks, post-synthetic introduction of catalytically active molecules into the framework, or an attachment of metal atoms at secondary functional groups of organic ligands.³⁵ On the basis of the above, an organic linker that could undergo post-synthetic modification resulting in the introduction of an asymmetric catalytic centre and a chiral non-racemic building block equipped with secondary functional groups available for the instalment of catalytically active sites were seen as the most beneficial components for optically active MOFs and therefore their synthesis will be presented further on in this PhD thesis.

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Chapter 2
Results and Discussion

2.1. Aim of the project

The aim of the research described in this chapter was to design and synthesise chiral non-racemic organic linkers as building blocks for metal-organic frameworks (MOFs) that could subsequently be applied in heterogeneous asymmetric catalysis.

As part of a collaborative project between the Universities of East Anglia, Bath and Edinburgh, the focus of this research project was on the synthesis of components for chiral non-racemic metal-organic frameworks. It was envisioned that the actual assembly of the MOFs would be carried out by the Burrows group (University of Bath), and that the measurements of diffusion and adsorption properties to establish the movement of reagents into the pores of MOFs and the host-guest interactions would be performed in the Düren group (University of Edinburgh).

Interest in methodology to obtain enantiomerically (and diastereomerically) pure organic compounds increased dramatically especially in the pharmaceutical industry when it became clear that the enantiomers of certain drugs can behave differently in the body. One enantiomer may have the desired therapeutic effect whereas the other may even be toxic.¹ Thalidomide (Softeon), the cause of tragic birth defects, is a famous example.² Enantiomeric (and diastereomeric) purity ('single chirality' is a popular term often used to denote enantiomeric purity) is, of course, a hallmark of chiral organic compounds in nature. Virtually all naturally occurring amino acids, sugars, nucleic acids, *etc.*, are enantiomerically pure.

Many drugs, especially new ones on the market, are enantiomerically pure and often derived from natural sources.³ If material from a natural source (chiral pool) cannot serve as the source of enantiomerically pure material then the two most commonly used methods for the preparation of optically active compounds are resolution of racemates and asymmetric synthesis.¹ Much effort has been put into the development of asymmetric catalysts over the past two decades.⁴ In an industrial environment one is interested in the efficiency of the catalysis and also the opportunities for recovery and recycling of the catalyst. Heterogeneous catalysis is a popular approach within industry, and the preparation and application of porous materials such as chiral non-racemic zeolites has drawn the attention of researchers. However, the synthesis of enantiomerically pure zeolites is not trivial and no chiral zeolites have been synthesised in enantiopure form to date. This invites the development of new strategies for the preparation of chiral non-racemic porous materials.¹ Chiral non-racemic metal-organic frameworks present a unique class of porous and crystalline hybrid solids that have emerged as attractive

candidates for various enantioselective applications, including the enantioseparation of chiral compounds and asymmetric heterogeneous catalysis.⁵

The two most effective ways to synthesise optically active MOF catalysts are the following methods: precatalyst and post-synthetic modification method. In the precatalyst method the well-designed organic ligands containing asymmetric catalytic sites are connected with metal ions and are therefore directly incorporated into the MOF framework. In the post-synthetic modification method the chiral non-racemic MOF is constructed from enantiomerically pure organic linkers that contain primary and secondary functional groups. The primary functional groups direct the MOF assembly whereas the secondary functional groups undergo post-synthetic modification to convert them into catalytically active sites.⁶

It was envisaged that the design of appropriate ligands would allow the preparation of MOF catalysts for the subsequent investigation of heterogeneous asymmetric catalysis. Target ligand compounds chosen included highly rigid 1,4-bis(pyridin-4-ylethynyl)benzene (**74**), 7-bis(pyridin-4-ylethynyl)-1*H*-indene-2,2(3*H*)-dicarboxylate (**75**), and (2*S*,2'*S*)-dimethyl 3,3'-((1,4-phenylenebis(ethyne-2,1-diy))bis(4,1-phenylene))bis(2-((*t*-butoxycarbonyl)amino)propanoate) (**76**), as well as (*S*)-BINOL-derived organic linkers **77 – 86** (Figure 2.1).

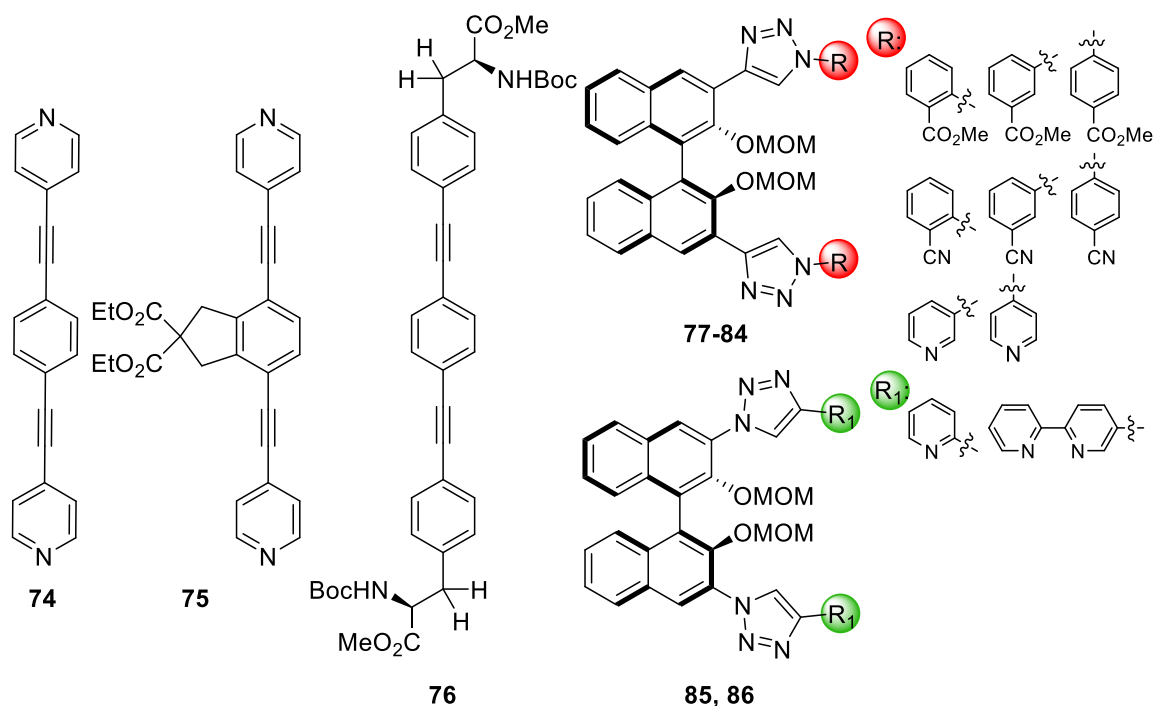
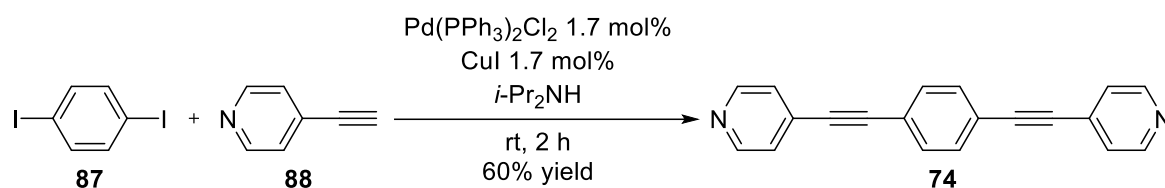


Figure 2.1 Organic building blocks as synthetic targets for optically active MOFs.

2.2. Synthesis of 1,4-bis(pyridin-4-ylethynyl)benzene (**74**)

Before initiating the multi-step synthesis of diester functionalised linker **75**, a preparation of a simpler analogue 1,4-bis(pyridin-4-ylethynyl)benzene (bpeb) (**74**) was explored. An investigation of its potential as a simple linker in the synthesis of a MOF was required in order to develop an efficient protocol that could serve as a ‘springboard’ towards the synthesis of a novel MOF assembled from **75**.

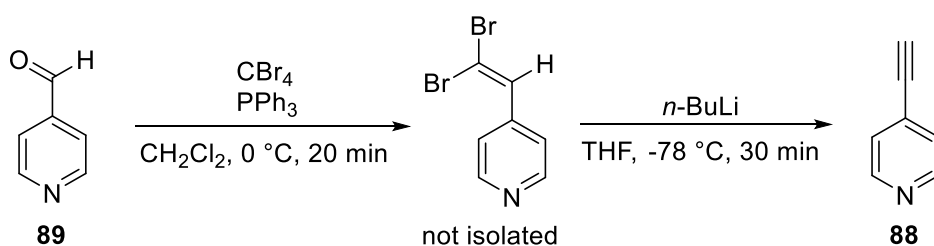
A literature survey revealed that Fasina *et al.*⁷ had already reported the synthesis of **74** via Sonogashira coupling starting from 1,4-diiodobenzene (**87**) and 4-ethynylpyridine (**88**) (Scheme 2.1).



Scheme 2.1 Synthesis of 1,4-bis(pyridin-4-ylethynyl)benzene (**74**) reported by Fasina *et al.*⁷

In order to examine the effectiveness of this protocol, 4-ethynylpyridine (**88**) needed to be synthesised. It was decided to employ Corey-Fuchs methodology to transform 4-pyridinecarboxyaldehyde (**89**) into an alkyne **88**.

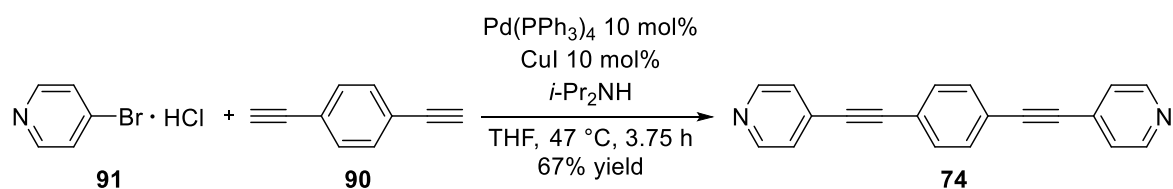
Adopting the procedure reported by Pelphrey *et al.*,⁸ the anticipated 4-ethynylpyridine (**88**) was synthesised (Scheme 2.2). However, its purification and handling proved to be problematic as **88** was prone to decomposition (light sensitive compound⁹). Therefore the yield of the reaction was not determined.



Scheme 2.2 Synthesis of 4-ethynylpyridine (**88**).

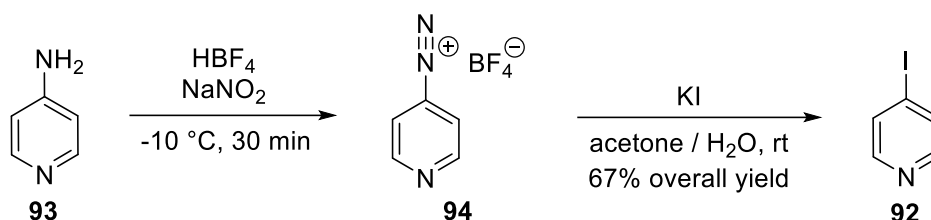
Discouraged by the complications of isolating pure **88**, it was decided to explore an alternative approach to the required 1,4-bis(pyridin-4-ylethynyl)benzene (**74**).

The protocol reported by Grunder *et al.*⁹ was of significance to this research. The preparation of 1,4-bis(pyridin-4-ylethynyl)benzene (**74**) in 67% yield employing 1,4-diethynylbenzene (**90**) and 4-bromopyridine hydrochloride (**91**) had been described (Scheme 2.3).



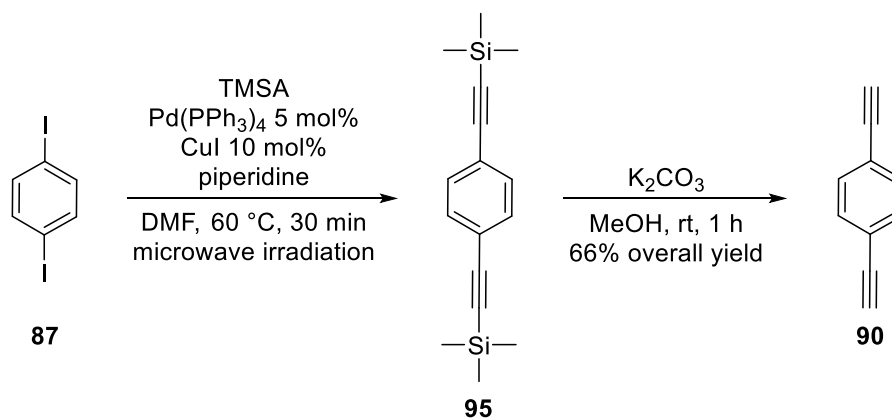
Scheme 2.3 Synthesis of **74** reported by Grunder *et al.*⁹

In the first instance, the use of commercially available 4-bromopyridine hydrochloride (**91**) as the starting material was considered. However, Bartucci *et al.*¹⁰ reported the tendency of **91** to polymerise and thus deliver inconsistent coupling results. Instead, multigram quantities of 4-iodopyridine (**92**) from 4-aminopyridine (**93**) *via* diazonium salt **94** were prepared in an overall 67% yield after two steps (**Scheme 2.4**) following a diazotization-iodination protocol that had been reported by Spivey *et al.*¹¹



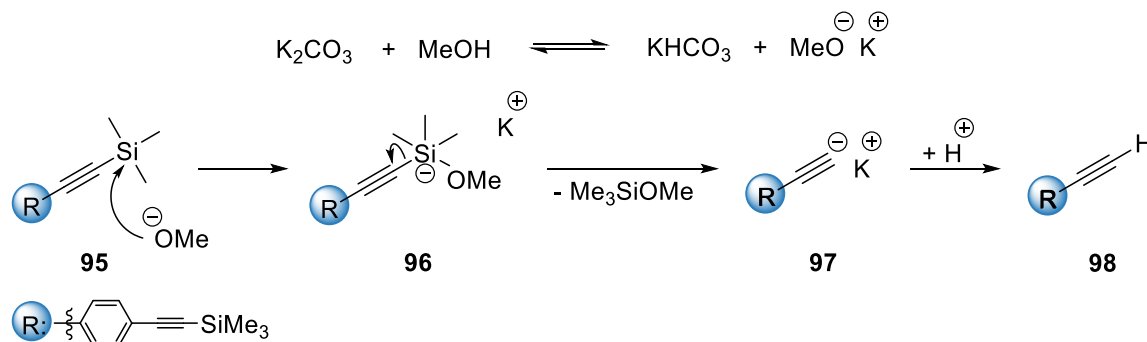
Scheme 2.4 Synthesis of 4-iodopyridine (**92**) reported by Spivey *et al.*¹¹

Having successfully prepared 4-iodopyridine (**92**), the synthesis of 1,4-diethynylbenzene (**90**) was investigated. Coupling of 1,4-diiodobenzene (**87**) with trimethylsilylacetylene under Sonogashira conditions¹² was expected to afford the intermediate **95**. Furthermore, conducting the Sonogashira coupling under microwave irradiation significantly reduced the reaction time from 16 hours at room temperature to 30 minutes at 60 °C. The deprotection of a trimethylsilyl protected alkyne **95** with potassium carbonate in methanol at room temperature generated 1,4-diethynylbenzene (**90**) after 1 hour in an overall 66% yield after two steps (**Scheme 2.5**).



Scheme 2.5 Synthesis of 1,4-diethynylbenzene (**90**).

The proposed mechanistic pathway for the removal of trimethylsilyl protecting group in a potassium carbonate / methanol mixture and generation of a terminal alkyne is outlined in **Scheme 2.6**.

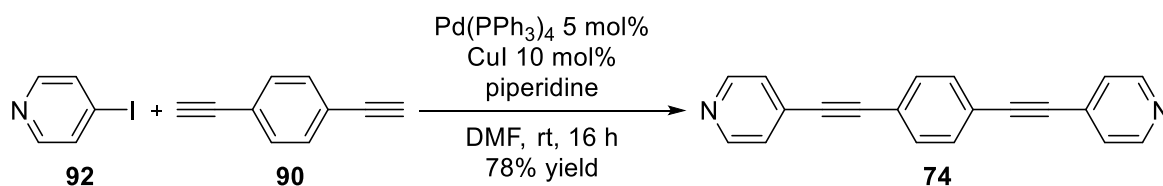


Scheme 2.6 The proposed mechanistic pathway for the deprotection of a trimethylsilyl protected alkyne in a potassium carbonate / methanol mixture.

Note that Platonov *et al.*,¹³ in a report published in 2002, found that an acid-base reaction between potassium carbonate and methanol results in generation of potassium bicarbonate and potassium methoxide.

In the proposed mechanistic pathway the cleavage of a C-Si bond proceeds *via* a nucleophilic attack of the *in situ* generated methoxide ion on silicon atom in **95** with the formation of a pentavalent methoxysiliconate intermediate **96**. The intermediate **96** decomposes with the loss of a trimethylmethoxysilane and an acetylide ion **97**, which undergoes protonation in the presence of methanol to generate the terminal alkyne **98**.

With 4-iodopyridine (**92**) and 1,4-diethynylbenzene (**90**) in hand, the synthesis of 1,4-bis(pyridin-4-ylethynyl)benzene (**74**) *via* a Sonogashira coupling was explored (**Scheme 2.7**).

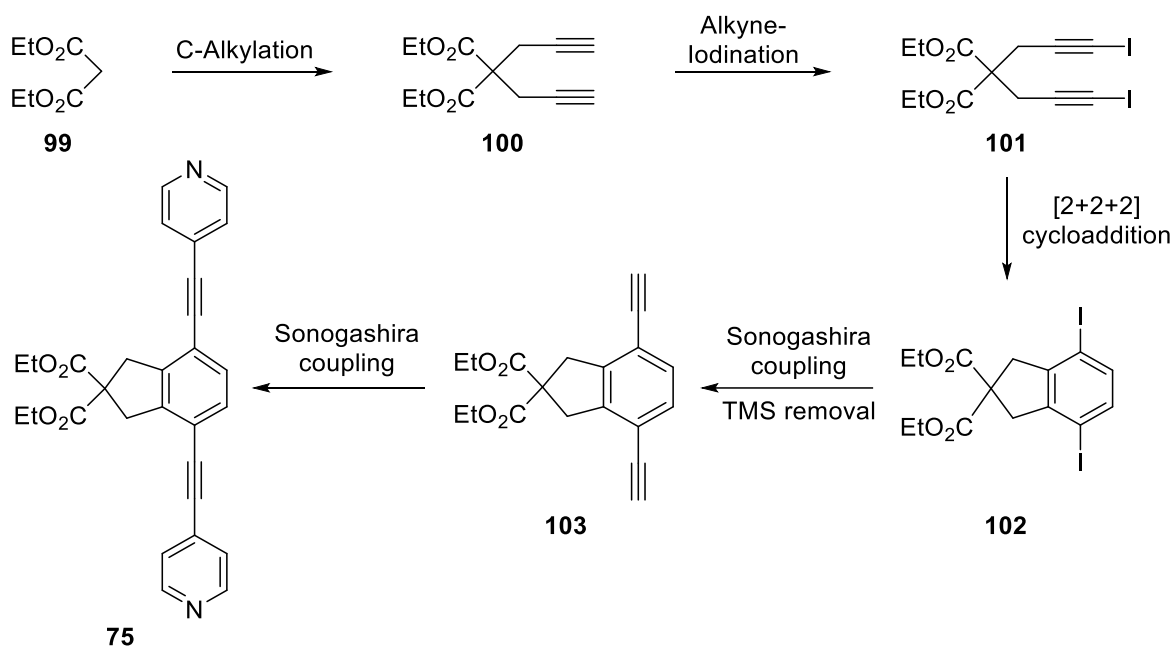


Scheme 2.7 Synthesis of 1,4-bis(pyridin-4-ylethynyl)benzene (**74**).

Coupling of 4-iodopyridine (**92**) to 1,4-diethynylbenzene (**90**) in the presence of tetrakis(triphenylphosphine)palladium(0) (5 mol%), copper(I) iodide (10 mol%) and piperidine (3 equivalents) in *N,N*-dimethylformamide afforded after 16 hours at room temperature the anticipated 1,4-bis(pyridin-4-ylethynyl)benzene (**74**) in 78% yield.

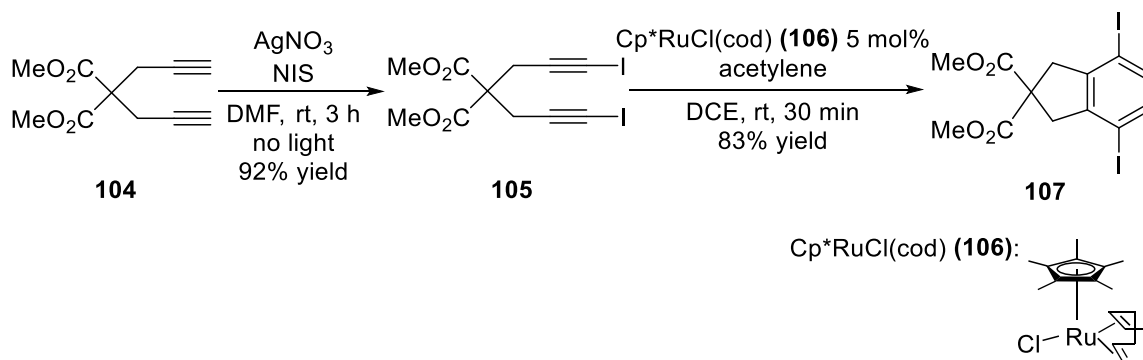
2.3. Synthesis of diethyl 4,7-bis(pyridin-4-ylethynyl)-1*H*-indene-2,2(3*H*)-dicarboxylate (75)

Having successfully prepared the bipyridine ligand **74** the synthesis of a more complex diester functionalised linker **75** was investigated. The strategy for synthesis of **75** included C-alkylation, iodination, [2+2+2] cycloaddition, Sonogashira coupling and trimethylsilyl group removal (Scheme 2.8).



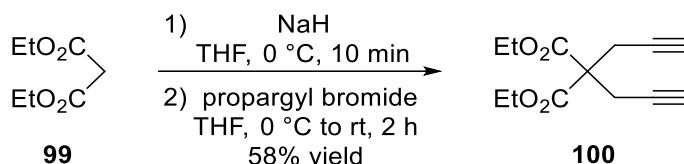
Scheme 2.8 Proposed synthesis of diester functionalised linker **75**.

The preparation of **100** was expected to be straightforward as protocols for its synthesis had been previously reported and have been in use since 1985.¹⁴ Compounds **101** and **102**, both unreported in the literature, were envisaged to be prepared following protocols published by Yamamoto *et al.*¹⁵ for an iodination of **104** and a [2+2+2] cycloaddition of **105** (Scheme 2.9) whereas compounds **103** and **75** were envisioned to be synthesised adopting the previously examined Sonogashira conditions and the deprotection of a trimethylsilyl protected alkyne in a potassium carbonate / methanol mixture (Scheme 2.5).



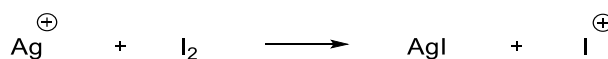
Scheme 2.9 Synthesis of **105** and **107** published by Yamamoto *et al.*¹⁵

As a starting point, diethyl 2,2-di(prop-2-yn-1-yl)malonate (**100**) was synthesised from commercially available diethyl malonate (**99**) according to a protocol published by Genin *et al.*¹⁶ The reaction of **99** with sodium hydride and subsequent treatment with propargyl bromide afforded propargylic diester **100** in 58% yield (**Scheme 2.10**).



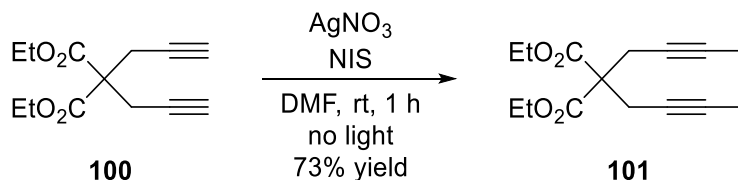
Scheme 2.10 Synthesis of diethyl 2,2-di(prop-2-yn-1-yl)malonate (**100**).

With diethyl 2,2-di(prop-2-yn-1-yl)malonate (**100**) in hand, its conversion into diethyl 2,2-bis(3-iodoprop-2-yn-1-yl)malonate (**101**) utilising the protocol reported by Yamamoto *et al.*¹⁵ was explored. Employing **100** in an attempted silver-catalysed iodination using 10 mol% of silver nitrate and *N*-iodosuccinimide (3 equivalents) in *N,N*-dimethylformamide did not provide the anticipated 2,2-bis(3-iodoprop-2-yn-1-yl)malonate (**101**). It was suspected that the catalyst was deactivated by molecules of iodine present in the reaction mixture (**Scheme 2.11**).



Scheme 2.11 Deactivation of silver catalyst by traces of iodine.

Repeating the protocol, but using one equivalent of silver nitrate instead of 10 mol% afforded diethyl 2,2-bis(3-iodoprop-2-yn-1-yl)malonate (**101**) in 73% yield (**Scheme 2.12**).



Scheme 2.12 Conversion of **100** into 2,2-bis(3-iodoprop-2-yn-1-yl)malonate (**101**).

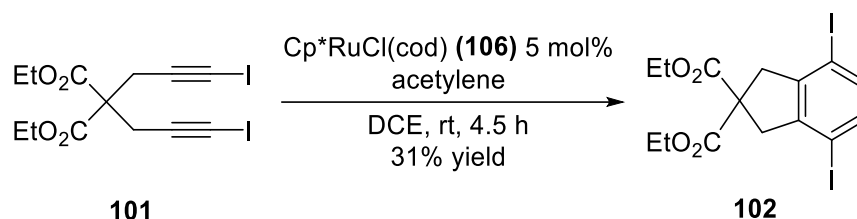
The ¹H-NMR spectrum of **101** revealed the disappearance of a triplet at δ 2.03 ppm characteristic for the hydrogen atom of terminal alkynes indicating that iodine substitution had taken place. Due to a heavy-atom effect, the ¹³C-NMR spectrum displayed a significant upfield shift for the iodine-bearing carbon (δ -2.2 ppm).

With regard to the mechanism, it is postulated that due to the coordination of a silver ion to the terminal alkyne and activation of the *sp* carbon-hydrogen bond alkynyl silver is formed *in situ*. This intermediate is most probably nucleophilic enough to react with the *N*-iodosuccinimide present in the reaction mixture to furnish the desired iodoalkyne and succinimide as a by-product.¹⁷

Having successfully prepared diethyl 2,2-bis(3-iodoprop-2-yn-1-yl)malonate (**101**), the synthesis of diethyl 4,7-diiido-1*H*-indene-2,2-(3*H*)-dicarboxylate (**102**) *via* a [2+2+2]

cycloaddition of **101** adopting Yamamoto's procedure¹⁵ was investigated.

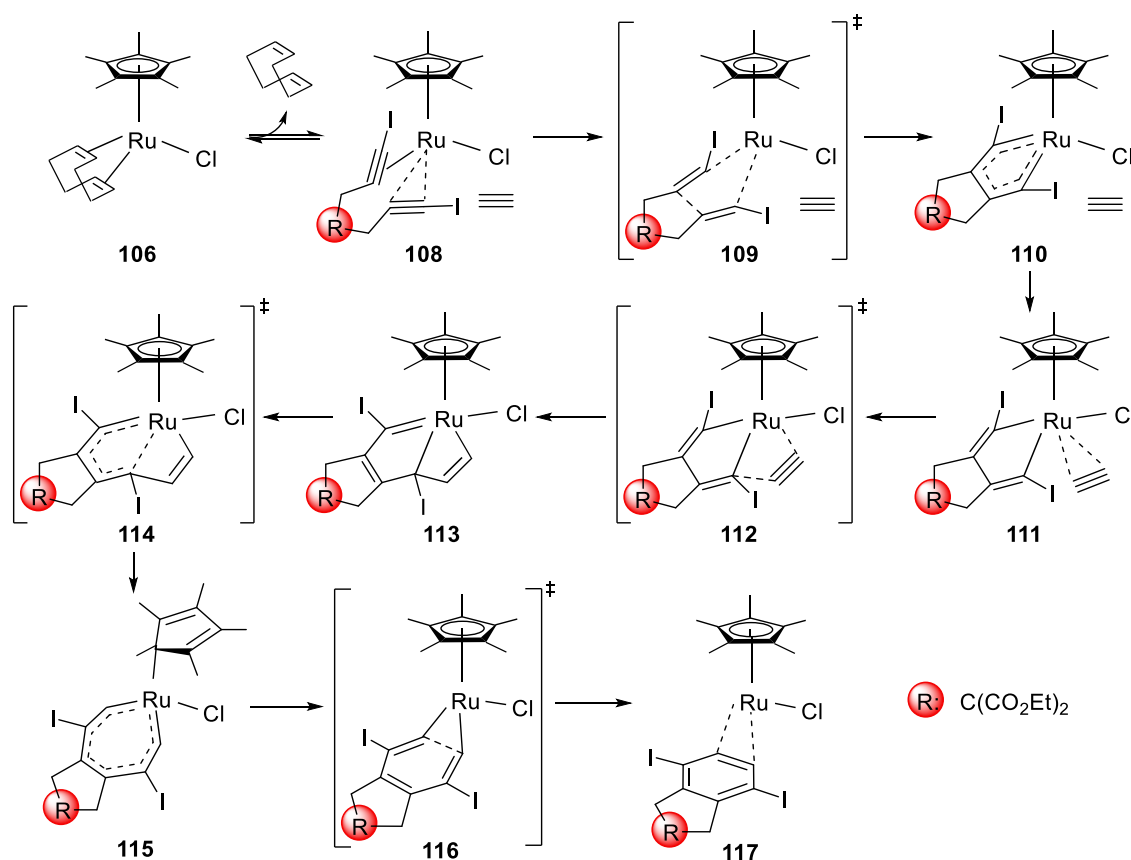
Chloro(pentamethylcyclopentadienyl)(cyclooctadiene)ruthenium(II) (**106**) catalysed the cycloaddition of **101** with acetylene in 1,2-dichloroethane at room temperature affording **102** in 31% yield after 4.5 hours (TLC analysis indicated presence of the starting material) (**Scheme 2.13**).



Scheme 2.13 The Cp^{*}RuCl(cod)-catalysed [2+2+2] cycloaddition of **101** with acetylene.

The structure of **102** was verified by analysis of the ¹H- and ¹³C-NMR spectral data. In addition to the expected absorptions for the ethyl groups and methylene groups of the 5-membered ring the ¹H-NMR spectrum displayed a singlet at δ 7.24 ppm for the aromatic protons, whereas ¹³C-NMR spectrum revealed peaks at δ 145.3, 138.1 and 92.7 ppm for the aromatic carbons.

The proposed alkyne cyclotrimerisation pathway reported by Yamamoto *et al.*¹⁸ is outlined in **Scheme 2.14**.



Scheme 2.14 The proposed mechanistic pathway for the [2+2+2] cycloaddition of **101** with acetylene reported by Yamamoto *et al.*¹⁸

The chloro(pentamethylcyclopentadienyl)(cyclooctadiene)ruthenium(II) (**106**) releases the labile 1,5-cyclooctadiene (cod) ligand and coordinates two alkyne units to afford **108**. Bisalkyne complex **108** is converted *via* a transition state **109** into the highly delocalised ruthenacycle **110**. The ruthenacycle **110**, after coordinating one molecule of acetylene, is converted into ruthenacycle-(alkyne) complex **111**. The acetylene insertion takes place as a result of [5+2] cycloaddition of **111** with the acetylene *via* a transition state **112** to afford the ruthenabicyclo[3.2.0]-heptatriene **113**. Consecutive breakage of the central ruthenium-carbon bond and ring enlargement proceeds *via* transition state **114** to afford ruthenacycloheptatriene complex **115**. The reductive elimination of **115** *via* transition state **116** leads to a complex **117**.

Repeating the same protocol, but using *N,N*-dimethylformamide (solubility of acetylene in *N,N*-dimethylformamide at 25 °C 1.501 mol L⁻¹ bar⁻¹ versus solubility in 1,2-dichloroethane at 25 °C 0.218 mol L⁻¹ bar⁻¹)¹⁹ as solvent increased the yield of the reaction to 38%.

Among various transition metal catalysts for the [2+2+2] cycloaddition reaction, rhodium catalysts are usually the most effective for promotion of the acetylene cyclotrimerisation.²⁰ The first generation of rhodacyclopentatriene complexes from 1,6-diynes and synthesis of new aromatic systems was reported by Müller in 1974.²¹ In 1982 Grigg *et al.*²² reported the first catalytic acetylene trimerisation utilising chlorotris(triphenylphosphine)rhodium(I) (Wilkinson's catalyst) without trimerisation of the monalkyne and no, or only minor, dimerisation of 1,6-diynes. Since this discovery, rhodium catalysts have been the most heavily investigated for a [2+2+2] cycloaddition of alkynes.

It was thought important for this research project to investigate the efficiency of various rhodium catalysts for a [2+2+2] cycloaddition of **101** with acetylene (**Table 2.1**).

Catalyst	mol%	Solvent	Temperature	Time (h)	Yield of 102 (%)
[Rh(cod) ₂]OTf	5	DMF	rt	4.5	0
[(C ₂ H ₄) ₂ RhCl] ₂	5	DMF	rt	4.5	0
HRh(CO)(PPh ₃) ₃	5	DMF	rt	4.5	0
Rh(CO) ₂ (C ₅ H ₇ O ₂)	5	DMF	rt	4.5	6
Rh(PPh ₃) ₃ Cl	5	DMF	rt	4.5	8
Cp*RuCl(cod)	5	DMF	rt	4.5	38

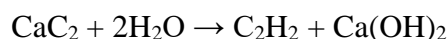
Table 2.1 Attempted [2+2+2] cycloaddition reaction in *N,N*-dimethylformamide using various rhodium catalysts.

However, none of the employed rhodium catalysts delivered better results for the [2+2+2] cycloaddition of **101** with acetylene and the starting material **101** was recovered in each reaction (based on TLC analysis).

Concerned by the low conversion of **101** it was decided to repeat the protocol with chloro(pentamethylcyclopentadienyl)(cyclooctadiene)ruthenium(II) (**106**) in 1,2-dichloroethane (*N,N*-dimethylformamide was abandoned due to the more difficult work-up), but this time employing a syringe pump to deliver diethyl 2,2-bis(3-iodoprop-2-yn-1-yl)malonate (**101**) over 1 hour to the reaction mixture. It was thought that slow addition of **101** to the catalyst solution would ensure its complete consumption during the oxidative cyclisation (rate-determining step) to generate the ruthenacycle intermediate **110**. Unfortunately, this had no positive effect on the reaction yield, which was only 28%. In a further modification of the procedure, the solvent was degassed *via* freeze-pump-thaw. However, this also failed to improve the yield of the reaction (30%).

With a poor yield but no evidence of the formation of any by-products during the reaction (based on TLC analysis), the possibility of catalyst **106** deactivation was considered. To investigate this hypothesis, the protocol (**Scheme 2.13**) delivering catalyst **106** in two portions (2.5 mol% each) was repeated. Subsequently, product **102** was isolated in 48% yield. Changing the percentage of catalyst **106** from 5 mol% to 10 mol% (delivered in two portions) further increased the yield of the reaction to 55%. These results substantiated the belief that chloro(pentamethylcyclopentadienyl)(cyclooctadiene)ruthenium(II) (**106**) was deactivated during the reaction. It was thought that the system of traps used for the purification²³ of the technical grade acetylene was not efficient enough and that the impurities still present in acetylene accounted for the deactivation of catalyst **106**.

Different means to generate high purity acetylene were explored. It was decided to consider the manufacturing process in which acetylene is produced by the chemical reaction between calcium carbide and water (**Scheme 2.15**).



Scheme 2.15 Production of acetylene *via* the reaction of calcium carbide with water.

Although it was possible to obtain acetylene gas *via* this method, the high risk of explosion (the reaction produces a considerable amount of heat), the difficulty in maintaining a stable flow of the gas and low delivery pressure discouraged use of this approach. A search for alternative methods of generating high purity acetylene was necessary.

Hyman and Arp²⁴ reported that commercially available acetylene cylinders may contain high concentrations of various contaminants depending on the source of the gas (**Table 2.2**).

Gas	H ₂	O ₂	N ₂	CH ₄	C ₂ H ₄	C ₂ H ₆	C ₃ H ₈	PH ₃	Acetone
Concentration (μL / L)	2087	65	7971	732	49	68	222	420	11377

Table 2.2 Contaminants present in commercial grade acetylene reported by Hyman and Arp.²⁴

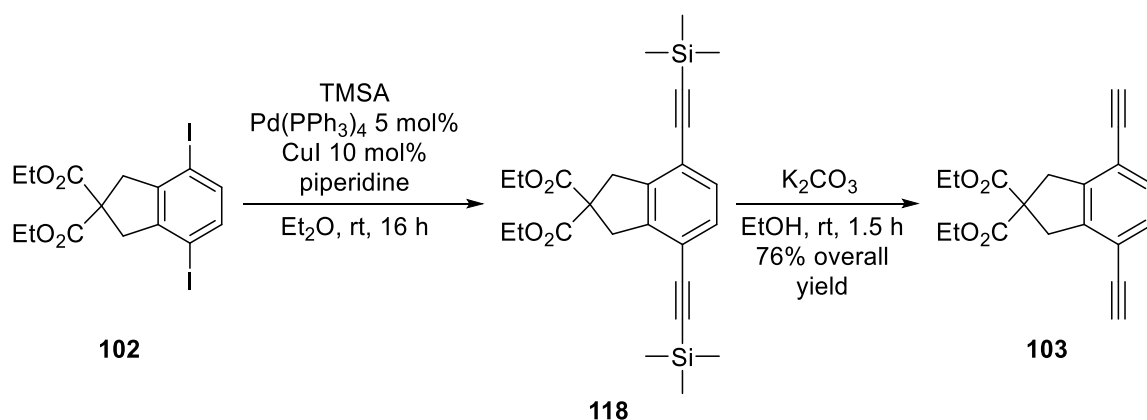
Ammonia and hydrogen sulfide were also mentioned in this report²⁴ as common contaminants in acetylene. However, because they were not analysed and data about the levels of concentrations were not provided those contaminants are not included in the **Table 2.2**.

Acetone, ammonia and phosphine, as well as hydrogen sulfide were considered the contaminants that could account for catalyst **106** deactivation. It was thought that those compounds could coordinate to the ruthenium catalyst **106** causing the loss of its catalytic activity.

To increase the efficiency of the reaction, it was important to establish a reliable system for the purification of acetylene and therefore eliminate catalyst **106** deactivation. Attempts at optimising the purification procedure proved to be successful when the following system of traps was applied and the acetylene gas was successively passed through: water, concentrated sulfuric acid (two Drechsel bottles), 0.2 M aqueous potassium permanganate solution, water, and a drying tube containing indicating silica gel.

Repetition of the [2+2+2] cycloaddition procedure (**Scheme 2.13**) using diethyl 2,2-bis(3-iodoprop-2-yn-1-yl)malonate (**101**), but now with application of the aforementioned purification process of acetylene together with 10 mol% of chloro(pentamethylcyclopentadienyl)(cyclooctadiene)ruthenium(II) (**106**) afforded diethyl 4,7-diiodo-1*H*-indene-2,2(3*H*)-dicarboxylate (**102**) in a reasonable 65% yield after 4.5 hours.

With a reliable protocol for the synthesis of **102** in hand, the preparation of diethyl 4,7-diethynyl-1*H*-indene-2,2(3*H*)-dicarboxylate (**103**) was investigated (**Scheme 2.16**).



Scheme 2.16 Synthesis of 4,7-diethynyl-1*H*-indene-2,2(3*H*)-dicarboxylate (**103**).

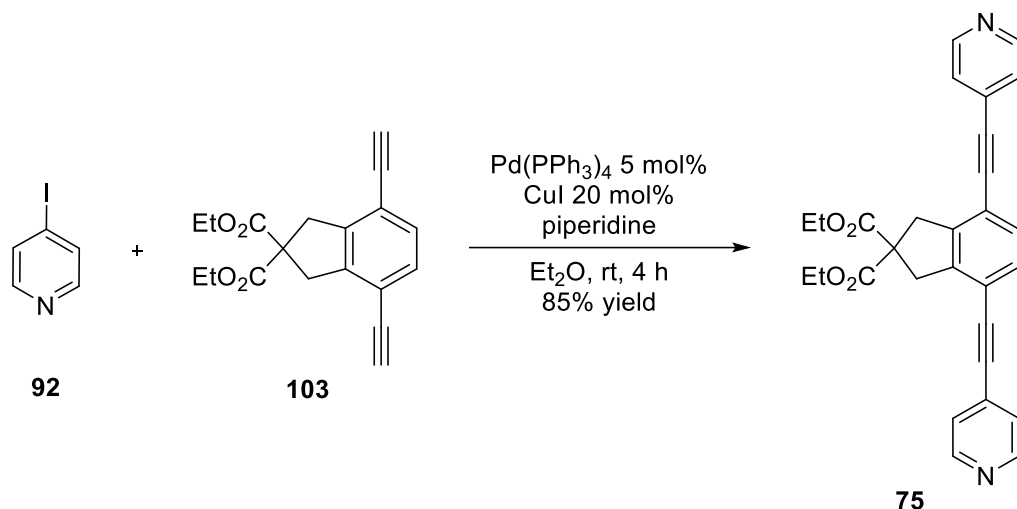
Coupling of **102** with trimethylsilylacetylene in the presence of tetrakis(triphenylphosphine)palladium(0) (5 mol%), copper(I) iodide (10 mol%) and piperidine (3 equivalents) in diethyl ether afforded after 16 hours at room temperature the desired intermediate **118** (not isolated).

In the first instance, *N,N*-dimethylformamide was employed as the reaction solvent. However, more impurities were observed in the reaction mixture (based on TLC analysis), which discouraged the use of **118** in the C-silyl group deprotection without purification. Changing the solvent of the reaction from *N,N*-dimethylformamide to diethyl ether increased the purity of **118**. Perhaps in a low polarity solvent one or more of the components of the reaction is less soluble and therefore inhibits the formation of any by-products of the reaction.

First attempts at removing trimethylsilyl groups from **118** with potassium carbonate in methanol did not provide the desired product **103**. This seemingly straightforward transformation afforded a mixture of compounds. The $^1\text{H-NMR}$ spectrum of the impure mixture revealed the presence of a singlet at δ 3.70 ppm. Initially it was thought that this additional peak may arise due to the residual methanol solvent. However, the $^1\text{H-NMR}$ chemical shift for methanol in CDCl_3 is δ 3.49 ppm. It was suspected that the product had undergone partial transesterification under the conditions for the trimethylsilyl group removal. Repeating the reaction protocol using ethanol in place of methanol eliminated the problem and allowed the synthesis of **103** in an overall 76% yield after two steps.

The $^1\text{H-}$ and $^{13}\text{C-NMR}$ spectral data were in accordance with the structure of **103**. The $^1\text{H-NMR}$ spectrum displayed a singlet at δ 3.31 ppm consistent with the presence of a hydrogen atom of the terminal alkynes. Furthermore the $^{13}\text{C-NMR}$ spectrum revealed peaks at δ 82.4 and 81.4 ppm for the alkyne carbons.

The last step of the synthetic route to generate diethyl 4,7-bis(pyridin-4-ylethynyl)-1*H*-indene-2,2(3*H*)-dicarboxylate (**75**) involved a coupling of 4-iodopyridine (**92**) with **103** by means of a Sonogashira coupling (**Scheme 2.17**).



Scheme 2.17 Synthesis of **75** employing a Sonogashira coupling.

Following the previously established procedure for Sonogashira coupling (**Scheme 2.16**) the anticipated product **75** was synthesised in a disappointing 34% yield (TLC analysis indicated presence of starting materials).

As an explanation for the poor yield and low conversion of starting materials, an inhibition of the palladium catalytic cycle by coordination of the terminal alkyne moiety present in **103** to active palladium(0) species prior to the oxidative addition step was considered. To confirm this hypothesis, the protocol was repeated whereby diethyl 4,7-diethynyl-1*H*-indene-2,2(3*H*)-dicarboxylate (**103**) was added after pre-stirring the rest of the components of the reaction for 30 minutes. By doing so, the competing process of the coordination of terminal alkynes to active palladium(0) species should be inhibited. Consistent with this analysis the anticipated product **75** was obtained in 68% yield. Changing the percentage of copper(I) iodide from 10 mol% to 20 mol% further increased the yield of the reaction to 85% yield.

The analysis of physicochemical data confirmed that **75** had been synthesised. The melting point of **75** was 175 – 177 °C. The FT-IR spectrum displayed the characteristic peak for the carbonyl group at 1727 cm⁻¹. The ¹H-NMR spectrum (**Figure 2.2**) revealed a doublet at δ 8.63 ppm for the aromatic protons adjacent to the nitrogen atom of the pyridines and a multiplet at δ 7.43 – 7.36 ppm for the remaining aromatic protons of the pyridines and aromatic protons of the benzene moiety. A quartet and a triplet at δ 4.26 and 1.29 ppm respectively were observed for the protons of the ester groups, and a singlet at δ 3.79 ppm

for the protons of the methylene groups of the 5-membered ring. Furthermore the ^{13}C -NMR spectrum (**Figure 2.3**) displayed peaks at δ 171.4, 62.3 and 14.2 ppm for the carbons of the ester groups, peaks at δ 150.0, 143.3, 131.1, 130.7, 125.7 and 119.3 ppm for the aromatic carbons, peaks at δ 59.1 and 40.8 ppm for the α -carbon of the ester groups and the carbon of the methylene groups of the 5-membered ring respectively, and peaks at δ 92.1 and 91.5 ppm for the alkyne carbons. High-resolution mass spectrometry (NSI) revealed m/z 465.1804 (calculated for $\text{C}_{29}\text{H}_{25}\text{N}_2\text{O}_4$ [M+H] 465.1809) verifying the identity of **75**.

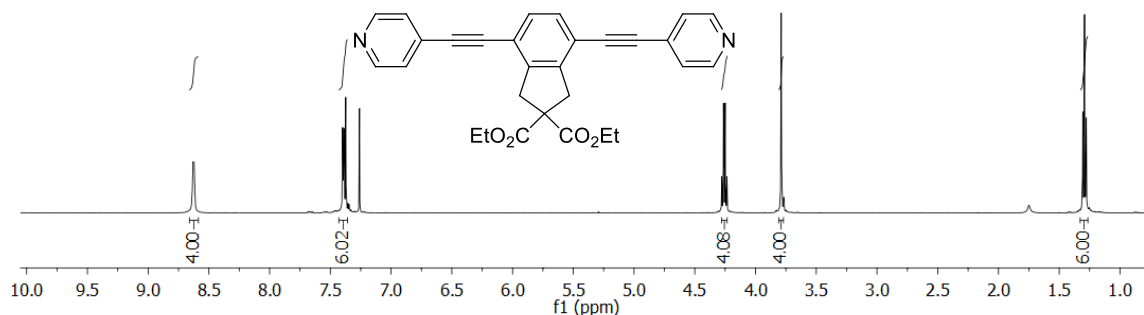


Figure 2.2 The ^1H -NMR (CDCl_3) spectrum of **75**.

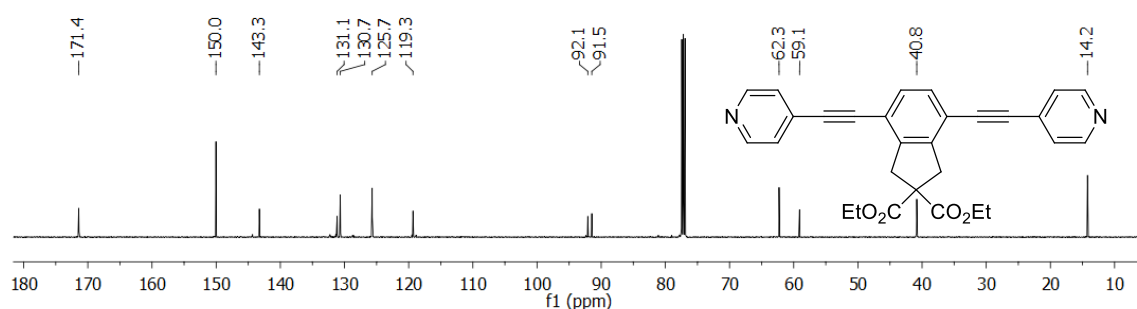


Figure 2.3 The ^{13}C -NMR (CDCl_3) spectrum of **75**.

2.4. Synthesis of (2*S*,2'*S*)-dimethyl 3,3'-((1,4-phenylenebis(ethyne-2,1-diyl))bis(4,1-phenylene))bis(2-((*t*-butoxycarbonyl)amino)propanoate) (**76**)

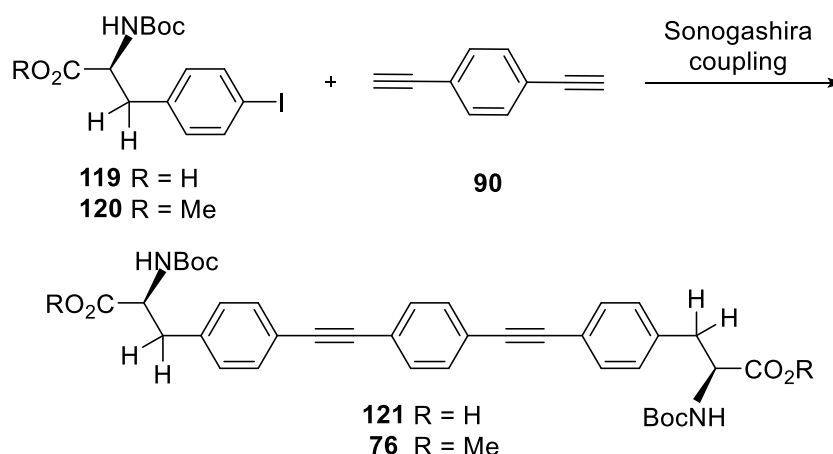
The physical and chemical characteristics of MOFs make them potential candidates for biological and medical applications such as drug delivery and storage, an area that has emerged only recently.^{25,26}

MOFs are a unique class of porous materials with a wide range of compositions and structures, tuneable pore sizes and flexible networks; characteristics that make them more advantageous applicants for drug delivery and storage comparing to other carriers like inorganic porous solids (zeolites) or organic polymers.²⁷ Due to their very high porosity, large loadings of biologically active molecules could be entrapped within the pores and delivered into the body. The possibility of adjusting functional groups of the framework

could lead to opportunities of controlling the interactions with guest molecules and therefore tune the drug release process into the environment.²⁵

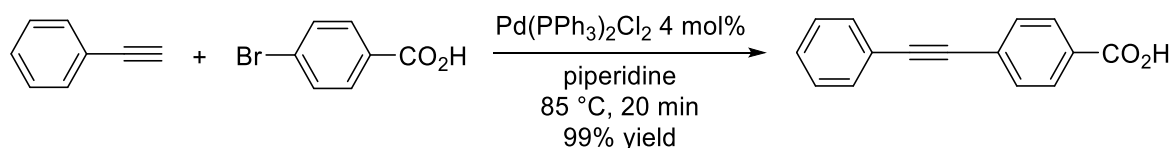
One of the most challenging aspects in drug delivery studies is to find an efficient way of delivering the drugs into the body using non-toxic nanocarriers.²⁶ To make MOFs more attractive candidates for biological and medical applications, two synthetic methods became of a great interest; MOFs built from endogenous organic linkers derived from amino acids and MOFs built from the drugs themselves as linkers.²⁵

Owing to this interest in the development of a potential bioMOF, the synthesis of a (*S*)-tyrosine-derived organic linker was envisaged. It was planned to use (*S*)-2-((*t*-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoic acid (**119**) or its methyl ester **120** and previously prepared 1,4-diethynylbenzene (**90**) in a Sonogashira coupling to generate the optically active α -amino acid-based organic linker **121** or **76** (Scheme 2.18).



Scheme 2.18 Proposed synthesis of optically active α -amino acid-based organic linker **121** or **76**.

A literature survey revealed that Gu *et al.*²⁸ had reported a protocol for a copper-free Sonogashira coupling of haloaryl carboxylic acids with terminal alkynes that avoids the carboxyl group protection and deprotection steps (Scheme 2.19).



Scheme 2.19 Copper-free Sonogashira coupling reported by Gu *et al.*²⁸

Before undertaking a copper-free Sonogashira coupling, the *N*-Boc protection of an amino moiety of (*S*)-2-amino-3-(4-iodophenyl)propanoic acid (readily available in the research laboratory and prepared by former PhD student) was required.

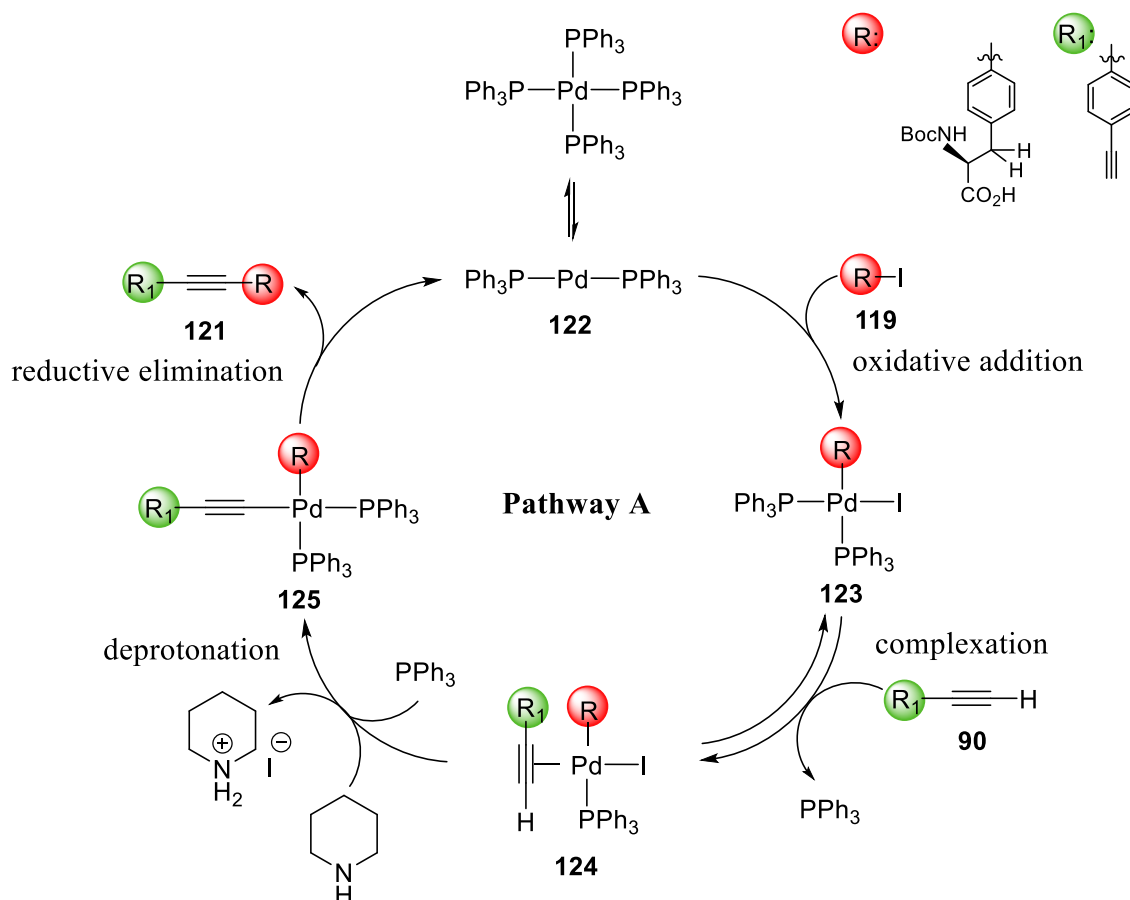
Following a procedure reported by Shendage *et al.*,²⁹ (*S*)-2-((*t*-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoic acid (**119**) was prepared. Reaction of (*S*)-2-amino-3-(4-

iodophenyl)propanoic acid with sodium bicarbonate and di-*t*-butyl dicarbonate in a mixture of tetrahydrofuran and water afforded, after 16 hours, **119** in 77% yield. The ^1H - and ^{13}C -NMR spectral data corresponded closely to those reported in the literature and confirmed the structure of **119**.³⁰

With (*S*)-2-((*t*-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoic acid (**119**) in hand, the use of a copper-free Sonogashira coupling for the synthesis of optically active α -amino acid-based organic linker **121** was investigated.

Two mechanistic pathways have been considered for a copper-free Sonogashira coupling.³¹ They share the first two steps; the generation of an active and coordinatively unsaturated palladium(0) species **122** and an oxidative addition of the aryl halide to generate **123**. The next step depends on the amine and an alkyne used in the reaction. If the amine is a poorer ligand than the alkyne for the palladium centre in **123** the reaction proceeds *via* **Pathway A** (**Scheme 2.20**). However, if the amine is a better ligand than the competing alkyne for the palladium centre in **123**, the reaction proceeds *via* **Pathway B** (**Scheme 2.21**).

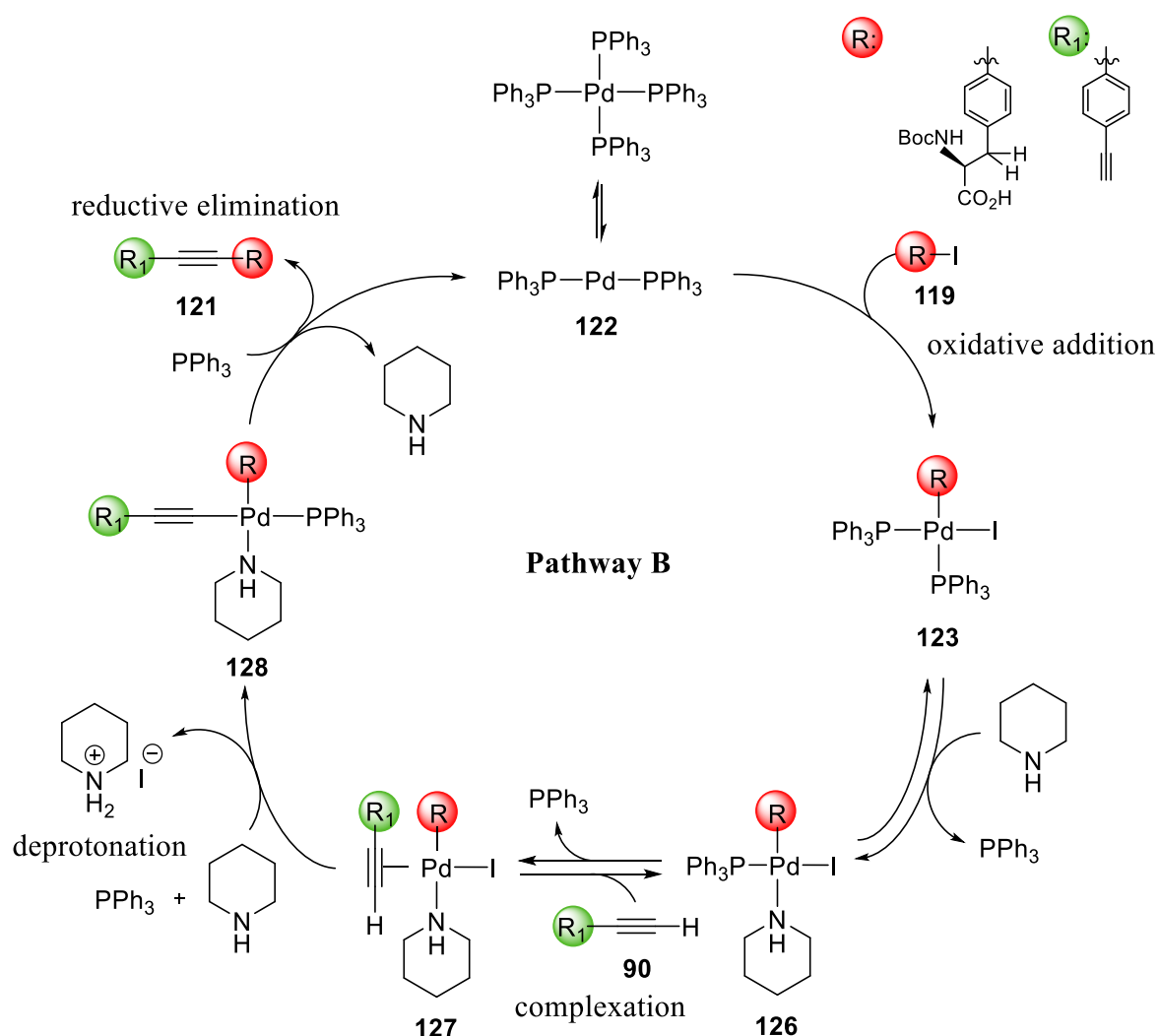
The proposed mechanistic **Pathway A** for a copper-free Sonogashira coupling reported by Tougeri *et al.*³² is outlined in **Scheme 2.20**.



Scheme 2.20 The proposed mechanistic **Pathway A** for a copper-free Sonogashira coupling reported by Tougeri *et al.*³²

Tetrakis(triphenylphosphine)palladium(0), introduced as a catalyst precursor, is converted to an active palladium(0) species **122** allowing the oxidative addition of (*S*)-2-((*t*-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoic acid (**119**) to generate palladium(II) complex **123**. The complexation of 1,4-diethynylbenzene (**90**) to **123** and release of triphenylphosphine ligand affords palladium(II)-alkyne complex **124**. Deprotonation of the alkyne by piperidine generates palladium(II)-alkyne complex **125** (rate-determining step), which undergoes a reductive elimination affording the coupling product **121** and the active palladium(0) species **122**.

The proposed mechanistic **Pathway B** for a copper-free Sonogashira coupling reported by Tougeri *et al.*³² is outlined in **Scheme 2.21**.

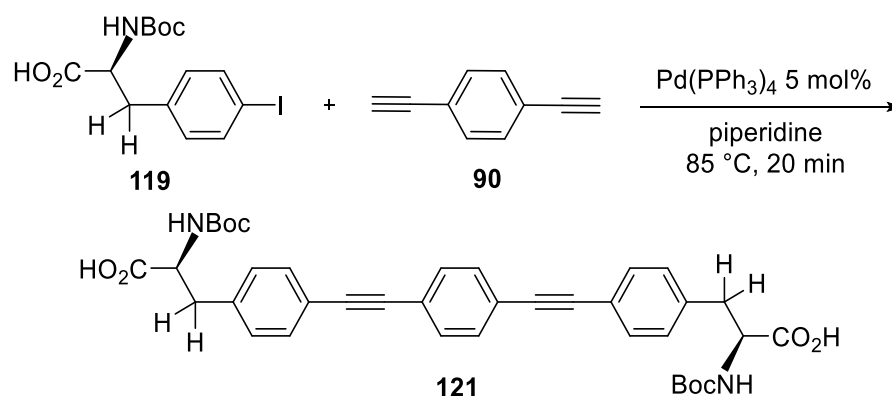


Scheme 2.21 The proposed mechanistic **Pathway B** for a copper-free Sonogashira coupling reported by Tougeri *et al.*³²

Tetrakis(triphenylphosphine)palladium(0) is converted to an active palladium(0) species **122**. An oxidative addition of (*S*)-2-((*t*-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoic

acid (**119**) to **122** affords palladium(II) complex **123**. Substitution of a triphenylphosphine ligand in **123** by piperidine generates a palladium(II)-amine intermediate **126** (rate-determining step). Complexation of the palladium centre in **126** by 1,4-diethynylbenzene (**90**) and loss of a triphenylphosphine ligand leads to the formation of a palladium(II)-alkyne complex **127**. Deprotonation of the coordinated terminal alkyne in **127** by piperidine affords a palladium(II)-alkyne complex **128**, which releases the desired product **121** by a reductive elimination step regenerating the active palladium(0) species **122**.

Adopting the procedure reported by Gu *et al.*,²⁸ the desired optically active α -amino acid-based organic linker **121** was synthesised. Coupling of **119** with 1,4-diethynylbenzene (**90**) in the presence of tetrakis(triphenylphosphine)palladium(0) (5 mol%) and excess of piperidine (10 equivalents) at 85 °C afforded after 20 minutes the desired (*S*)-tyrosine-based organic linker **121** (Scheme 2.22) as judged from inspection of the ¹H-NMR spectrum of the impure **121**.



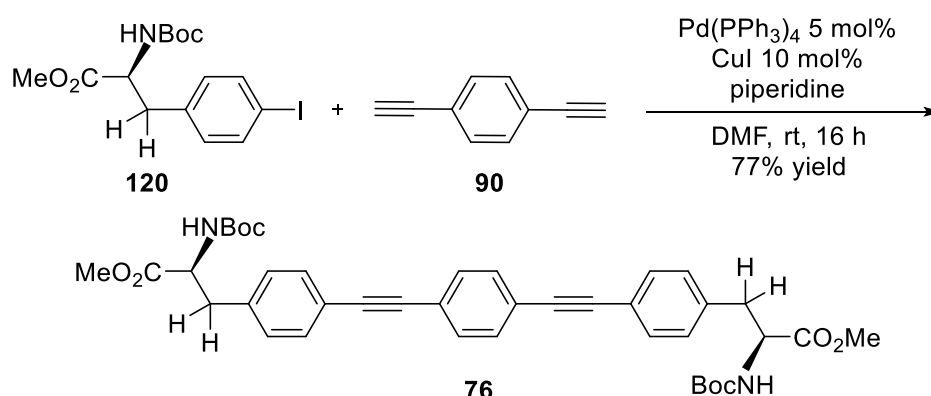
Scheme 2.22 Synthesis of **121** via a copper-free Sonogashira coupling.

Although the generation of **121** via a copper-free Sonogashira coupling was possible, difficulties in purifying it were encountered and therefore the yield of the reaction was not determined. In view of this difficulty the decision was taken to employ the methyl ester of **119** instead of the free carboxylic acid and synthesise the methyl ester protected optically active α -amino acid-based organic linker **76** under standard Sonogashira coupling conditions.

In order to use (*S*)-methyl 2-amino-3-(4-iodophenyl)propanoate (prepared by a former PhD student and therefore readily available in the research laboratory) in a Sonogashira coupling it was necessary to first protect its amino moiety. The *N*-Boc protection was performed following the previously described protocol reported by Shendage *et al.*²⁹ affording (*S*)-methyl 2-((*t*-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoate (**120**) in 75% yield. The ¹H-NMR spectrum revealed a singlet at δ 1.42 ppm for the protons of the

N-Boc protecting groups, whereas the ^{13}C -NMR spectrum displayed peaks at δ 155.1, 80.2 and 28.4 ppm for the carbons of the *N*-Boc protecting groups (no ^{13}C -NMR spectral data have been previously reported in the literature).

With (*S*)-methyl 2-((*t*-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoate (**120**) in hand, standard Sonogashira coupling conditions were explored. Coupling of **120** to 1,4-diethynylbenzene (**90**) in the presence of tetrakis(triphenylphosphine)palladium(0), copper(I) iodide and piperidine (3 equivalents) in *N,N*-dimethylformamide afforded after 16 hours at room temperature **76** in 77% yield (**Scheme 2.23**). The structure of **76** was verified by analysis of the physicochemical data that corresponded closely to those reported in the literature.³³

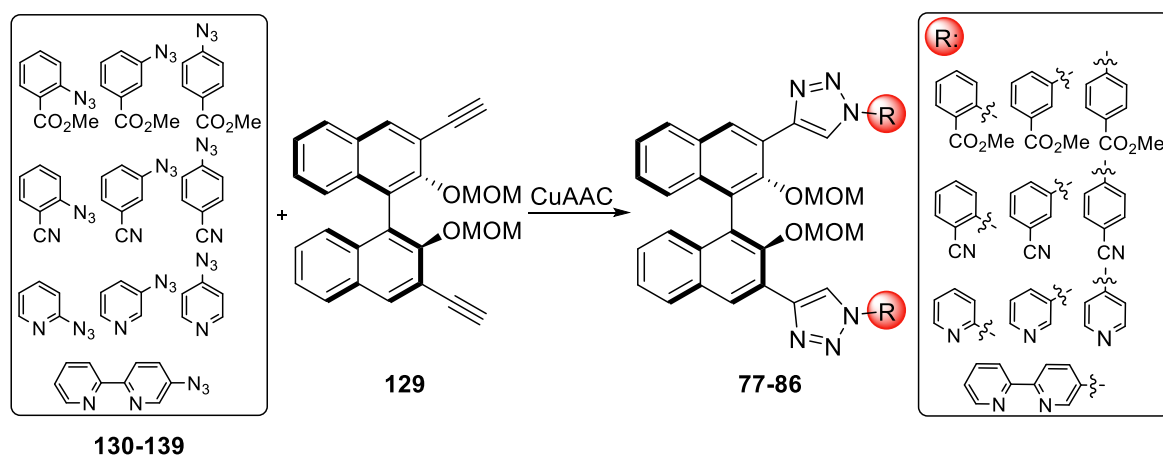


Scheme 2.23 Synthesis of (*S*)-tyrosine-derived organic linker **76**.

2.5. Synthesis of (*S*)-BINOL-derived organic linkers **77** – **86**

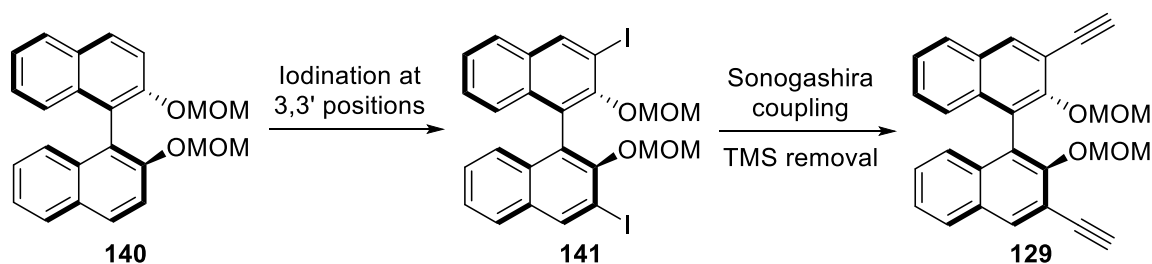
It was of interest to this research project to synthesise organic building blocks derived from an axially chiral non-racemic [1,1'-binaphthalene]-2,2'-diol (BINOL) as it is one of the most widely used chiral ligands in asymmetric catalysis.³³ This would allow the preparation of optically active MOFs by direct incorporation of the axially chiral non-racemic [1,1'-binaphthalene]-2,2'-diol into the MOF framework.

The synthetic approach to (*S*)-BINOL-derived building blocks **77** – **86** was based on the idea that this common building block could be modified readily into derivatives by use of 'click chemistry', namely the synthesis of [1,4]-triazoles. The approach comprises three parts (**Scheme 2.24**). The first part focused on the synthesis of (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**), the second on the preparation of an array of aryl azides **130** – **139**, and the third on the copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) of these azides to **129** to afford axially chiral (*S*)-BINOL-derived [1,4]-triazole ligands **77** – **86**.



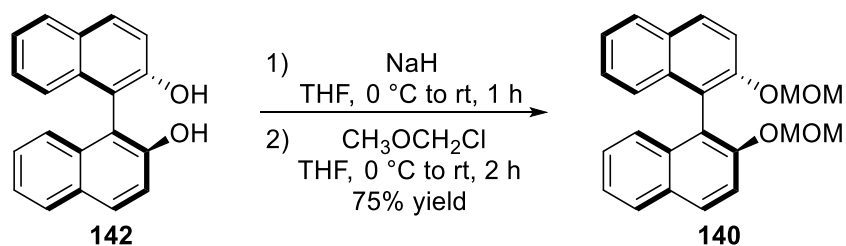
Scheme 2.24 Proposed synthesis of an array of (*S*)-BINOL-derived organic linkers **77 – 86**.

It was envisaged that the synthesis of (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**) from (*S*)-[1,1'-binaphthalene]-2,2'-diol could be achieved *via* iodine substitution at the 3,3' positions of the *O*-MOM-protected (*S*)-BINOL **140** followed by a Sonogashira coupling on the resulting aryl iodide **141** using trimethylsilylacetylene and subsequent trimethylsilyl group deprotection affording **129** (Scheme 2.25).



Scheme 2.25 Proposed synthesis of **129**.

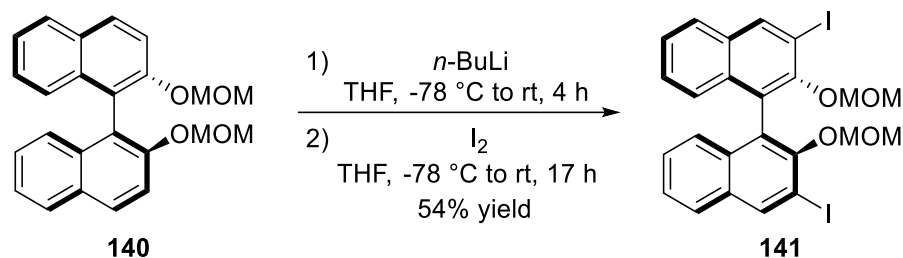
In order to initiate the aforementioned synthetic route it was necessary to protect the hydroxyl groups of (*S*)-BINOL. Adopting a protocol reported by Wu *et al.*,³⁴ the preparation of multigram quantities of (*S*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**140**) from commercially available (*S*)-[1,1'-binaphthalene]-2,2'-diol (**142**) was achieved in 75% yield (Scheme 2.26). The structure of **140** was confirmed by the ¹H- and ¹³C-NMR spectral data that corresponded closely to those reported in the literature.³⁵



Scheme 2.26 Preparation of (*S*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**140**).

With (*S*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**140**) in hand, the synthesis of (*S*)-3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**141**) was explored.

A procedure reported by Recsei and McErlean³⁶ was followed and afforded **141** in 54% yield (**Scheme 2.27**). The analysis of physicochemical data and comparison to the data reported in the literature³⁷ confirmed that **141** had been synthesised.



Scheme 2.27 Synthesis of (*S*)-3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**141**).

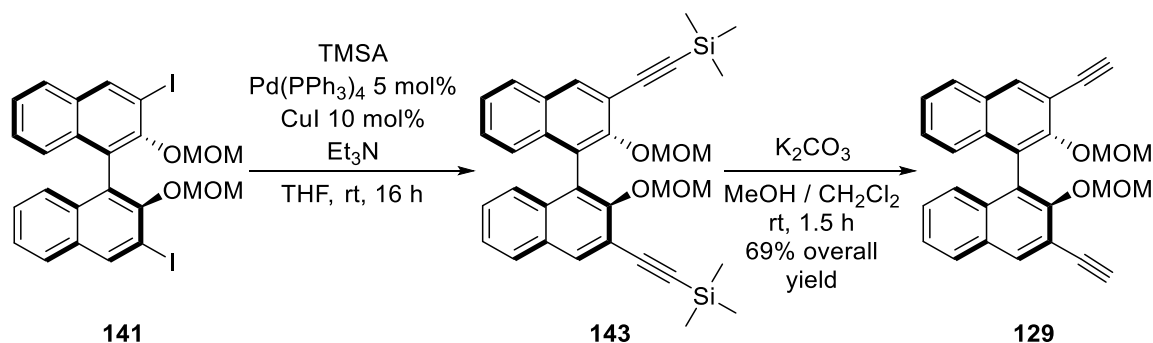
The moderate yield of the iodination reaction was a result of the formation of a mixture of products, including mono and diiodo substituted *O*-MOM-protected (*S*)-BINOL (based on ¹H-NMR spectral data and TLC analysis). (*S*)-3,3'-Diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**141**) was purified by flash column chromatography on a silica gel.

Although the synthesis of **141** was successful, the yield of diiodination is, at best, modest. A critical step in the synthesis is the (double) *ortho*-lithiation of **140**. It is clear that deprotonation should be highly regioselective and nearly exclusive *ortho*-lithiation may be anticipated. However, **140** must undergo double *ortho*-lithiation. Although the two naphthyl groups electronically should be nearly independent it is not clear whether a second deprotonation of a lithiated species will be as fast as deprotonation of non-lithiated **140**. Owing to introduction of an extra charge into the molecule the second deprotonation could well be slower than the first. The fact that monoiodo substituted **140** was isolated with the desired diiodo product suggests that, under the conditions employed, dilithiation, even with excess of *n*-butyllithium, may not be entirely complete. Further optimisation of the double *ortho*-lithiation reaction protocol was not attempted owing to the fact that sufficient amount of diiodo compound **141** had been synthesised.

Having successfully synthesised (*S*)-3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**141**), the preparation of (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**) via a Sonogashira coupling with trimethylsilylacetylene and subsequent trimethylsilyl group deprotection was investigated.

Coupling of (*S*)-3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**141**) with trimethylsilylacetylene in the presence of tetrakis(triphenylphosphine)palladium(0) (5 mol%), copper(I) iodide (10 mol%) and triethylamine (3 equivalents) in tetrahydrofuran at room temperature after 16 hours was expected to provide the intermediate **143**, which

was not isolated (**Scheme 2.28**). The C-silyl cleavage was accomplished according to a protocol reported by Recsei and McErlean³⁶ which involves reaction of the intermediate **143** with potassium carbonate in a mixture of methanol and dichloromethane, to afford (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**) in an overall 69% yield over the two steps (**Scheme 2.28**).



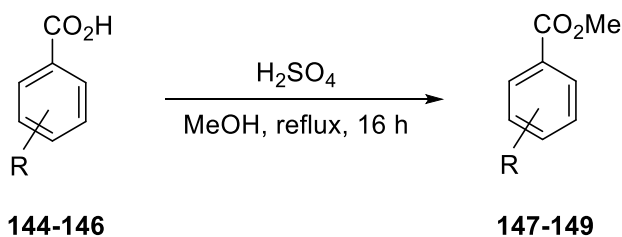
Scheme 2.28 Synthesis of **129** via a Sonogashira coupling and subsequent desilylation.

The ¹H- and ¹³C-NMR spectral data confirmed the structure of **129** and corresponded closely to those reported in the literature.³⁶ The ¹H-NMR spectrum revealed a singlet at δ 3.34 ppm for the hydrogen atom of the terminal alkynes whereas the ¹³C-NMR spectrum displayed two peaks at δ 81.7 and 80.7 ppm for the alkyne carbons.

With a reliable protocol in hand for the synthesis of **129**, the preparation of the azide library **130** – **139** (**Scheme 2.24**) was investigated.

The synthesis of methyl azidobenzoates **130** – **132** was initiated by a conversion of aminobenzoic acids **144** – **146** (commercially available) into the corresponding methyl esters **147** – **149** (**Scheme 2.29**). It was expected that this straightforward transformation would be beneficial for the purification of the final products generated via copper(I)-catalysed azide-alkyne cycloaddition of methyl azidobenzoates **130** – **132** with (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**).

The protocol reported by Chen *et al.*³⁸ for the Fischer esterification was adopted and the methyl esters of aminobenzoic acids **147** – **149** were synthesised in a straightforward manner (**Scheme 2.29**, **Table 2.3**).



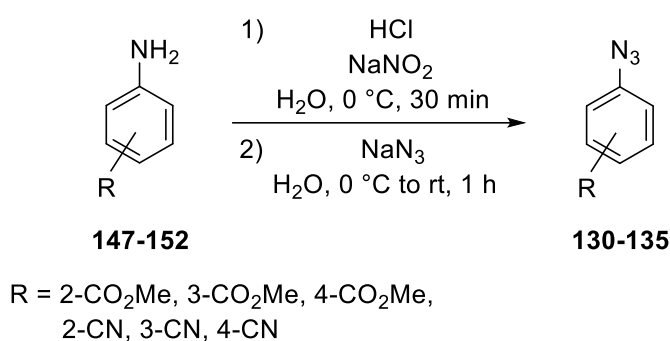
R = 2-NH₂, 3-NH₂, 4-NH₂

Scheme 2.29 Synthesis of methyl aminobenzoates **147** – **149**.

Compound number	R	H ₂ SO ₄ (equiv)	Yield (%)
147	2-NH ₂	3.9	48
148	3-NH ₂	3.9	69
149	4-NH ₂	3.9	78

Table 2.3 Preparation of **147 – 149** via the Fischer esterification.

The conversion of methyl aminobenzoates **147 – 149** into azide derivatives **130 – 132** and aminobenzonitriles **150 – 152** (commercially available) into azidobenzonitriles **133 – 135** was successfully accomplished via a diazotization-azidation method following protocols reported by Suwal and Pflum³⁹ (**130 – 132**) and Nakhai *et al.*⁴⁰ (**133 – 135**) (Scheme 2.30, Table 2.4).



Scheme 2.30 Synthesis of methyl azidobenzoates **130 – 132** and azidobenzonitriles **133 – 135**.

Compound number	R	NaNO ₂ (equiv)	NaN ₃ (equiv)	Yield (%)
130	2-CO ₂ Me	1	10	57
131	3-CO ₂ Me	1	10	57
132	4-CO ₂ Me	1	10	78
133	2-CN	1.1	1	80 ^a
134	3-CN	1.1	1	72 ^a
135	4-CN	1.1	1	64 ^a

^a NaOAc (1.2 equivalents) was used in the reaction to act as a buffer and minimise generation of the toxic hydrazoic acid.

Table 2.4 Preparation of **130 – 135** via a diazotization-azidation method.

Having successfully prepared methyl azidobenzoates **130 – 132** and azidobenzonitriles **133 – 135**, the synthesis of azidopyridines **136 – 138** (Scheme 2.24) was explored.

Ito *et al.*⁴¹ have described three different methods for the preparation of 2-, 3-, and 4-azidopyridine (**136** – **138**). 2-Azidopyridine (**136**) had been efficiently prepared in a reaction between *N*-fluoropyridium triflate (commercially available) and sodium azide, 3-azidopyridine (**137**) *via* the previously reported diazotization-azidation method, and 4-azidopyridine (**138**) in a reaction between 4-chloropyridine hydrochloride and sodium azide.

Adopting the protocols reported by Ito *et al.*,⁴¹ Suwal and Pflum,³⁹ and Jia and Zhu,⁴² 2-, 3-, and 4-azidopyridines (**136**, **137**, and **138** respectively) were synthesised (Table 2.5).

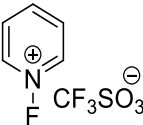
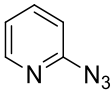
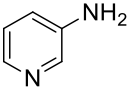
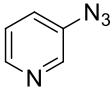
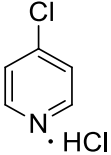
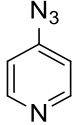
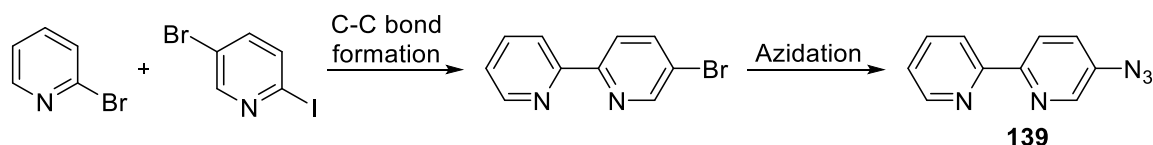
Compound number	Substrate	Product	Time (h)	Yield (%)
136			2	76
137			1.5	58
138			1	68

Table 2.5 Synthesis of 2-, 3-, and 4-azidopyridines (**136** – **138**).

Inclusion of a ligand with a pronounced ability to chelate metal ions was also considered a very useful addition to the library of ligands for this research project. It is well known that 2,2'-bipyridines are among the most widely utilised chelating ligands in coordination chemistry owing to their ability to generate stable complexes with a number of metal ions of different sizes and charges.⁴³

The compound 5-azido-2,2'-bipyridine (**139**) was considered an obvious target. It was envisaged that the preparation of **139** could be achieved *via* a two-step synthetic route *via* C-C bond formation reaction and azidation (**Scheme 2.31**).



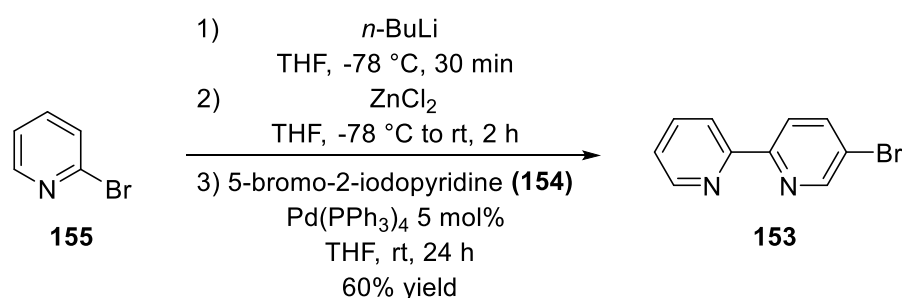
Scheme 2.31 Proposed synthesis of 5-azido-2,2'-bipyridine (**139**).

A literature survey substantiated that over the past three decades transition metal-catalysed C-C coupling reactions have become important methods for the preparation of

2,2'-bipyridines, with Stille and Negishi coupling strategies being presently the most often used.^{43,44}

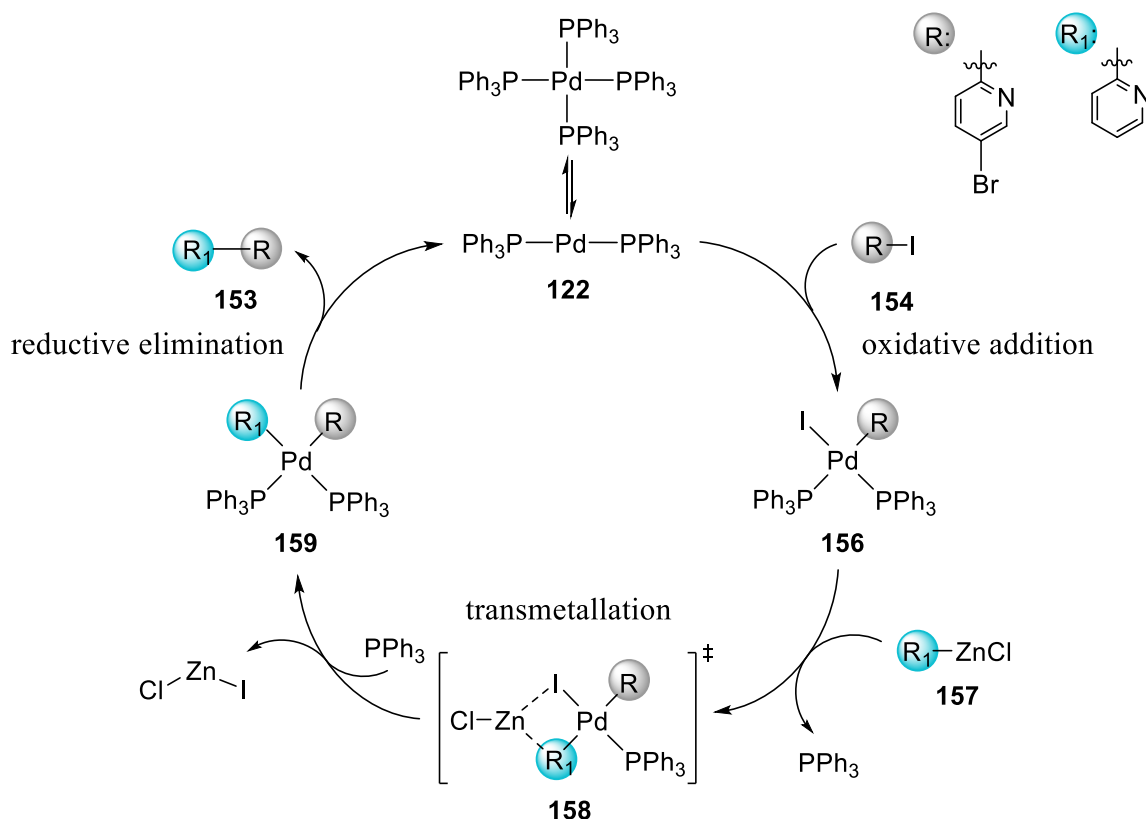
To avoid the use of toxic organotin reagents and difficulties in the separation of organotin by-products from the anticipated product (both drawbacks distinctive for a Stille coupling), it was decided to employ Negishi coupling for the synthesis of 5-bromo-2,2'-bipyridine (**153**).

A protocol reported by Soliman *et al.*⁴⁵ was of significance. The preparation of **153** via Negishi coupling of 5-bromo-2-iodopyridine (**154**) with 2-bromopyridine (**155**) in 60% yield has been described (**Scheme 2.32**).



Scheme 2.32 Synthesis of 5-bromo-2,2'-bipyridine (**153**) reported by Soliman *et al.*⁴⁵

The mechanistic pathway for a Negishi coupling proposed by Li *et al.*⁴⁶ is outlined in **Scheme 2.33**.

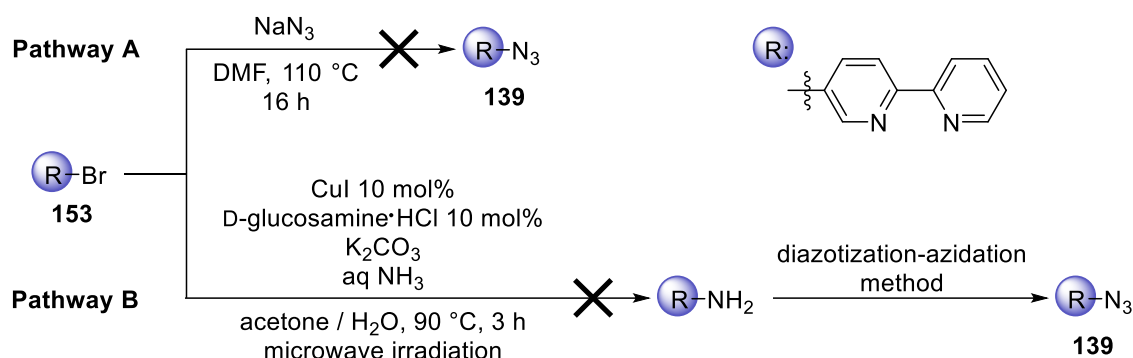


Scheme 2.33 The proposed mechanistic pathway for a Negishi coupling reported by Li *et al.*⁴⁶

Tetrakis(triphenylphosphine)palladium(0), introduced as a catalyst precursor, is converted to an active palladium(0) species **122** allowing the oxidative addition to the carbon-iodo bond of 5-bromo-2-iodopyridine (**154**) to generate palladium(II) complex **156**. Transmetalation of **156** with an organozinc chloride **157**, prepared by the transmetalation of the corresponding organolithium species with zinc(II) chloride, proceeds *via* a transition state **158** affording a palladium(II) complex **159**. Consecutive reductive elimination yields the anticipated 5-bromo-2,2'-bipyridine (**153**) and the regenerated active palladium(0) species **122**.

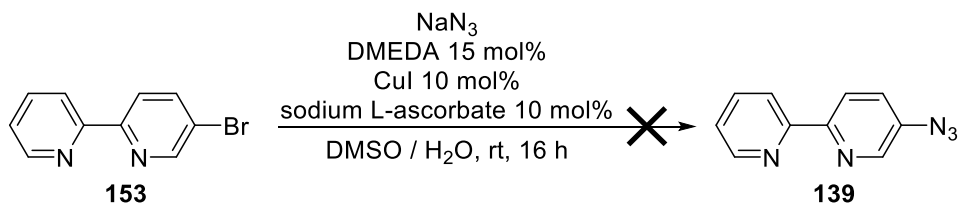
The protocol reported by Soliman *et al.*⁴⁵ was followed. Treatment of 2-bromopyridine (**155**) with *n*-butyllithium in tetrahydrofuran at -78 °C and subsequent reaction with zinc(II) chloride after 2.5 hours was expected to provide an organozinc intermediate. Subsequent reaction of the organozinc intermediate with 5-bromo-2-iodopyridine (**154**) in the presence of tetrakis(triphenylphosphine)palladium(0) (5 mol%) in tetrahydrofuran at room temperature afforded after 24 hours the desired **153** in 45% yield. The ¹H- and ¹³C-NMR spectral data confirmed the structure of **153** and corresponded closely to those reported in the literature.⁴⁵ The moderate yield of the reaction is most likely due to the coordinative ability of the synthesised 5-bromo-2,2'-bipyridine (**153**), a common drawback in the synthesis of 2,2'-bipyridines *via* coupling reactions.⁴³ The generation of **153** introduces a chelating ligand into the reaction system which, upon coordination to the palladium in tetrakis(triphenylphosphine)palladium(0), can inhibit further catalytic activity.⁴³

With **153** in hand, the synthesis of its azide derivative **139** was investigated. An aromatic nucleophilic substitution of **153** with sodium azide was expected to be arduous, as pyridines preferentially undergo an aromatic nucleophilic substitution in 2- and 4-positions as the intermediate anion is stabilised by resonance with the electronegative nitrogen. Because **153** is a 3-bromopyridine derivative any attempts at direct nucleophilic substitution using, for example, the protocols illustrated in **Pathways A** and **B** in **Scheme 2.34** (**Pathway A** according to a procedure reported by Colombano *et al.*⁴⁷; **Pathway B** according to procedures reported by Thakur *et al.*⁴⁸ and Ito *et al.*⁴¹ respectively) were expected to be futile. An alternative approach to the synthesis of **139** was required.



Scheme 2.34 Attempted syntheses towards **139**.

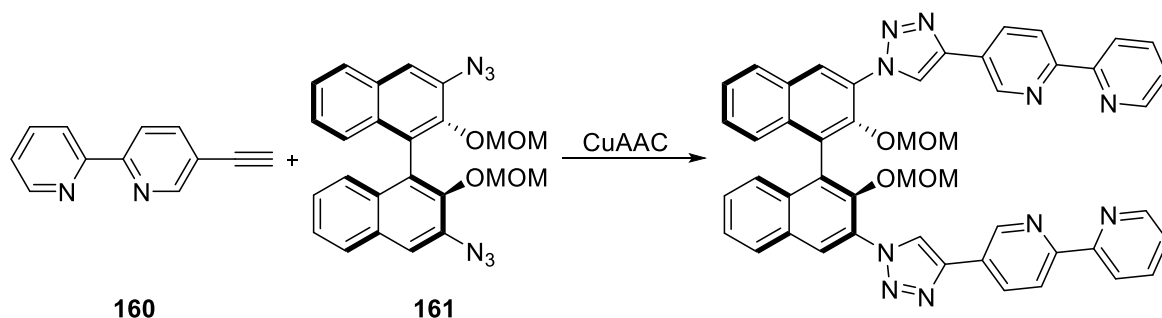
A literature survey revealed a protocol reported by Saikia *et al.*⁴⁹ for the preparation of azides from their iodo derivatives *via* a diamine-promoted copper(I)-catalysed coupling reaction. This protocol was investigated for the synthesis of **139**. However, reaction of 5-bromo-2,2'-bipyridine (**153**) with sodium azide in the presence of *N,N*-dimethylethylenediamine (15 mol%), copper(I) iodide (10 mol%) and sodium L-ascorbate (10 mol%) in a mixture of dimethyl sulfoxide and water (5 : 1) failed to produce any **139** (the ¹H-NMR spectral data revealed only unreacted starting material) (**Scheme 2.35**).



Scheme 2.35 Attempted synthesis of 5-azido-2,2'-bipyridine (**139**).

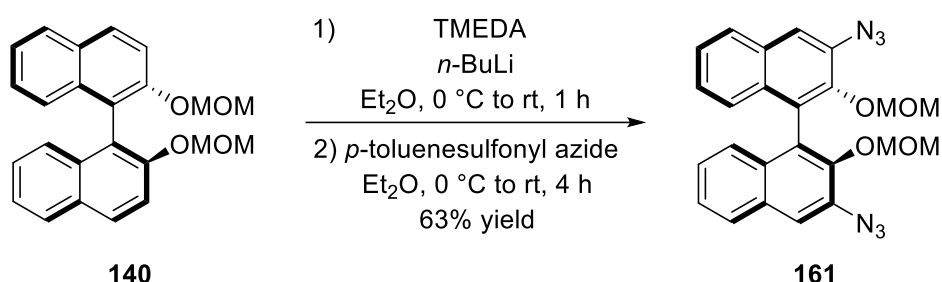
It was speculated that the starting material **153** could coordinate to the copper(I) species and stop the catalytic cycle of the reaction. To investigate this hypothesis, the protocol was repeated using 1.1 equivalents of copper(I) iodide instead of 10 mol%. Again, no reaction was observed. Undertaking the reaction under microwave irradiation at 100 °C instead of at room temperature was also without effect; 5-bromo-2,2'-bipyridine (**153**) remained inert under the copper-catalysed reaction conditions.

In view of the difficulties in synthesising **139**, it was thought appropriate to discontinue further attempts at its synthesis using 5-bromo-2,2'-bipyridine (**153**). An alternative approach for the preparation of an (*S*)-BINOL-derived organic linker with a 2,2'-bipyridine moiety was considered. Preparation of 5-ethynyl-2,2'-bipyridine (**160**) instead of 5-azido-2,2'-bipyridine (**139**) and (*S*)-3,3'-diazido-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**161**) instead of (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**) as the starting materials for the copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) was explored (**Scheme 2.36**).



Scheme 2.36 The CuAAC reaction of **160** with **161**.

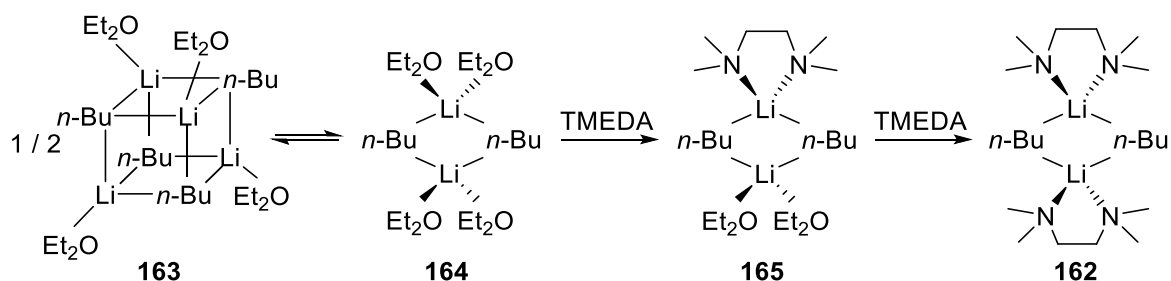
A literature survey revealed only one protocol, reported by Beckendorf and Garcia Mancheño,⁵⁰ for the synthesis of (*S*)-3,3'-diazido-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**161**) in 63% yield (**Scheme 2.37**).



Scheme 2.37 Synthesis of (*S*)-3,3'-diazido-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**161**) reported by Beckendorf and Garcia Mancheño.⁵⁰

In 2006, Qu and Collum⁵¹ published a report that focused on the determination of structures of *n*-butyllithium in diamine / dialkyl ether mixtures as they are one of the crucial factors to the understanding of the *n*-butyllithium / diamine-mediated *ortho*-lithiation mechanism.

n-Butyllithium in a mixture of *N,N,N',N'*-tetramethylethylenediamine and diethyl ether exists fully in a bis-*N,N,N',N'*-tetramethylethylenediamine-solvated dimer form **162** (**Scheme 2.38**).



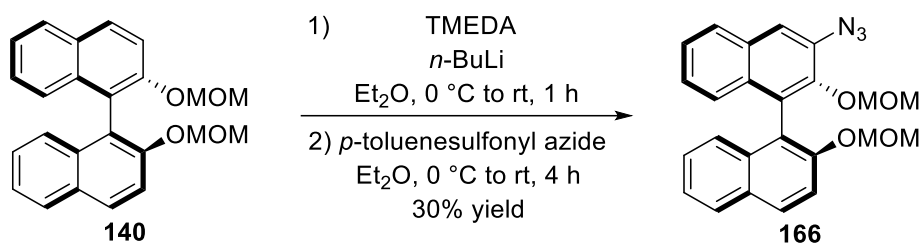
Scheme 2.38 *n*-Butyllithium structures in a mixture of *N,N,N',N'*-tetramethylethylenediamine and diethyl ether reported by Qu and Collum.⁵¹

The tetrameric form **163** of *n*-butyllithium in diethyl ether is in equilibrium with diethyl ether-solvated (homo-solvated) dimer **164**. Addition of

N,N,N',N'-tetramethylethylenediamine results in a transformation of **164** via *N,N,N',N'*-tetramethylethylenediamine / diethyl ether-solvated (mixed-solvated) dimer **165** into bis-*N,N,N',N'*-tetramethylethylenediamine-solvated dimer **162**.

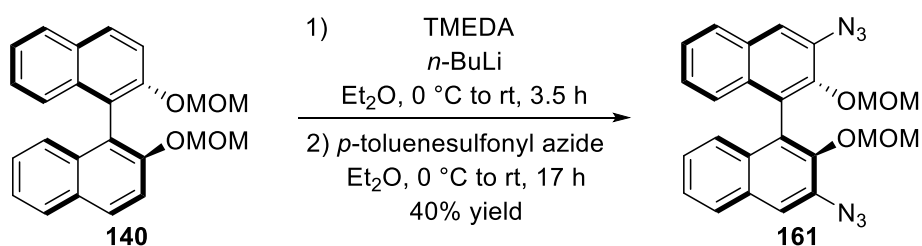
Based on their studies, Qu and Collum^{51,52} determined not only the structure of *n*-butyllithium in a *N,N,N',N'*-tetramethylethylenediamine / diethyl ether mixture but also established that diethyl ether and *N,N,N',N'*-tetramethylethylenediamine function cooperatively in the rate-limiting transition state during the mechanism of directed *ortho*-lithiation.

Following the protocol reported by Beckendorf and Garcia Mancheño,⁵⁰ only the mono substituted (*S*)-3-azido-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**166**) was obtained in a poor 30% yield (**Scheme 2.39**).



Scheme 2.39 Attempted synthesis of **161** with the generation of **166**.

In view of the generation of monosubstituted **166** but no evidence of the formation of disubstituted (*S*)-3,3'-diazido-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**161**) it was hypothesised that only monolithiated intermediate was generated during the reaction, which resulted in the mono substitution at 3-position in *O*-MOM-protected (*S*)-BINOL. To substantiate this hypothesis, the protocol was repeated utilising twice the amount of reagents, *i.e.*, 8 equivalents of *N,N,N',N'*-tetramethylethylenediamine instead of 4 equivalents, 5.5 equivalents of *n*-butyllithium instead of 2.75 equivalents, and 6 equivalents of *p*-toluenesulfonyl azide instead of 3 equivalents, and increasing the time of the reaction from 5 to 20.5 hours. Owing to the changes in protocol described above, the anticipated disubstituted **161** was afforded in 40% yield (**Scheme 2.40**). The structure of **161** was verified by the ¹H-NMR spectral data that corresponded closely to those reported in the literature.⁵⁰



Scheme 2.40 Synthesis of (*S*)-3,3'-diazido-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**161**).

Although the desired **161** had been synthesised, the yield of the reaction (40%) remained lower than that reported by Beckendorf and Garcia Mancheño⁵⁰ (63%). The product generated was a mixture of mono and disubstituted compounds, **166** and **161** respectively, in a 1 : 1.8 ratio. Consequently, the purification of **161** was troublesome as the separation of **161** from **166** by flash column chromatography on silica gel was not efficient enough and the mono-substituted product **166** was still present in the desired **161**. Subsequent recrystallisation from ethyl acetate and *n*-hexane (1 : 10) proved to be effective and pure **161** was isolated as pale yellow crystals in 40% yield. The crystals were suitable for X-ray diffraction analysis. The crystal structure (**Figure 2.4**) verified the postulated structure of **161**.

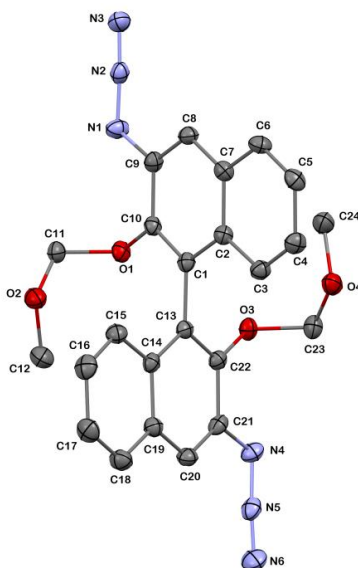
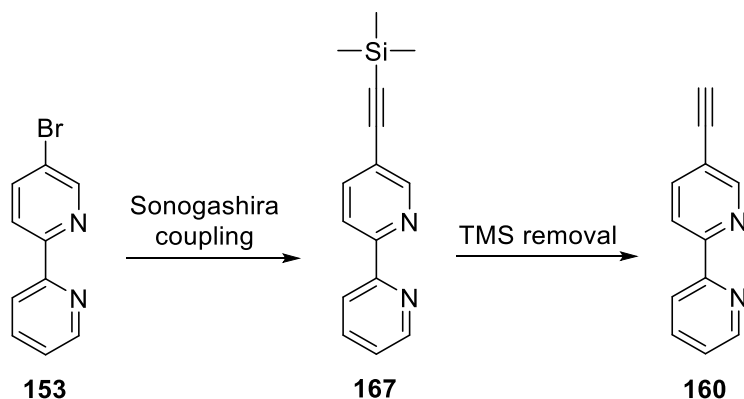


Figure 2.4 ORTEP drawing of (*S*)-3,3'-diazido-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**161**) showing atomic displacement parameters at the 50% probability level; hydrogen atoms have been omitted for clarity.

The chirality of **161** originates from hindered rotation. The dihedral angle of two planes is approximately 79.6°. The MOM protecting groups are out-of-plane (the C10–O1–C11 bond angle is 116.84°, and the C22–O3–C23 bond angle is 115.81°), whereas the azide groups are in-plane with the naphthyl rings. Additionally the azide groups point away from the aromatic rings (the C8–C9–N1 bond angle is 124.20°, and the C20–C21–N4 bond angle is 123.77°) with linear arrangement of the N atoms (the N1–N2–N3 bond angle is 175.26°, and the N4–N5–N6 bond angle is 174.39°). The azide groups are open to approach by substrates and reagents - an important characteristic required for a further triazole synthesis.

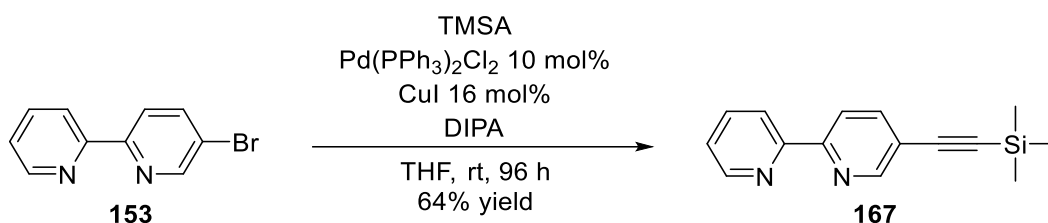
With (*S*)-3,3'-diazido-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**161**) in hand, the synthesis of 5-ethynyl-2,2'-bipyridine (**160**) was explored. It was envisaged that

the synthesis of **160** could be performed *via* a Sonogashira coupling of 5-bromo-2,2'-bipyridine (**153**) with trimethylsilylacetylene and consecutive trimethylsilyl group deprotection using a potassium carbonate / methanol mixture (**Scheme 2.41**).



Scheme 2.41 A two-step synthesis of **160**.

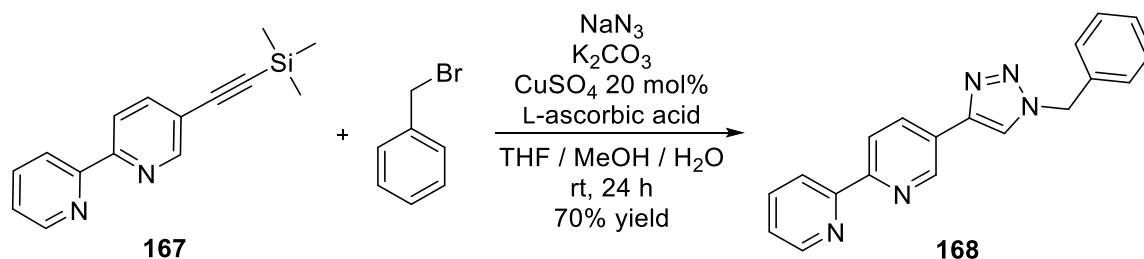
Employing a procedure reported by Soliman *et al.*,⁴⁵ 5-((trimethylsilyl)ethynyl)-2,2'-bipyridine (**167**) was prepared (**Scheme 2.42**).



Scheme 2.42 Synthesis of **167** *via* Sonogashira coupling.

Coupling of 5-bromo-2,2'-bipyridine (**153**) with trimethylsilylacetylene in the presence of bis(triphenylphosphine)palladium(II) dichloride (10 mol%), copper(I) iodide (16 mol%) and diisopropylamine (25 equivalents) in tetrahydrofuran at room temperature afforded, after 96 hours, the anticipated **167** in 64% yield. Analysis of the physicochemical data confirmed the structure of **167** and corresponded closely to those reported in the literature.⁴⁵

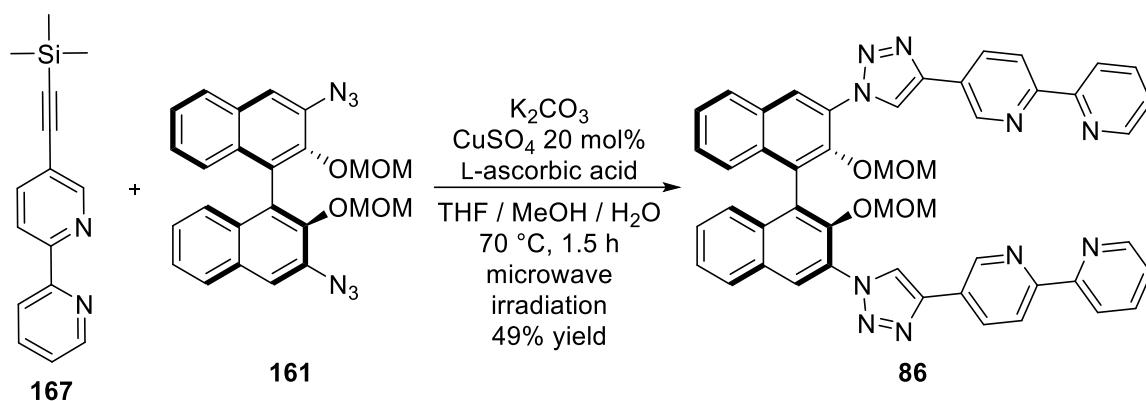
Ladouceur *et al.*⁵³ have reported a one-pot three-step synthesis of 1,4-disubstituted 1,2,3-triazoles from trimethylsilyl-protected aryl alkynes *via in situ* deprotection of a trimethylsilyl group and generation of an alkyl azide, followed by the CuAAC reaction (**Scheme 2.43**).



Scheme 2.43 A one-pot three-step synthesis of **168** reported by Ladouceur *et al.*⁵³

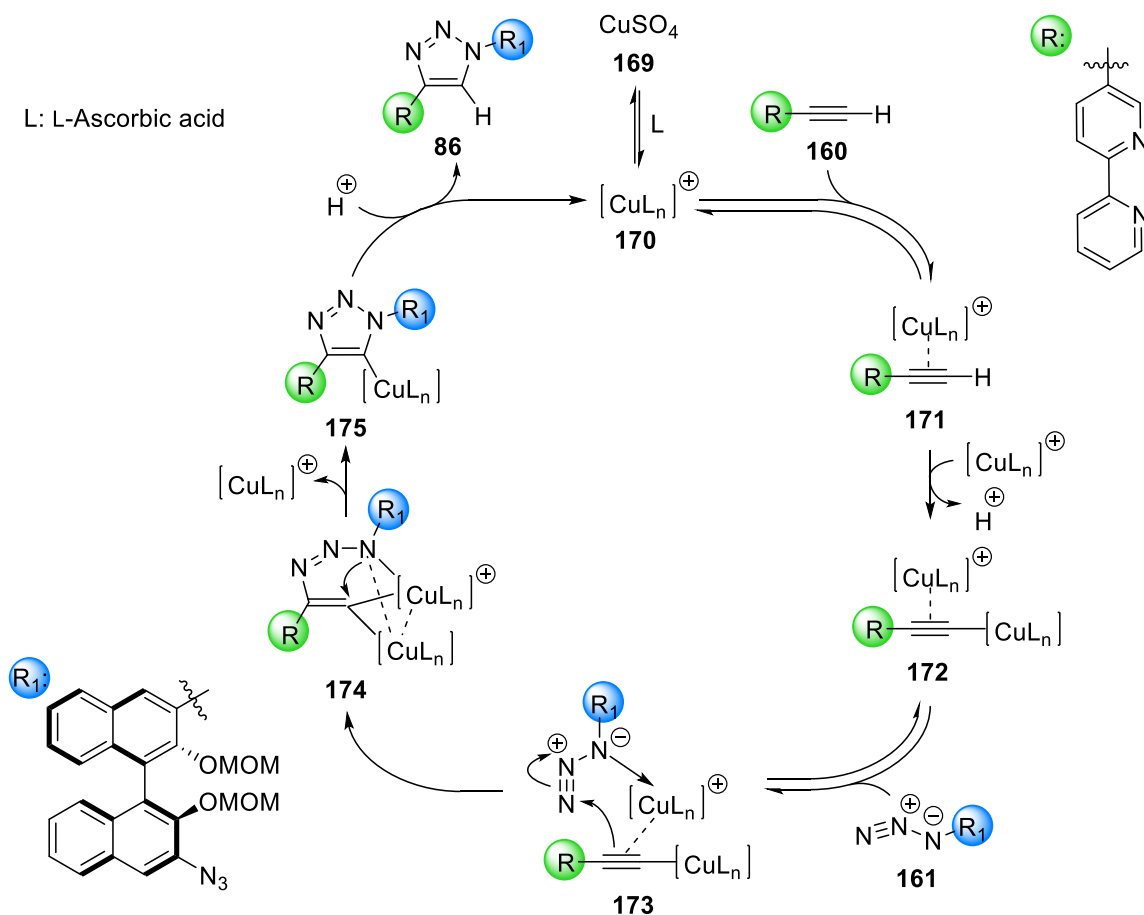
It was decided to examine the aforementioned protocol in the synthesis of 2,2'-bipyridine-containing *O*-MOM-protected (*S*)-BINOL from the previously prepared 5-((trimethylsilyl)ethynyl)-2,2'-bipyridine (**167**) and (*S*)-3,3'-diazido-2,2'-bis(methoxy methoxy)-1,1'-binaphthalene (**161**) as it avoids the additional step of C-silyl cleavage and generation of 5-ethynyl-2,2'-bipyridine (**160**).

Adopting a protocol reported by Ladouceur *et al.*⁵³ but eliminating the generation of an alkyl azide from the system and performing the reaction under microwave irradiation at 70 °C for 1.5 hours instead of 24 hours at room temperature, afforded the anticipated **86** in 49% yield (**Scheme 2.44**).



Scheme 2.44 The synthesis of **86** according to a modified procedure reported by Ladouceur *et al.*⁵³

The proposed mechanistic pathway for the copper(I)-catalysed azide-alkyne cycloaddition reported by Worrell *et al.*⁵⁴ is outlined in **Scheme 2.45**.



Scheme 2.45 The proposed mechanistic pathway for the CuAAC involving two copper atoms reported by Worrell *et al.*⁵⁴

Copper(II) sulfate (**169**) is reduced to a copper(I) species **170** in the presence of L-ascorbic acid. Coordination of **170** to 5-ethynyl-2,2'-bipyridine (**160**) (generated *in situ* by trimethylsilyl group deprotection of 5-((trimethylsilyl)ethynyl)-2,2'-bipyridine (**167**) in a potassium carbonate / methanol mixture according to the mechanistic pathway outlined in **Scheme 2.6**) affords copper(I)-alkyne complex **171**. Deprotonation and coordination of a second copper(I) species to **171** yields the copper(I)-alkyne complex **172**, which now contains two metal ions. Reversible coordination of the azide **161** to **172** generates complex **173**. Nucleophilic attack at the N-3 of the azide by **173** forms the Cu-N bonded intermediate **174**. Formation of a second C-N bond results in a ring closure and generation of **175**. Subsequent protonation affords the anticipated (*S*)-BINOL-derived [1,4]-triazole organic linker **86** and closes the catalytic cycle.

The non-catalysed azide-alkyne cycloaddition, known as Huisgen reaction, results in the formation of a mixture of 1,4- and 1,5-disubstituted triazoles. Copper catalysts were found to significantly change the outcome of the reaction. In their presence the reaction of terminal alkynes and azides proceeds with complete selectivity towards

the 1,4-disubstituted triazoles.⁵⁵ In comparison, in 2005, ruthenium cyclopentadienyl complexes were found to catalyse the cycloaddition reaction of terminal alkynes and azides with the generation of the 1,5-disubstituted triazoles.⁵⁶

(*S*)-BINOL-derived [1,4]-triazole organic linker **86** was optically active with a specific rotation $[\alpha]_{\text{D}}^{20} +203.90$ (*c* 1.0, CHCl₃). The melting point of **86** was 112 – 114 °C. The ¹H-NMR spectrum (**Figure 2.5**) revealed three singlets at δ 9.22, 8.70 and 8.66 ppm, a doublet at δ 8.04 ppm, a triplet at δ 7.83 ppm, and four multiplets at δ 8.56 – 8.38, 7.59 – 7.56, 7.47 – 7.44 and 7.35 – 7.30 ppm for the aromatic protons and proton of a 1,2,3-triazole ring with the integration accounting for twenty six hydrogen atoms, two doublets at δ 4.53 and 4.43 ppm for the protons of the methylene groups, and a singlet at δ 2.61 ppm for the protons of the methyl groups. Furthermore the ¹³C-NMR spectrum (**Figure 2.6**) displayed peaks at δ 156.0, 155.8, 149.3, 146.6, 146.5, 145.2, 137.1, 134.0, 133.8, 130.4, 130.3, 128.9, 128.6, 127.0, 126.9, 126.5, 126.2, 124.0, 122.7 and 121.3 ppm for the aromatic carbons and carbons of a 1,2,3-triazole ring (two ¹³C signals were not observed separately in the aromatic region due to an overlap of signals), a peak at δ 99.8 ppm for the carbon of the methylene groups, and a peak at δ 56.8 ppm for the carbon of the methyl groups. High-resolution mass spectrometry (NSI) displayed *m/z* 817.2994 (calculated for C₄₈H₃₇N₁₀O₄ [M+H] 817.2994) verifying the identity of **86**.

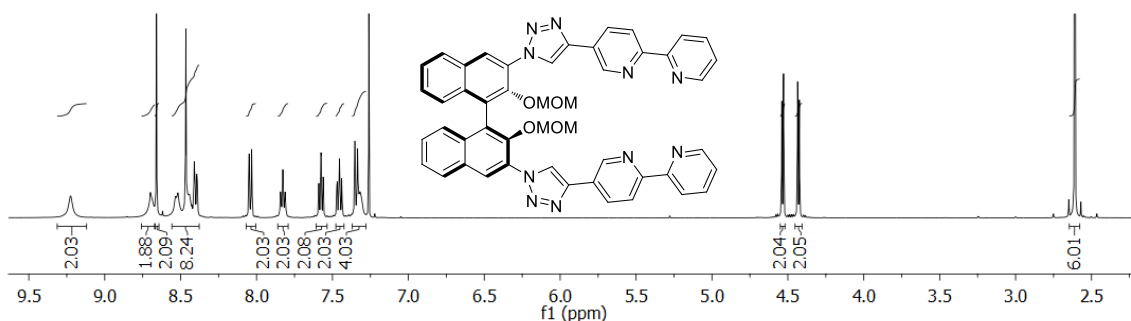


Figure 2.5 The ¹H-NMR (CDCl₃) spectrum of **86**.

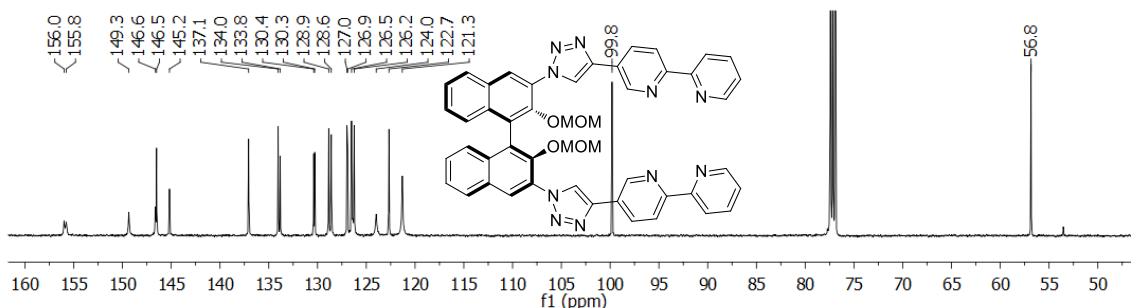
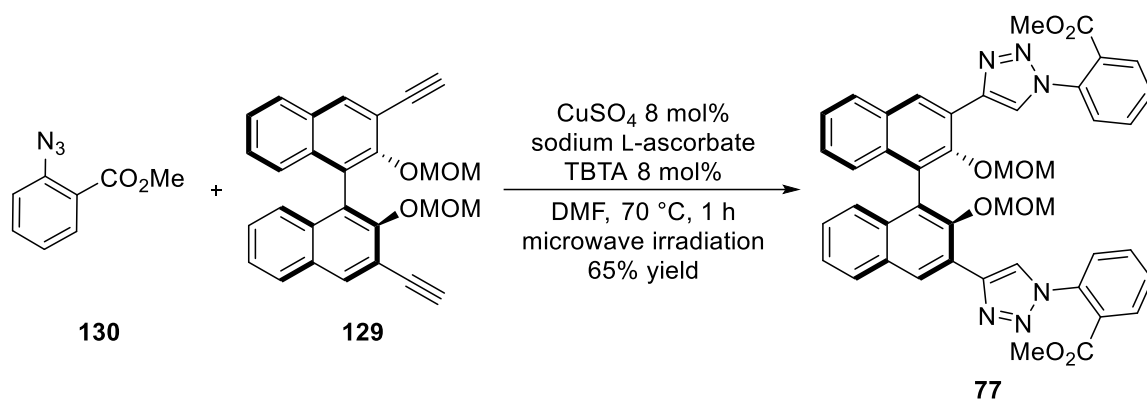


Figure 2.6 The ¹³C-NMR (CDCl₃) spectrum of **86**.

Having successfully prepared **86**, the CuAAC between the previously prepared (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**) and azides (**130 – 138**) was investigated (**Scheme 2.24**).

Exploration of the CuAAC was initiated by reaction of (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**) with methyl 2-azidobenzoate (**130**) in the presence of copper(II) sulfate pentahydrate (8 mol%) (reduced *in situ* to copper(I) species with sodium L-ascorbate) and tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) (8 mol%) in *N,N*-dimethylformamide under microwave irradiation at 70 °C affording, after 1 hour, the anticipated product **77** in 65% yield (**Scheme 2.46**). Analysis of the physicochemical data verified the structure of **77**.



Scheme 2.46 The synthesis of **77** via copper(I)-catalysed azide-alkyne cycloaddition.

Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) has been found to be a highly efficient ligand for the CuAAC reaction promoting catalysis.⁵⁷ The copper(I) species involved in the catalytic cycle is characterised by low stability, which can result in its oxidation to a copper(II) species and / or disproportionation to copper(0) and copper(II) species.⁵⁸ It is postulated that the binding ability of TBTA results in an enclosure of the copper(I) centre leaving no free binding sites and therefore preventing it from any potential interactions that could provide to destabilisation.⁵⁸

Analysis of the physicochemical data verified the structure of **77**. The melting point of **77** was 63 – 65 °C. The specific rotation $[\alpha]_D^{20}$ of **77** was +168.2 (*c* 1.0, CHCl₃) confirming that **77** was optically active. The FT-IR spectroscopy displayed the characteristic peak for the carbonyl group at 1731 cm⁻¹. The ¹H-NMR spectrum (**Figure 2.7**) displayed two singlets at δ 9.05 and 8.60 ppm, a triplet of doublets at δ 7.68 ppm, and four multiplets at δ 8.07 – 7.99, 7.63 – 7.53, 7.50 – 7.46 and 7.36 – 7.28 ppm for the aromatic protons and proton of the 1,2,3-triazole rings with the integration accounting for twenty hydrogen atoms, two doublets at δ 4.69 and 4.44 ppm for the protons of the methylene groups, a singlet at δ 3.72 ppm for the protons of the methyl groups present on methyl esters, and a peak at δ 2.65 ppm for the protons of the methyl groups present in MOM protecting groups.

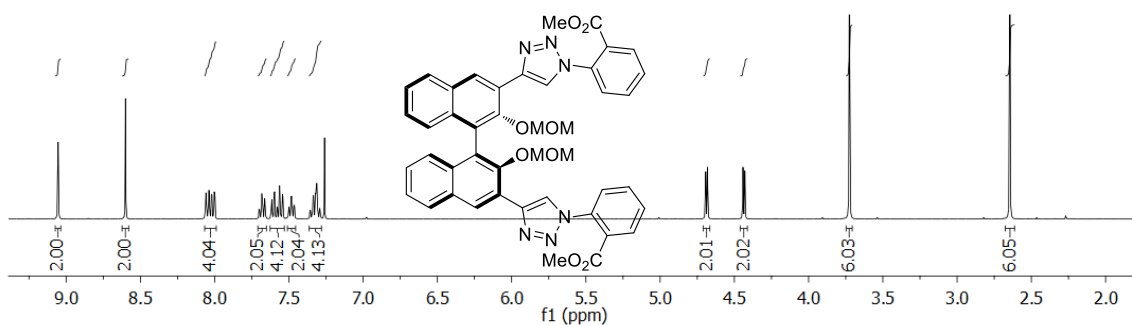


Figure 2.7 The $^1\text{H-NMR}$ (CDCl_3) spectrum of **77**.

Additionally the $^{13}\text{C-NMR}$ spectrum (**Figure 2.8**) revealed a peak at δ 165.6 ppm for the carbonyl carbons, peaks at δ 149.8, 143.2, 136.2, 133.8, 132.7, 131.3, 131.0, 129.9, 128.72, 128.68, 127.5, 127.1, 126.6, 126.1, 125.9, 125.7, 125.1 and 124.2 ppm for the aromatic carbons and two carbons of the 1,2,3-triazole rings, a peak at δ 98.6 ppm for the carbon of the methylene groups, a peak at δ 56.9 ppm for the carbon of the methyl groups present in MOM protecting groups, and a peak at δ 52.6 ppm for the carbon of the methyl groups present on the methyl esters. High-resolution mass spectrometry (NSI) displayed m/z 777.2669 (calculated for $\text{C}_{44}\text{H}_{37}\text{N}_6\text{O}_8$ [$\text{M}+\text{H}$] 777.2667) verifying the identity of **77**.

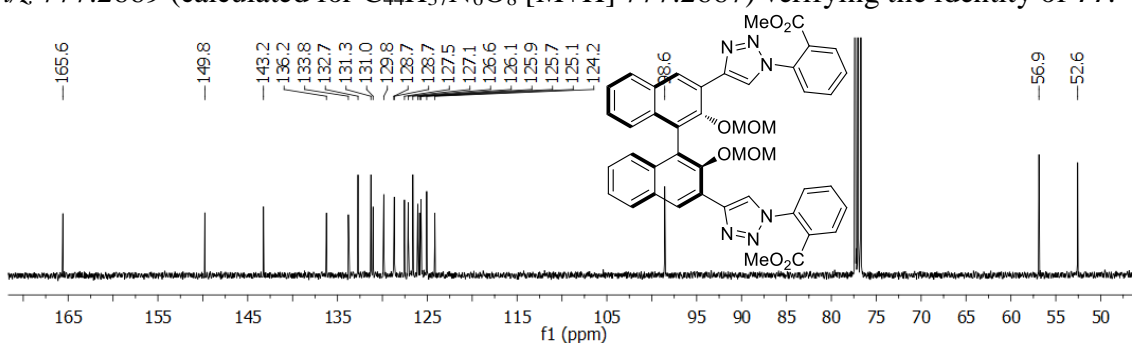
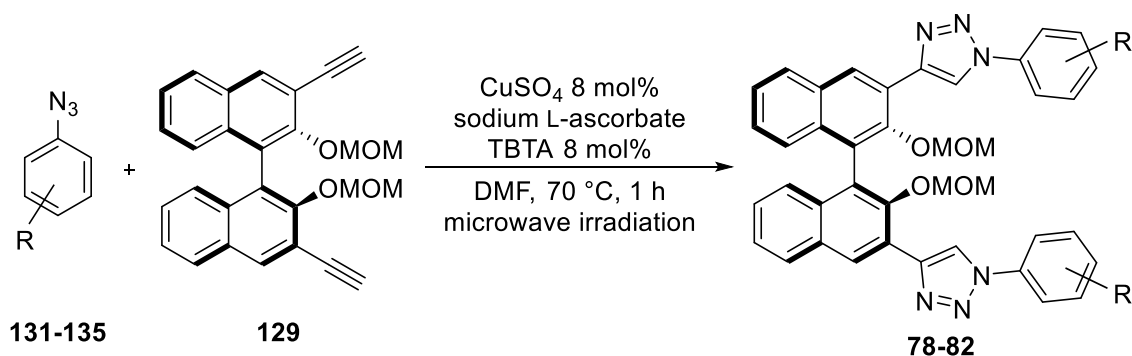


Figure 2.8 The $^{13}\text{C-NMR}$ (CDCl_3) spectrum of **77**.

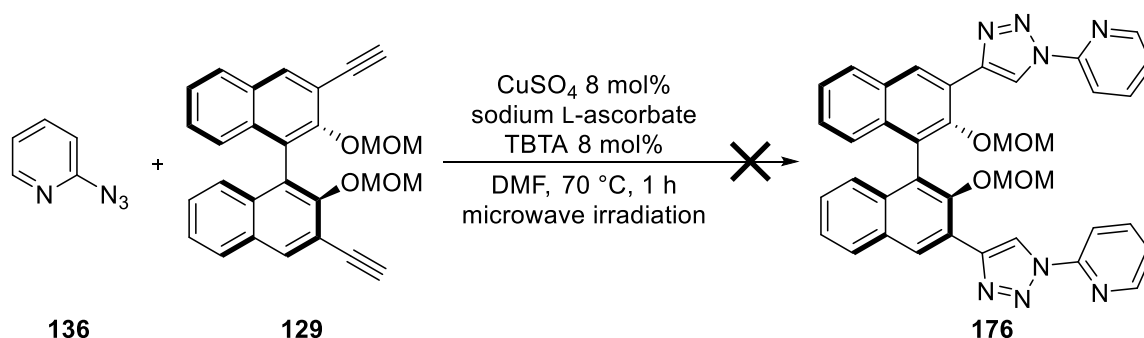
Utilising the same protocol, (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**) was allowed to react with previously prepared azides **131** – **135** in the presence of copper(II) sulfate pentahydrate (8 mol%) (reduced *in situ* to copper(I) species with sodium L-ascorbate) and tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) (8 mol%) in *N,N*-dimethylformamide under microwave irradiation at 70 °C affording, after 1 hour, corresponding (*S*)-BINOL-derived organic linkers **78** – **82** (**Scheme 2.47**, **Table 2.6**).

Scheme 2.47 Synthesis of **78 – 82** via CuAAC.

Compound number	R	CuSO ₄ (mol%)	Solvent	Temperature (°C)	Time (h)	Yield (%)
78	3-CO ₂ Me	8	DMF	70	1	89
79	4-CO ₂ Me	8	DMF	70	1	73
80	2-CN	8	DMF	70	1	86
81	3-CN	8	DMF	70	1	79
82	4-CN	8	DMF	70	1	77

Table 2.6 Preparation of (*S*)-BINOL-derived organic linkers **78 – 82** via CuAAC of **129** with the azides **131 – 135**.

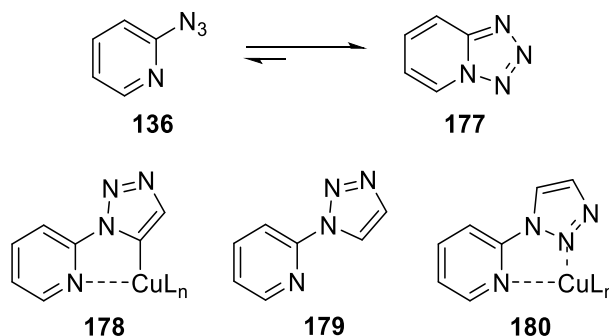
Having successfully prepared **78 – 82**, the CuAAC of (*S*)-3,3'-diethynyl-2,2'-bis(methoxy methoxy)-1,1'-binaphthalene (**129**) with azidopyridines **136 – 138** was investigated. A reaction of **129** with 2-azidopyridine (**136**) adopting the aforementioned protocol did not, however, provide the desired product **176** (TLC analysis indicated no conversion of the starting materials **136** and **129**) (Scheme 2.48).

Scheme 2.48 Attempted synthesis of **176**.

In the first instance it was thought that **136** may coordinate to the copper(I) species in a process that stops the catalytic cycle of the reaction. However, on repeating the reaction with 200 mol% of copper(II) sulfate pentahydrate instead of 8 mol% and heating the reaction mixture under microwave irradiation at 120 °C instead of 70 °C the outcome of

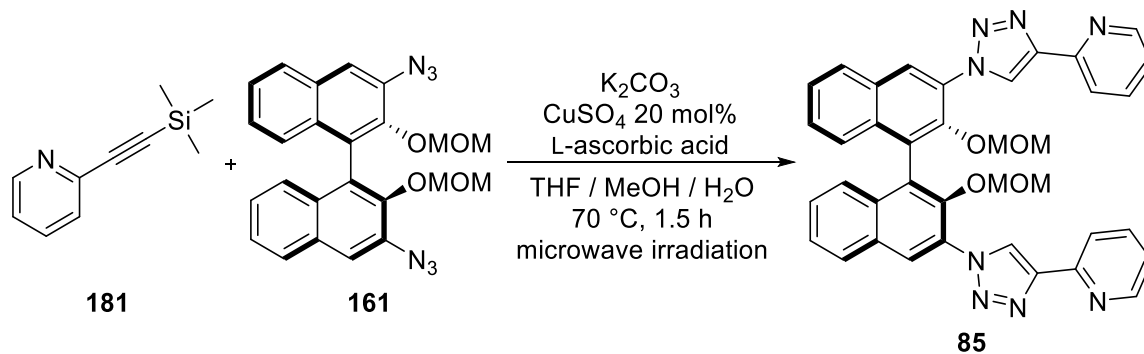
the reaction was unchanged and the starting materials **136** and **129** remained unreactive under these modified reaction conditions.

A more comprehensive literature survey revealed that although the copper(I)-catalysed azide-alkyne cycloaddition is the most efficient way for the preparation of 1,2,3-triazoles, utilisation of 2-azidopyridine (**136**) in CuAAC leads to difficulties in obtaining the desired products. In a report published by Zhang *et al.*⁵⁹ three factors were identified that could be responsible for the low efficiency of CuAAC employing 2-azidopyridine (**136**) (**Scheme 2.49**); a) the existence of 2-azidopyridine (**136**) in its closed form as a tetrazole **177** in the solid state and in equilibrium between its closed and open form in solution; b) a coordination of pyridine in the 1,2,3-triazole intermediate to a copper(I) species and generation of the complex **178** therefore making the protonation of C-Cu bond more problematic; and c) a coordination of the product **179** to a copper(I) species affording complex **180** thereby inhibiting the catalytic cycle of the reaction.



Scheme 2.49 2-Azidopyridine (**136**) and its closed form **177**, the proposed intermediates **178** and **180**, and the CuAAC product **179** reported by Zhang *et al.*⁵⁹

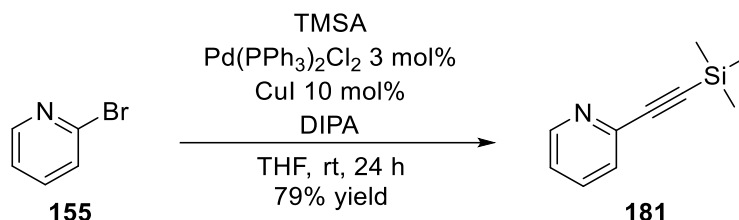
To avoid the use of 2-azidopyridine (**136**) an alternative approach to the required (*S*)-BINOL-derived organic linker containing 2-pyridine moiety was investigated. The employment of 2-((trimethylsilyl)ethynyl)pyridine (**181**) and previously prepared (*S*)-3,3'-diazido-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**161**) for the synthesis of **85** according to a modified Ladouceur *et al.*⁵³ protocol was considered (**Scheme 2.50**).



Scheme 2.50 Proposed synthesis of **85**.

In order to investigate this procedure, a route to 2-((trimethylsilyl)ethynyl)pyridine (**181**) was needed.

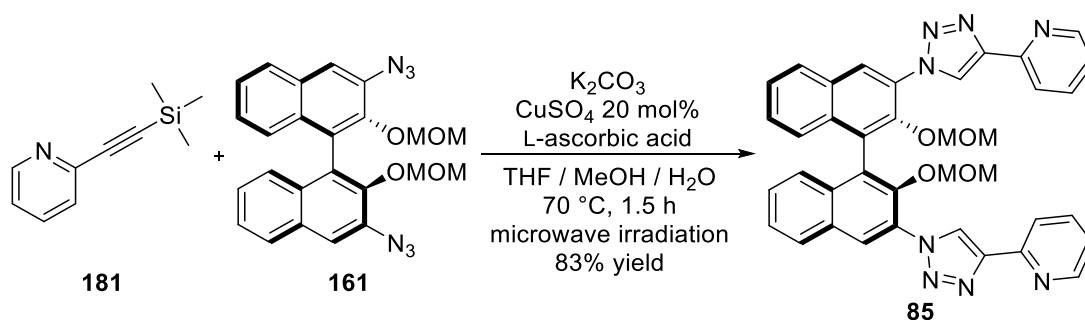
Employing a protocol reported by Huang *et al.*,⁶⁰ the anticipated **181** was synthesised in 79% yield (**Scheme 2.51**). The ¹H- and ¹³C-NMR spectral data and comparison with the literature data⁶¹ confirmed the structure of **181**.



Scheme 2.51 Synthesis of **181** via a Sonogashira coupling of **155** with trimethylsilylacetylene.

Having successfully prepared 2-((trimethylsilyl)ethynyl)pyridine (**181**), the generation of **85** via *in situ* deprotection of trimethylsilyl group and subsequent CuAAC according to the previously utilised and modified Ladouceur *et al.*⁵³ protocol was examined.

Reaction of **181** with (*S*)-3,3'-diazido-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**161**) in the presence of potassium carbonate, copper(II) sulfate (20 mol%) and L-ascorbic acid in a mixture of tetrahydrofuran, methanol and water (1 : 1 : 1) under microwave irradiation at 70 °C afforded, after 1.5 hours, the anticipated **85** in a high 83% yield (**Scheme 2.52**). The structure of **85** was verified by analysis of the physicochemical data.

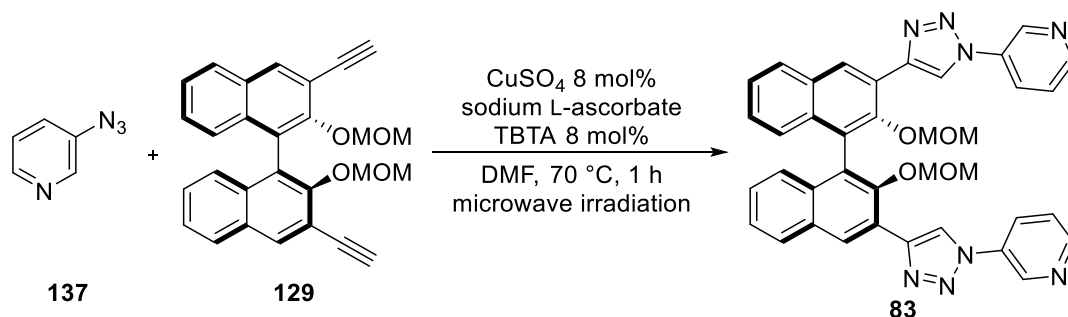


Scheme 2.52 Synthesis of **85** via *in situ* deprotection of trimethylsilyl group and consecutive CuAAC.

With **85** in hand, the preparation of (*S*)-BINOL-derived organic linkers **83** and **84** via CuAAC of (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**) with 3- and 4-azidopyridine, **137** and **138** respectively, was explored.

Adopting the previously established protocol for the CuAAC (**Scheme 2.47**), (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**) was allowed to react with **137** in the presence of copper(II) sulfate pentahydrate (8 mol%) (reduced *in situ* to

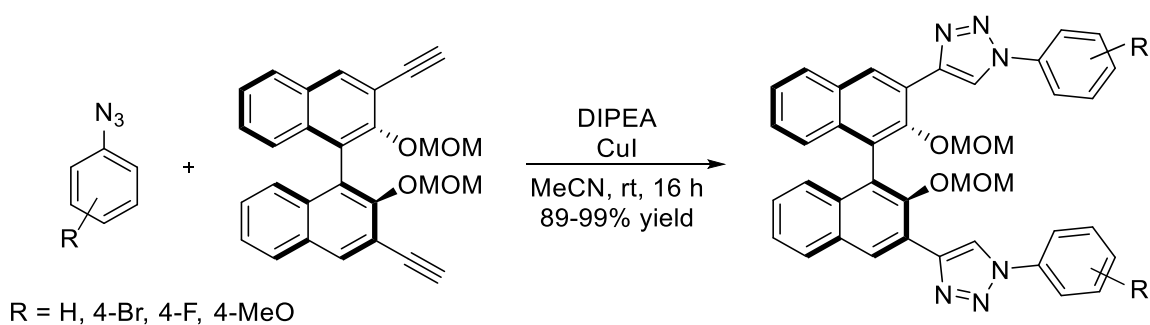
copper(I) species with sodium L-ascorbate) and tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) (8 mol%) dissolved in *N,N*-dimethylformamide and heated under microwave irradiation at 70 °C affording, after 1 hour, the desired product **83** (Scheme 2.53).



Scheme 2.53 Synthesis of **83** via CuAAC.

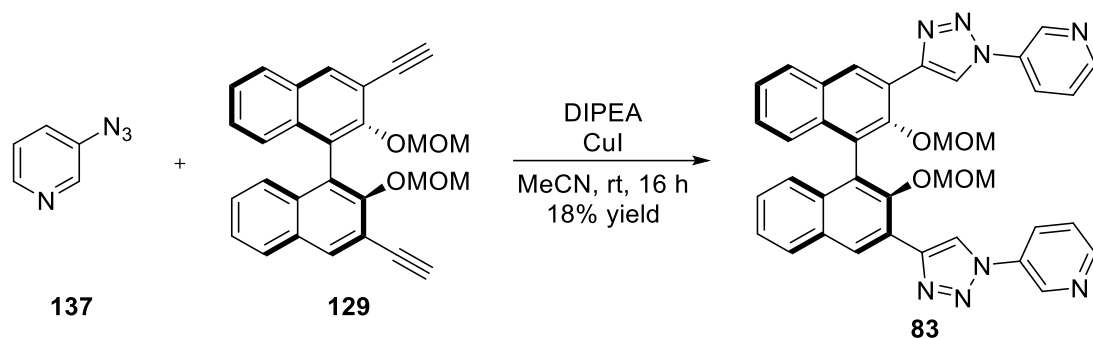
Although **83** was generated, it was isolated as a mixture of products that was difficult to separate by flash column chromatography on silica gel (TLC analysis displayed 4 spots situated close to each other). It was thought that the low efficiency of the reaction was caused by coordination of **137** to copper(I) species and therefore inhibiting its catalytic activity.

A literature survey revealed a protocol reported by Recsei and McErlean³⁶ in which the synthesis of a series of (*S*)-BINOL-based ligands via CuAAC utilising copper(I) iodide and *N,N*-diisopropylethylamine in an excellent 89% to 99% yields was described (Scheme 2.54).



Scheme 2.54 Synthesis of an array of (*S*)-BINOL-based ligands reported by Recsei and McErlean.³⁶

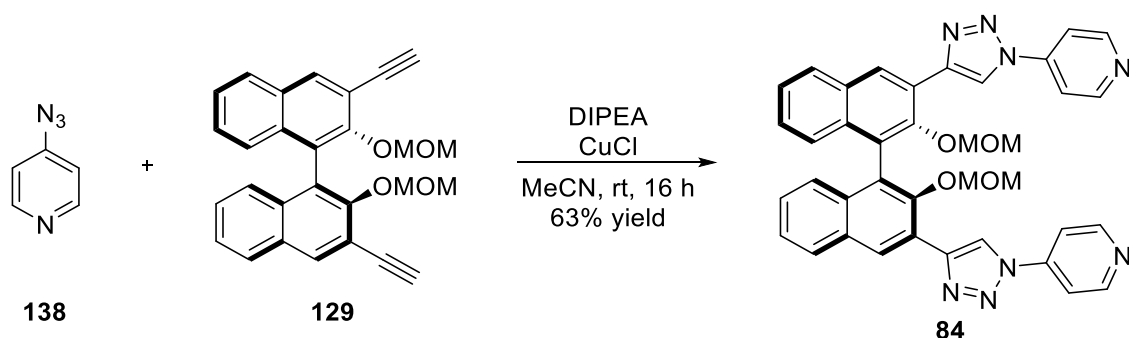
It was thought important to explore this procedure for the synthesis of **83**. Reaction of (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**) with 3-azidopyridine (**137**) in the presence of copper(I) iodide (1 equivalent) and excess of *N,N*-diisopropylethylamine (40 equivalents) in acetonitrile at room temperature afforded, after 16 hours, the anticipated **83** in a disappointing 18% yield (TLC analysis displayed presence of the starting materials **137** and **129**) (Scheme 2.55).



Scheme 2.55 Preparation of **83** adopting a protocol reported by Recsei and McErlean.³⁶

It was suspected that the low 18% yield of the reaction was caused by traces of iodine present in the reaction mixture interrupting the catalytic cycle and inhibiting the full conversion of starting materials. To investigate this hypothesis, the protocol was repeated using copper(I) chloride instead of copper(I) iodide as the reaction catalyst. Ultimately, the desired **83** was generated in 69% yield. Analysis of the physicochemical data verified the structure of **83**.

Encouraged by the effectiveness of the aforementioned procedure, its application for the preparation of **84** was examined (**Scheme 2.56**).



Scheme 2.56 Generation of **84** employing a modified protocol reported by Recsei and McErlean.³⁶

(*S*)-3,3'-Diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**) was allowed to react with 4-azidopyridine (**138**) in the presence of copper(I) chloride (1 equivalent) and excess of *N,N*-diisopropylethylamine (40 equivalents) in acetonitrile at room temperature. After 16 hours the anticipated **84** was afforded in 63% yield.

The structure of **84** was verified by analysis of the physicochemical data. The desired **84** was optically active with the specific rotation $[\alpha]_{\text{D}}^{20} +255.30$ (*c* 1.0, CHCl_3). The melting point of **84** was 93 – 95 °C. The ¹H-NMR spectrum (**Figure 2.9**) displayed three singlets at δ 9.07, 8.95 and 8.80 ppm, three doublets at δ 8.08, 7.80 and 7.31 ppm, and two multiplets at δ 7.53 – 7.50 and 7.38 – 7.35 ppm for the aromatic protons and a proton of the 1,2,3-triazole rings with the overall integration accounting for twenty hydrogen atoms, two

doublets at δ 4.63 and 4.41 ppm for the protons of the methylene groups, and a singlet at δ 2.76 ppm for the protons of the methyl groups.

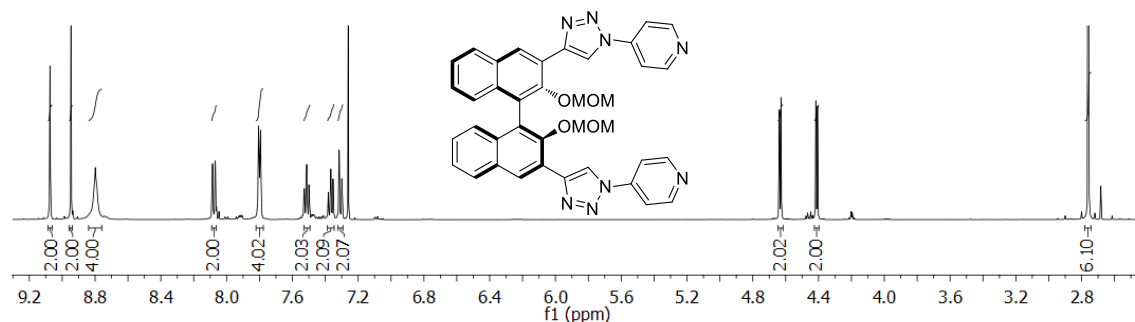


Figure 2.9 The $^1\text{H-NMR}$ (CDCl_3) spectrum of **84**.

Additionally the $^{13}\text{C-NMR}$ spectrum (**Figure 2.10**) displayed peaks at δ 151.9, 149.9, 144.7, 143.2, 134.0, 131.1, 129.1, 129.0, 127.7, 126.1, 126.0, 125.8, 123.5, 120.5 and 113.7 ppm for the aromatic carbons and carbons of the 1,2,3-triazole rings (two ^{13}C signals were not observed in the aromatic region due to an overlap of signals), a peak at δ 99.0 ppm for the carbon of the methylene groups, and a peak at δ 57.4 ppm for the carbon of the methyl groups. High-resolution mass spectrometry (NSI) displayed m/z 663.2461 (calculated for $\text{C}_{38}\text{H}_{31}\text{N}_8\text{O}_4$ $[\text{M}+\text{H}]$ 663.2463) confirming the identity of **84**.

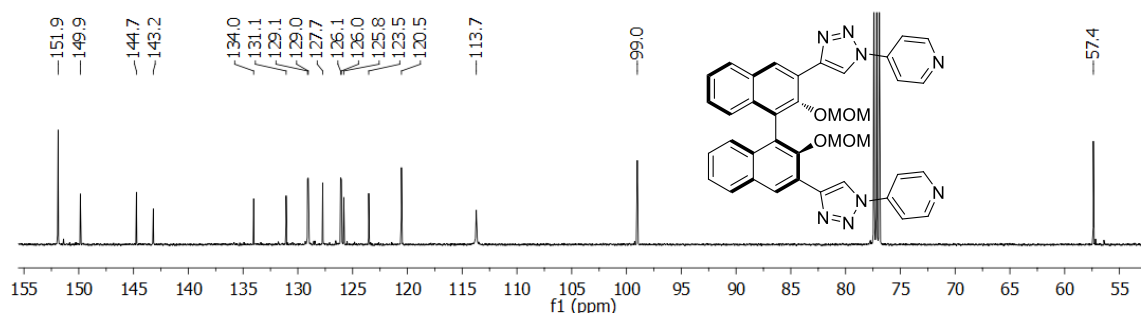


Figure 2.10 The $^{13}\text{C-NMR}$ (CDCl_3) spectrum of **84**.

2.6. Conclusion and future work

At the outset of this research project the synthesis of a range of novel chiral non-racemic organic linkers was proposed. It was envisaged that the design of appropriate ligands may allow for their use as building blocks in the preparation of optically active metal-organic frameworks (MOFs) that could consecutively be applied in heterogeneous asymmetric catalysis. In the first section of this chapter, the generation of a highly rigid 1,4-bis(pyridin-4-ylethynyl)benzene (**74**) was described. The second section of this chapter illustrates the synthesis of a novel linear linker **75** equipped with ester functional groups for the future introduction of a chiral centre. During this part of the research project a successful modification of a procedure for a [2+2+2] cycloaddition was achieved and

an effective purification system for acetylene was developed. In the third section, the synthesis of (2*S*,2'*S*)-dimethyl3,3'-((1,4-phenylenebis(ethyne-2,1-diyl))bis(4,1-phenylene))bis(2-((*t*-butoxy carbonyl)amino)propanoate) (**76**) as a potential organic linker for the preparation of a bioMOF was outlined. In the last section of this chapter the synthesis of a series of novel building blocks derived from an axially chiral non-racemic [1,1'-binaphthalene]-2,2'-diol (BINOL) *via* copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) was described. The syntheses of (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**) as well as a range of aryl azides **130** – **139** were successful. Initial difficulties with preparation of pyridine- and 2,2'-bipyridine-containing (*S*)-BINOL-derived organic linkers were overcome either by use of copper(I) chloride and *N,N*-diisopropylethylamine in the CuAAC reaction when installing 3- or 4-pyridine moieties in a molecule, or by a synthesis of (*S*)-3,3'-diazido-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**161**) and its employment in a one-pot two-component procedure for the CuAAC reaction with 2-((trimethylsilyl)ethynyl)pyridine (**181**) or 5-((trimethylsilyl)ethynyl)-2,2'-bipyridine (**167**) for the introduction of 2-pyridine and 2,2'-bipyridine moieties into a molecule.

Further research may include the instalment of an optically active L-proline in the highly rigid diethyl 4,7-bis(pyridin-4-ylethynyl)-1*H*-indene-2,2(3*H*)-dicarboxylate (**75**), as it is a well-recognised organocatalyst in asymmetric synthesis. To avoid the interference of L-proline in the assembly of a framework, the amino group could be first *N*-Boc-protected and later deprotected to furnish the catalytically active site. Additional studies towards the introduction of a catalytic centre in the optically active (*S*)-BINOL-derived building blocks could be conducted. This would involve establishment of a protocol for the deprotection of the hydroxyl groups to make the secondary functional groups readily available for post-synthetic modification and instalment of a catalytic site. Additionally, derivatives of the organic linkers described that would vary in length could be synthesised. This would allow tailoring of the MOF framework and therefore the size of pores for the substrates of a specific asymmetric synthesis.

2.7. References

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Chapter 3
Experimental

3.1. General Methods

All reactions described as being carried out under a nitrogen atmosphere were always performed in flame-dried glassware, which was allowed to cool under an inert atmosphere. For those reactions not carried out under nitrogen atmosphere ordinary glassware was used without special precautions for drying. All reactions were stirred using a magnetic stirrer plate and a stirrer bar. Reactions carried out at 0 °C were held at that temperature using a water and ice bath, those at -10 °C using an ice and salt bath and those at -78 °C using an acetone and dry ice bath. Petroleum ether refers to the fraction that boils in the range 40 – 60 °C. Diethyl ether and tetrahydrofuran were freshly distilled over sodium benzophenone ketyl under an argon atmosphere. Acetonitrile, 1,2-dichloroethane, dichloromethane, diisopropylamine, ethanol, methanol, piperidine, propionitrile, pyridine and triethylamine were freshly distilled over calcium hydride under an argon atmosphere. Anhydrous *N,N*-dimethylformamide was purchased from Sigma Aldrich. Sodium hydride was used as a 60 wt.% dispersion in a mineral oil and washed with *n*-hexane prior to use. Technical grade acetylene was supplied in a metal cylinder and purified before use by successive passage through Drechsel bottles containing, in this order, water, concentrated sulfuric acid (two bottles), 0.2 M aqueous potassium permanganate solution, water, and a drying tube containing silica gel that contained moisture indicator. All other commercially available reagents were used as supplied unless otherwise specified. Column chromatography was carried out on Fluka silica gel (pore size 60 Å, 70-230 mesh). TLC was performed on Merck plates (aluminium coated with 0.2 mm silica gel 60 F₂₅₄). NMR solvent (CDCl₃) was dried over type 4 Å molecular sieves prior to use.

3.2. Characterisation

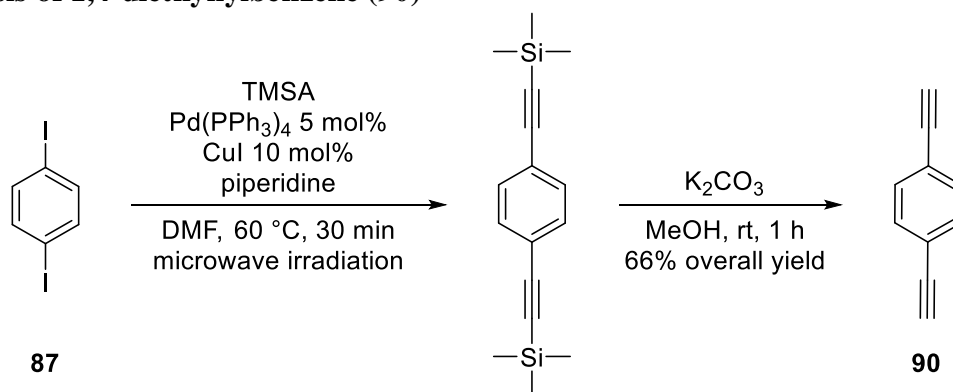
¹H- and ¹³C-NMR spectra were recorded on Varian Gemini 300 MHz and 400 MHz, Bruker UltraShield 400 MHz and Bruker Ascend 500 MHz spectrometers at the field strength indicated and deuterated solvents were used as specified. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent signal for ¹H-NMR (CDCl₃ = 7.26 ppm) and ¹³C-NMR (CDCl₃ = 77.16 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, br = broad), coupling constant (reported in Hertz), and integration. FT-IR spectra were recorded on a Perkin-Elmer Spectrum 100 spectrometer. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units and the mass spectra were measured out on Shimadzu LCMS and Axima-CFR MALDI-TOF

instruments. HRMS was carried out by EPSRC National Mass Spectrometry Service Centre at the Swansea University, Wales. Optical rotation values were measured on a Perkin-Elmer 241 polarimeter. Melting points were recorded using open capillary tubes on a melting point apparatus and are uncorrected. Microwave irradiations were carried out in Biotage Emrys Creator and Emrys Optimiser MW reactors.

3.3. Caution

Acetylene and azides are generally regarded as potentially explosive compounds. Although during the preparations described here no problems were encountered, it is advisable that appropriate handling precautions should be exercised while working with these materials.

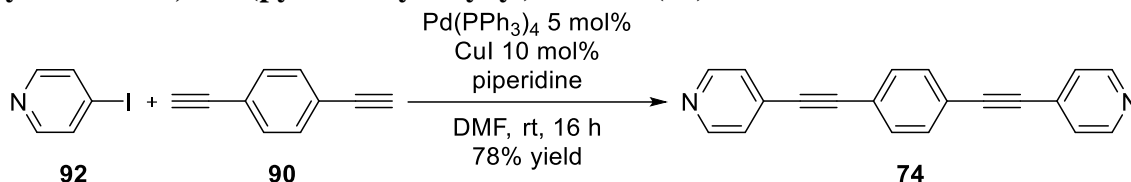
Synthesis of 1,4-diethynylbenzene (**90**)^{1,2}



1,4-Diiodobenzene (**87**) (1.0 g, 3.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.18 g, 0.15 mmol), copper(I) iodide (0.06 g, 0.30 mmol), and trimethylsilylacetylene (1.08 mL, 0.75 g, 7.60 mmol) were combined and stirred in anhydrous *N,N*-dimethylformamide (10 mL) in a Biotage 20 mL microwave vial sealed with a PTFE crimp cap at room temperature under a nitrogen atmosphere for 30 minutes. Piperidine (0.90 mL, 0.77 g, 9.10 mmol) was added *via* syringe and the reaction mixture submitted to a microwave irradiation (Biotage Emrys Creator MW synthesiser, 300 W) at 60 °C for 30 minutes. After cooling to room temperature, water (8 mL) was added, the mixture transferred to a separating funnel and the organic components extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water (3 × 100 mL), dried over magnesium sulfate and filtered. The solvent was evaporated *in vacuo*, and methanol (20 mL) and potassium carbonate (1.05 g, 7.60 mmol) added. The reaction mixture was stirred at room temperature for 1 hour and the methanol evaporated *in vacuo*. Purification by flash column chromatography on silica gel (diethyl ether / petroleum ether 5 : 95) afforded **90** as an off white solid (0.25 g, 2.0 mmol, 66% yield) with the following physicochemical characteristics.

$R_f = 0.70$ (silica gel, ethyl acetate / *n*-hexane 0.25 : 9.75); $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 7.44 (s, 4H, H_{Ar}), 3.17 (s, 2H, $\text{C}\equiv\text{CH}$) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 132.3, 122.8, 83.2 ($\text{C}\equiv\text{CH}$), 79.2 ($\text{C}\equiv\text{CH}$) ppm. The physicochemical analysis data corresponded closely to those reported in the literature by Plater *et al.*¹

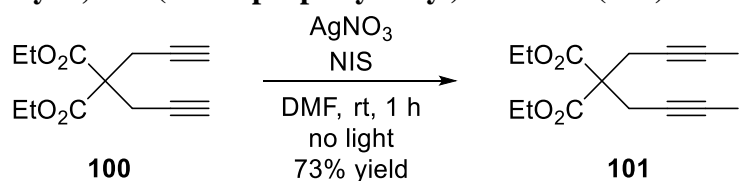
Synthesis of 1,4-bis(pyridin-4-ylethynyl)benzene (**74**)²



A mixture of 4-iodopyridine (**92**) (0.41 g, 2.0 mmol), 1,4-diethynylbenzene (**90**) (0.10 g, 0.80 mmol), tetrakis(triphenylphosphine)palladium(0) (0.12 g, 0.10 mmol), and copper(I) iodide (0.04 g, 0.20 mmol) was stirred in anhydrous *N,N*-dimethylformamide (10 mL) in a 25 mL round-bottom flask at room temperature under a nitrogen atmosphere for 30 minutes. Piperidine (0.59 mL, 0.51 g, 6.0 mmol) was added *via* syringe and the reaction mixture stirred at room temperature for 16 hours. Water (10 mL) was added, the mixture transferred to a separating funnel and the organic components extracted with ethyl acetate (3 \times 20 mL). The combined organic layers were washed with water (3 \times 100 mL), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (dichloromethane / ethyl acetate 3 : 7 with 1% of triethylamine), and filtration through a plug of Florisil[®] eluting with ethyl acetate afforded **74** as a pale yellow solid (0.17 g, 0.60 mmol, 78% yield) with the following physicochemical characteristics.

$R_f = 0.31$ (silica gel, dichloromethane / ethyl acetate 2 : 8 with 1% of triethylamine); $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 8.62 (m, 4H, H_{Ar}), 7.55 (s, 4H, H_{Ar}), 7.38 (m, 4H, H_{Ar}) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz) δ 150.0, 132.1, 131.1, 125.6, 123.0, 93.3 ($\text{C}\equiv\text{C}$), 88.9 ($\text{C}\equiv\text{C}$) ppm. The physicochemical analysis data corresponded closely to those reported in the literature by Yamauchi *et al.*³

Synthesis of diethyl 2,2-bis(3-iodoprop-2-yn-1-yl)malonate (**101**)⁴

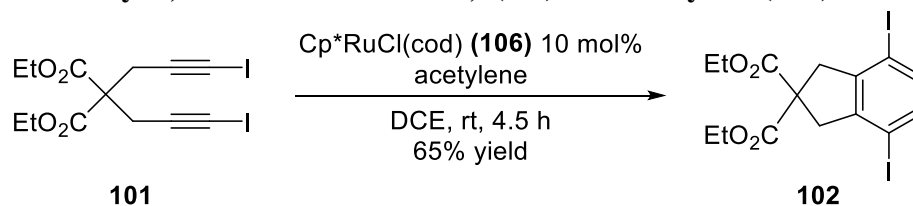


Diethyl 2,2-di(prop-2-yn-1-yl)malonate (**100**) (0.63 g, 2.70 mmol), *N*-iodosuccinimide (2.39 g, 8.10 mmol), and silver nitrate (0.45 g, 2.70 mmol) were combined and stirred in anhydrous *N,N*-dimethylformamide (20 mL) in a 100 mL round-bottom flask covered with

an aluminium foil at room temperature for 1 hour. Water (30 mL) was added, the mixture transferred to a separating funnel and the organic components extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium thiosulfate solution (2 × 50 mL), water (3 × 100 mL) and saturated aqueous sodium chloride solution (2 × 50 mL), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (diethyl ether / petroleum ether 2 : 8) afforded **101** as a pale yellow solid (0.95 g, 1.90 mmol, 73% yield) with the following physicochemical characteristics.

$R_f = 0.40$ (silica gel, diethyl ether / *n*-hexane 2 : 8); mp 77 – 79 °C; FT-IR (thin film) 2989, 1725 (C=O), 1287, 1193, 1028 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 4.22 (q, $J = 7.1$ Hz, 4H, CH_2CH_3), 3.12 (s, 4H, $\text{CH}_2\text{C}\equiv\text{C}$), 1.26 (t, $J = 7.1$ Hz, 6H, CH_2CH_3) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz) δ 168.5 (C=O), 88.7 ($\text{C}\equiv\text{CI}$), 62.3 (CH_3CH_2), 56.9 (CCH_2), 25.2 (CCH_2), 14.2 (CH_3CH_2), -2.2 ($\text{C}\equiv\text{CI}$) ppm; MS (EI) m/z 488.9 [M+H]; HRMS (NSI) Calculated for $\text{C}_{13}\text{H}_{15}\text{I}_2\text{O}_4$ [M+H] 488.9054, found 488.9058.

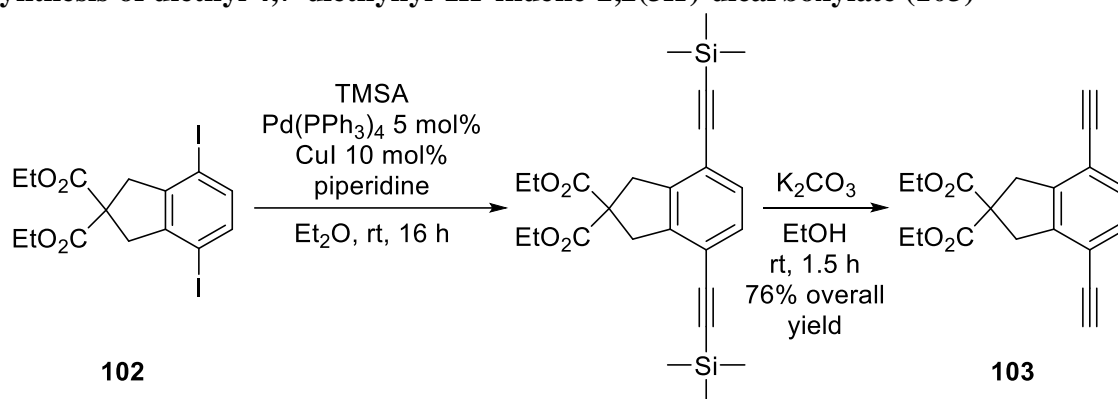
Synthesis of diethyl 4,7-diiodo-1*H*-indene-2,2(3*H*)-dicarboxylate (**102**)⁴



A solution of chloro(pentamethylcyclopentadienyl)(cyclooctadiene)ruthenium(II) (0.02 g, 0.05 mmol) in anhydrous 1,2-dichloroethane (7.5 mL) was stirred in a 50 mL two-neck round-bottom flask equipped with a syringe needle (acts as a gas outlet) at room temperature under an acetylene atmosphere (handling precautions should be taken: acetylene is a flammable gas, which can form explosive mixtures with air; for purification see section 3.1). Diethyl 2,2-bis(3-iodoprop-2-yn-1-yl)malonate (**101**) (0.50 g, 1.0 mmol) dissolved in anhydrous 1,2-dichloroethane (7.5 mL) was added dropwise *via* syringe and the reaction mixture stirred at room temperature under an acetylene atmosphere for 2 hours. A solution of chloro(pentamethylcyclopentadienyl)(cyclooctadiene)ruthenium(II) (0.02 g, 0.05 mmol) in anhydrous 1,2-dichloroethane (3 mL) was added dropwise *via* syringe, the reaction mixture stirred at room temperature under an acetylene atmosphere for a further 2.5 hours and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (diethyl ether / petroleum ether 2 : 8) afforded **102** as a pale yellow crystalline solid (0.34 g, 0.70 mmol, 65% yield) with the following physicochemical characteristics.

$R_f = 0.54$ (silica gel, diethyl ether / *n*-hexane 2 : 8); mp 78 – 80 °C; FT-IR (thin film) 2980, 1724 (C=O), 1439, 1387, 1363, 1242, 1181, 1071, 1003, 868, 809 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 7.24 (s, 2H, H_{Ar}), 4.23 (q, $J = 7.1$ Hz, 4H, CH_2CH_3), 3.68 (s, 4H, CCH_2C), 1.27 (t, $J = 7.1$ Hz, 6H, CH_2CH_3) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 171.3 (C=O), 145.3, 138.1, 92.7, 62.2 (CH_3CH_2), 56.9 (CCH_2), 47.1 (CCH_2), 14.1 (CH_3CH_2) ppm; MS (EI) m/z 514.9 [M+H]; HRMS (NSI) Calculated for $\text{C}_{15}\text{H}_{17}\text{I}_2\text{O}_4$ [M+H] 514.9211, found 514.9216.

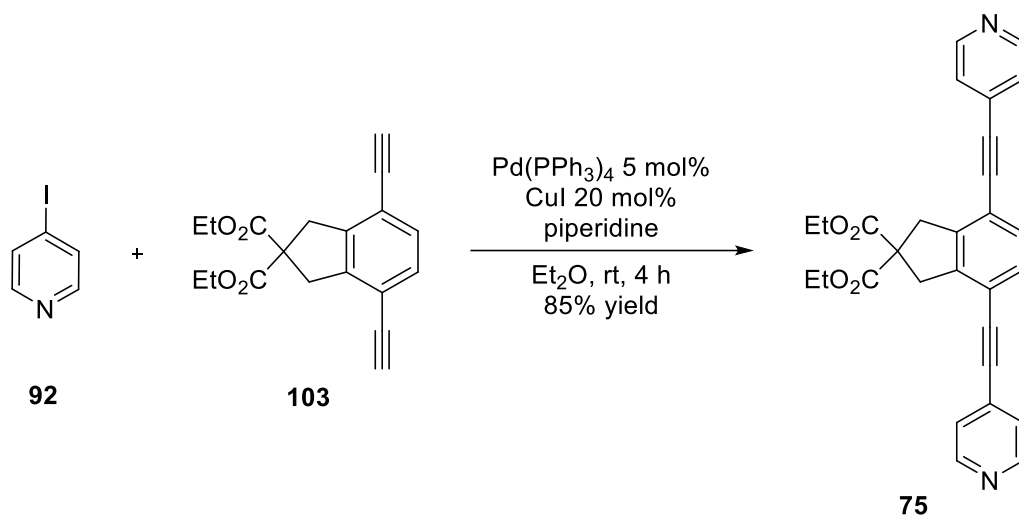
Synthesis of diethyl 4,7-diethynyl-1*H*-indene-2,2(3*H*)-dicarboxylate (**103**)^{1,2}



Diethyl 4,7-diiodo-1*H*-indene-2,2(3*H*)-dicarboxylate (**102**) (0.30 g, 0.60 mmol), tetrakis(triphenylphosphine)palladium(0) (0.03 g, 0.03 mmol), copper(I) iodide (0.01 g, 0.06 mmol), and trimethylsilylacetylene (0.21 mL, 0.14 g, 1.50 mmol) were combined and stirred in anhydrous diethyl ether (10 mL) in a 25 mL round-bottom flask at room temperature under a nitrogen atmosphere for 30 minutes. Piperidine (0.17 mL, 0.15 g, 1.80 mmol) was added *via* syringe and the reaction mixture stirred for a further 16 hours at room temperature. The resulting suspension was filtered through a plug of silica gel eluting with diethyl ether, the solvent evaporated *in vacuo*, and potassium carbonate (0.20 g, 1.40 mmol) and ethanol (12 mL) added to the flask. The reaction mixture was stirred at room temperature for 1.5 hours and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (diethyl ether / petroleum ether 2 : 8) afforded **103** as a pale yellow solid (0.14 g, 0.50 mmol, 76% yield) with the following physicochemical characteristics.

$R_f = 0.29$ (silica gel, diethyl ether / *n*-hexane 2 : 8); mp 79 – 81 °C; FT-IR (thin film) 3247 ($\text{C}\equiv\text{CH}$), 2996, 1729 (C=O), 1482, 1251, 1165, 1013, 848, 652 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 7.26 (s, 2H, H_{Ar}), 4.22 (q, $J = 7.1$ Hz, 4H, CH_2CH_3), 3.70 (s, 4H, CCH_2C), 3.31 (s, 2H, $\text{C}\equiv\text{CH}$), 1.27 (t, $J = 7.1$ Hz, 6H, CH_2CH_3) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ 171.5 (C=O), 143.4, 130.7, 119.0, 82.4 ($\text{C}\equiv\text{CH}$), 81.4 ($\text{C}\equiv\text{CH}$), 62.1 (CH_3CH_2), 59.0 (CCH_2), 40.8 (CCH_2), 14.2 (CH_3CH_2) ppm; MALDI-TOF-MS m/z 333.0 [M+Na]; HRMS (NSI) Calculated for $\text{C}_{19}\text{H}_{19}\text{O}_4$ [M+H] 311.1278, found 311.1285.

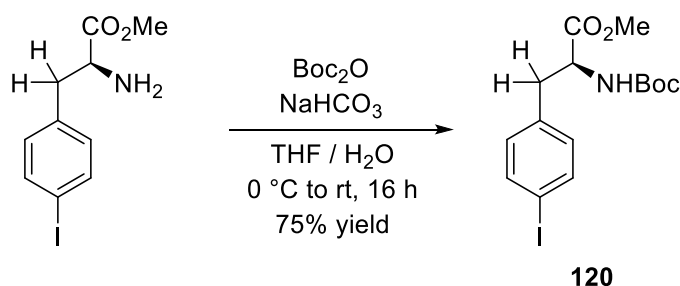
Synthesis of diethyl 4,7-bis(pyridin-4-ylethynyl)-1*H*-indene-2,2(3*H*)-dicarboxylate (**75**)²



A mixture of 4-iodopyridine (**92**) (0.05 g, 0.20 mmol), tetrakis(triphenylphosphine) palladium(0) (0.01 g, 0.01 mmol), copper(I) iodide (0.01 g, 0.02 mmol), and piperidine (0.07 mL, 0.06 g, 0.70 mmol) was stirred in anhydrous diethyl ether (2 mL) in a 10 mL round-bottom flask at room temperature under a nitrogen atmosphere for 30 minutes. Diethyl 4,7-diethynyl-1*H*-indene-2,2(3*H*)-dicarboxylate (**103**) (0.03 g, 0.10 mmol) dissolved in anhydrous diethyl ether (1 mL) was added and the reaction mixture stirred at room temperature under a nitrogen atmosphere for 2 hours. A mixture of tetrakis(triphenylphosphine)palladium(0) (0.01 g, 0.01 mmol) and copper(I) iodide (0.01 g, 0.02 mmol) in anhydrous diethyl ether (1 mL) was added. The reaction mixture was stirred for a further 2 hours under a nitrogen atmosphere and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (1st column: ethyl acetate 100% with 1% of triethylamine; 2nd column: dichloromethane / methanol 98 : 2) afforded **75** as a pale yellow solid (0.05 g, 0.10 mmol, 85% yield) with the following physicochemical characteristics.

R_f = 0.45 (silica gel, ethyl acetate 100%); mp 175 – 177 °C; FT-IR (thin film) 2978, 2215, 1727 (C=O), 1590, 1250, 1158, 1074, 821 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 8.63 (d, J = 5.3 Hz, 4H, H_{Ar}), 7.43 – 7.36 (m, 6H, H_{Ar}), 4.26 (q, J = 7.1 Hz, 4H, CH_2CH_3), 3.79 (s, 4H, CCH_2C), 1.29 (t, J = 7.0 Hz, 6H, CH_2CH_3) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz) δ 171.4 (C=O), 150.0, 143.3, 131.1, 130.7, 125.7, 119.3, 92.1 ($\text{C}\equiv\text{C}$), 91.5 ($\text{C}\equiv\text{C}$), 62.3 (CH_3CH_2), 59.1 (CCH_2), 40.8 (CCH_2), 14.2 (CH_3CH_2) ppm; MS (EI) m/z 465.2 [$\text{M}+\text{H}$]; HRMS (NSI) Calculated for $\text{C}_{29}\text{H}_{25}\text{N}_2\text{O}_4$ [$\text{M}+\text{H}$] 465.1809, found 465.1804.

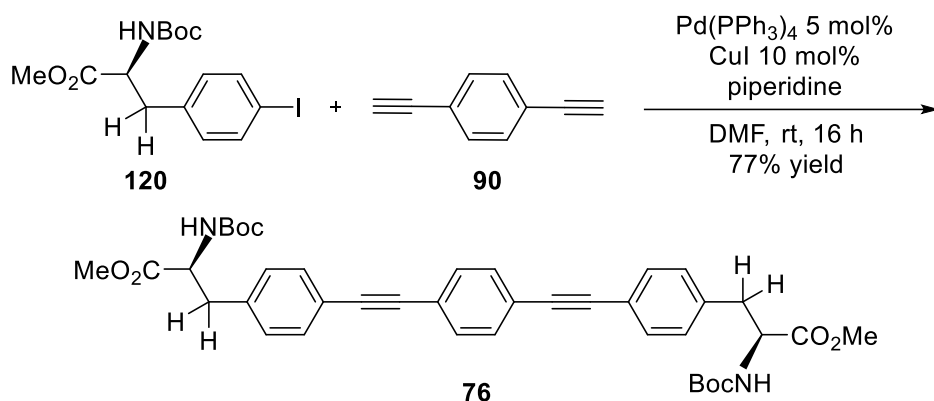
Synthesis of (*S*)-methyl 2-((*t*-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoate (**120**)⁵



A solution of (*S*)-methyl 2-amino-3-(4-iodophenyl)propanoate (0.54 g, 1.80 mmol) in a mixture of tetrahydrofuran (5 mL) and water (5 mL) was stirred in a 25 mL round-bottom flask at 0 °C. Sodium bicarbonate (0.44 g, 5.30 mmol) and di-*t*-butyl dicarbonate (0.48 mL, 0.46 g, 2.10 mmol) were successively added and the resulting mixture stirred at 0 °C for 30 minutes. The reaction mixture was allowed to warm to room temperature and stirred for a further 16 hours. The turbid solution was transferred to a separating funnel and the organic components extracted with diethyl ether (2 × 10 mL). The aqueous layer was acidified to pH ≈ 4 by the addition of a 1 M aqueous hydrochloric acid solution at 0 °C and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo* affording **120** as a white solid (0.54 g, 1.30 mmol, 75% yield) with the following physicochemical characteristics.

$R_f = 0.58$ (silica gel, ethyl acetate / *n*-hexane 2.5 : 7.5); $[\alpha]_D^{21} +44.80$ (c 1.0, CHCl_3); $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.61 (d, $J = 8.4$ Hz, 2H, H_{Ar}), 6.87 (d, $J = 8.2$ Hz, 2H, H_{Ar}), 4.97 (d, $J = 8.1$ Hz, 1H, NH), 4.59 – 4.54 (m, 1H, αCH), 3.71 (s, 3H, CH_3), 3.07 (dd, $J = 13.8, 5.7$ Hz, 1H, βCHH), 2.98 (dd, $J = 13.8, 5.9$ Hz, 1H, βCHH), 1.42 (s, 9H, $\text{C}(\text{CH}_3)_3$) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz) δ 172.2 ($\text{CH}_3\text{OC}=\text{O}$), 155.1 ($\text{NHC}=\text{O}$), 137.8, 135.9, 131.5, 92.7, 80.2 ($(\text{CH}_3)_3\text{C}$), 54.3 (αCH), 52.5 (CH_3O), 38.1 (βCH_2), 28.4 ($(\text{CH}_3)_3$) ppm. The physicochemical analysis data corresponded closely to those reported in the literature by Miyake-Stoner *et al.*⁶

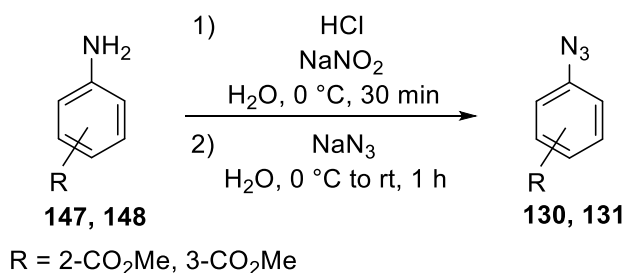
Synthesis of (2*S*,2'*S*)-dimethyl 3,3'-((1,4-phenylenebis(ethyne-2,1-diyl))bis(4,1-phenylene))bis(2-((*t*-butoxycarbonyl)amino)propanoate) (76**)²**



(*S*)-Methyl 2-((*t*-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoate (**120**) (0.21 g, 0.50 mmol), tetrakis(triphenylphosphine)palladium(0) (0.03 g, 0.03 mmol), copper(I) iodide (0.01 g, 0.05 mmol), and 1,4-diethynylbenzene (**90**) (0.03 g, 0.20 mmol) were combined and stirred in anhydrous *N,N*-dimethylformamide (5 mL) in a 25 mL round-bottom flask at room temperature under a nitrogen atmosphere for 45 minutes. Piperidine (0.16 mL, 0.13 g, 1.60 mmol) was added *via* syringe and the reaction mixture stirred at room temperature for 16 hours. Water (5 mL) was added, the mixture transferred to a separating funnel and the organic components extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (3 × 50 mL), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (diethyl ether / petroleum ether 1 : 1) afforded **76** as a pale yellow solid (0.13 g, 0.20 mmol, 77% yield) with the following physicochemical characteristics.

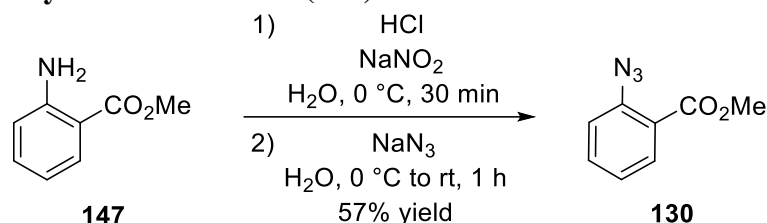
$R_f = 0.57$ (silica gel, ethyl acetate / petroleum ether 4 : 6); $[\alpha]_D^{21} +66.10$ (c 1.0, CHCl₃); ¹H-NMR (CDCl₃, 500 MHz) δ 7.49 (s, 4H, H_{Ar}), 7.46 (d, $J = 8.2$ Hz, 4H, H_{Ar}), 7.13 (d, $J = 8.1$ Hz, 4H, H_{Ar}), 4.99 (d, $J = 8.0$ Hz, 2H, NH), 4.62 – 4.58 (m, 2H, α CH), 3.72 (s, 6H, CH₃), 3.14 (dd, $J = 13.7, 5.8$ Hz, 2H, β CHH), 3.06 (dd, $J = 13.7, 6.0$ Hz, 2H, β CHH), 1.43 (s, 18H, C(CH₃)₃) ppm; ¹³C-NMR (CDCl₃, 75 MHz) δ 172.5 (CH₃OC=O), 155.3 (NHC=O), 136.9, 132.0, 131.8, 129.7, 123.3, 122.0, 91.2 (C \equiv C), 89.5 (C \equiv C), 80.2 ((CH₃)₃C), 54.5 (α CH), 52.4 (CH₃O), 38.5 (β CH₂), 28.4 ((CH₃)₃) ppm. The physicochemical analysis data corresponded closely to those reported in the literature by Kayser *et al.*⁷

General procedure for the conversion of methyl aminobenzoates **147, **148** into corresponding methyl azidobenzoates **130**, **131**⁸**



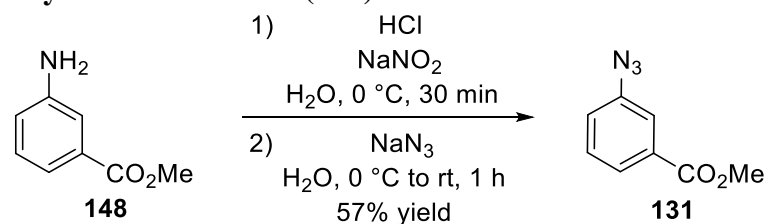
A mixture of methyl aminobenzoate **147**, **148** (1 equivalent) and concentrated hydrochloric acid (45 equivalents) was stirred in a 50 mL round-bottom flask at 0 °C. A 0.2 M aqueous sodium nitrite solution (1 equivalent) was added dropwise *via* syringe and the reaction mixture stirred at 0 °C for 30 minutes. A 0.7 M aqueous sodium azide solution (10 equivalents) was slowly added *via* syringe at 0 °C and the resulting mixture allowed to warm to room temperature and stirred for a further 1 hour. The aqueous solution was transferred to a separating funnel and the organic components extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over magnesium sulfate and filtered. The solvent was evaporated *in vacuo* affording the corresponding methyl azidobenzoate **130**, **131**, which was used in the next step without further purification.

Synthesis of methyl 2-azidobenzoate (130**)⁸**



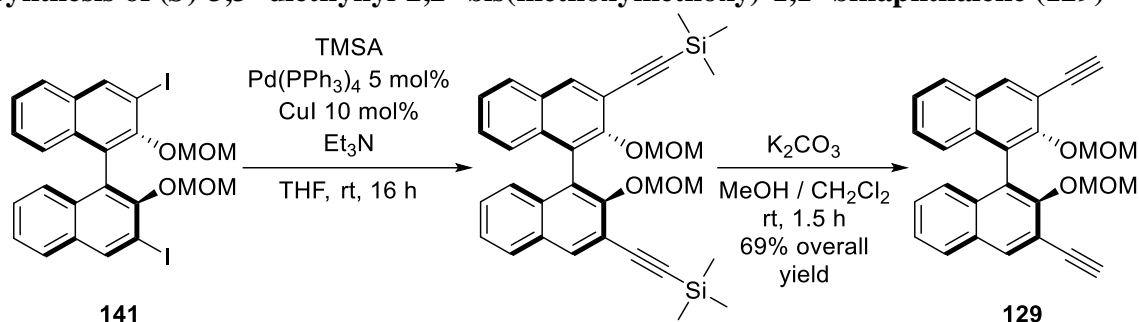
130 (0.10 g, 0.60 mmol, 57% yield) yellow oil. $R_f = 0.50$ (silica gel, diethyl ether / *n*-hexane 1 : 9); FT-IR (thin film) 2953, 2128 (N₃), 1730 (C=O), 1598, 1488, 1448, 1302, 1258, 1129, 1079, 753, 695 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 7.85 (dd, $J = 7.8$, 1.4 Hz, 1H, H_{Ar}), 7.55 – 7.51 (m, 1H, H_{Ar}), 7.24 (dd, $J = 8.1$, 0.8 Hz, 1H, H_{Ar}), 7.20 – 7.16 (m, 1H, H_{Ar}), 3.91 (s, 3H, CH₃) ppm; ¹³C-NMR (CDCl₃, 100 MHz) δ 165.8 (C=O), 140.0, 133.2, 131.8, 124.5, 122.6, 119.9, 52.3 (CH₃) ppm; MALDI-TOF-MS m/z 178.0 [M+H]; HRMS (APCI) Calculated for C₈H₈N₃O₂ [M+H] 178.0611, found 178.0611.

Synthesis of methyl 3-azidobenzoate (131**)⁸**



131 (0.13 g, 0.70 mmol, 57% yield) pale orange oil. $R_f = 0.65$ (silica gel, diethyl ether / *n*-hexane 1 : 9); FT-IR (thin film) 2953, 2115 (N_3), 1728 (C=O), 1586, 1485, 1445, 1299, 1140, 1082, 987, 884, 752 cm^{-1} ; 1H -NMR ($CDCl_3$, 400 MHz) δ 7.82 – 7.80 (m, 1H, H_{Ar}), 7.71 – 7.70 (m, 1H, H_{Ar}), 7.44 – 7.40 (m, 1H, H_{Ar}), 7.20 (ddd, $J = 8.0, 2.4, 1.0$ Hz, 1H, H_{Ar}), 3.93 (s, 3H, CH_3) ppm; ^{13}C -NMR ($CDCl_3$, 100 MHz) δ 166.2 (C=O), 140.6, 131.9, 129.8, 126.0, 123.4, 120.0, 52.4 (CH_3) ppm; MALDI-TOF-MS m/z 200.0 [$M+Na$]; HRMS (APCI) Calculated for $C_8H_8N_3O_2$ [$M+H$] 178.0611, found 178.0613.

Synthesis of (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**)⁹

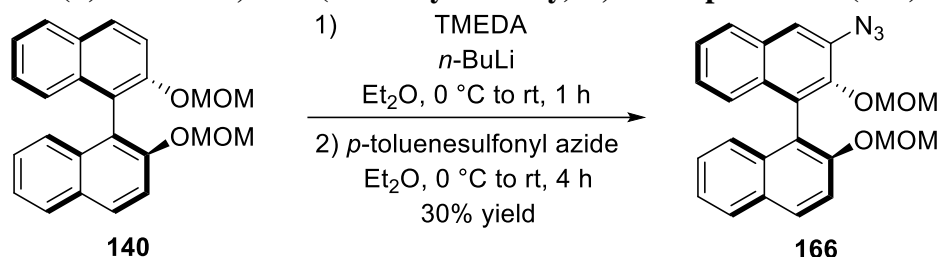


(*S*)-3,3'-Diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**141**) (0.60 g, 1.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.06 g, 0.05 mmol), and copper(I) iodide (0.02 g, 0.10 mmol) were combined and stirred in anhydrous tetrahydrofuran (8 mL) in a 25 mL round-bottom flask at room temperature under a nitrogen atmosphere. Triethylamine (0.40 mL, 0.29 g, 2.90 mmol) and trimethylsilylacetylene (0.34 mL, 0.24 g, 2.40 mmol) were successively added *via* syringe and the reaction mixture stirred at room temperature under a nitrogen atmosphere for 16 hours. Water (10 mL) was added, the mixture transferred to a separating funnel and the organic components extracted with ethyl acetate (3 \times 20 mL). The combined organic layers were dried over magnesium sulfate and filtered. The solvent was evaporated *in vacuo*, and potassium carbonate (1.20 g, 8.60 mmol) and a mixture of methanol (12 mL) and dichloromethane (1.5 mL) added. The reaction mixture was stirred at room temperature for 1.5 hours and solvents evaporated *in vacuo*. Purification by flash column chromatography on silica gel (ethyl acetate / petroleum ether 2 : 9) afforded **129** as a dark yellow solid (0.28 g, 0.70 mmol, 69% yield) with the following physicochemical characteristics.

$R_f = 0.10$ (silica gel, ethyl acetate / *n*-hexane 3 : 100); 1H -NMR ($CDCl_3$, 400 MHz) δ 8.20 (s, 2H, H_{Ar}), 7.84 (d, $J = 8.2$ Hz, 2H, H_{Ar}), 7.45 – 7.41 (m, 2H, H_{Ar}), 7.33 – 7.29 (m, 2H, H_{Ar}), 7.23 – 7.18 (m, 2H, H_{Ar}), 5.09 (d, $J = 6.1$ Hz, 2H, OCH_2O), 4.88 (d, $J = 6.1$ Hz, 2H, OCH_2O), 3.34 (s, 2H, $C\equiv CH$), 2.51 (s, 6H, CH_3) ppm; ^{13}C -NMR ($CDCl_3$, 100 MHz) δ 153.5, 135.4, 134.0, 130.2, 127.7, 127.6, 126.6, 125.9, 125.7, 116.3, 99.0 (CH_2), 81.7

($C\equiv CH$), 80.7 ($C\equiv CH$), 56.2 (CH_3) ppm. The physicochemical analysis data corresponded closely to those reported in the literature by Recsei and McErlean.⁹

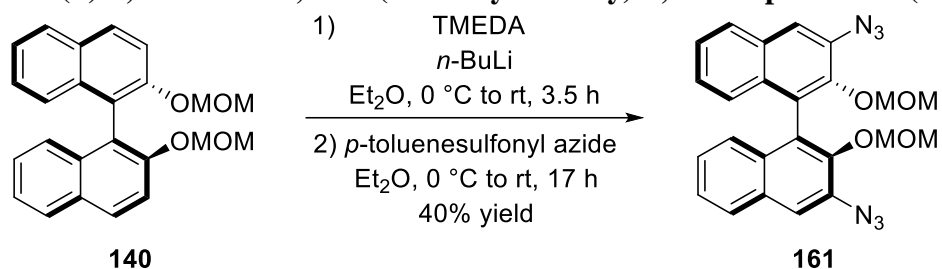
Synthesis of (*S*)-3-azido-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**166**)¹⁰



A solution of (*S*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**140**) (0.20 g, 0.50 mmol) and *N,N,N',N'*-tetramethylethylenediamine (0.32 mL, 0.25 g, 2.10 mmol) in anhydrous diethyl ether (12 mL) was stirred in a 25 mL round-bottom flask at 0 °C under a nitrogen atmosphere. *n*-Butyllithium (0.59 mL, 0.09 g, 1.50 mmol, 2.5 M solution in hexane) was added dropwise *via* syringe, the reaction mixture allowed to warm to room temperature and stirred for 1 hour. After cooling the reaction mixture to 0 °C, *p*-toluenesulfonyl azide (0.25 mL, 0.32 g, 1.60 mmol) was added dropwise *via* syringe and the reaction mixture stirred at 0 °C under a nitrogen atmosphere for 1 hour. The reaction mixture was allowed to warm to room temperature and stirred for a further 3 hours. Water (10 mL) was added and the mixture transferred to a separating funnel. The organic components were extracted with dichloromethane (3 × 10 mL) and the combined organic layers dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (ethyl acetate / petroleum ether 2 : 8), followed by recrystallisation from ethyl acetate and *n*-hexane (1 : 10), afforded **166** as pale yellow crystals (0.07 g, 0.20 mmol, 30% yield) with the following physicochemical characteristics.

R_f = 0.42 (silica gel, ethyl acetate / *n*-hexane 2 : 8); ¹H-NMR ($CDCl_3$, 500 MHz) δ 7.97 (d, J = 9.1 Hz, 1H, H_{Ar}), 7.87 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.82 (d, J = 8.2 Hz, 1H, H_{Ar}), 7.68 (s, 1H, H_{Ar}), 7.59 (d, J = 9.1 Hz, 1H, H_{Ar}), 7.43 – 7.40 (m, 1H, H_{Ar}), 7.38 – 7.34 (m, 1H, H_{Ar}), 7.30 – 7.26 (m, 1H, H_{Ar}), 7.22 – 7.14 (m, 3H, H_{Ar}), 5.14 (d, J = 7.0 Hz, 1H, OCH_2O), 5.05 (d, J = 7.0 Hz, 1H, OCH_2O), 4.78 (d, J = 5.7 Hz, 1H, OCH_2O), 4.72 (d, J = 5.7 Hz, 1H, OCH_2O), 3.21 (s, 3H, CH_3), 2.74 (s, 3H, CH_3) ppm; ¹³C-NMR ($CDCl_3$, 125 MHz) δ 153.0, 145.8, 134.0, 133.4, 131.5, 131.1, 130.1, 129.7, 129.0, 128.0, 126.9, 126.8, 126.2, 126.0, 125.8, 125.6, 124.3, 119.9, 117.5, 116.5, 99.0 (CH_2), 95.0 (CH_2), 56.6 (CH_3), 56.1 (CH_3) ppm. The physicochemical analysis data corresponded closely to those reported in the literature by Beckendorf and García Mancheño.¹⁰

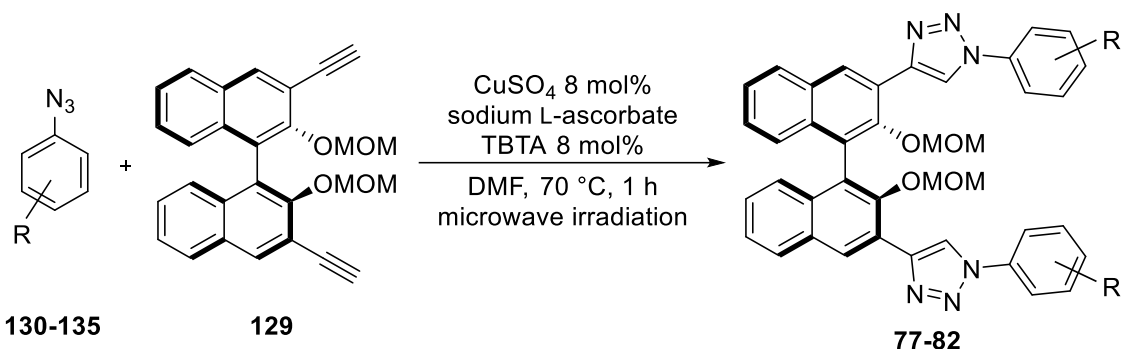
Synthesis of (*S*)-3,3'-diazido-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**161**)¹⁰



A solution of (*S*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**140**) (0.20 g, 0.50 mmol) and *N,N,N',N'*-tetramethylethylenediamine (0.32 mL, 0.25 g, 2.20 mmol) in anhydrous diethyl ether (12 mL) was stirred in a 25 mL round-bottom flask at 0 °C under a nitrogen atmosphere. *n*-Butyllithium (0.60 mL, 0.09 g, 1.50 mmol, 2.5 M solution in hexane) was added dropwise *via* syringe and the reaction mixture allowed to warm to room temperature and stirred for 1.5 hours. *N,N,N',N'*-Tetramethylethylenediamine (0.32 mL, 0.25 g, 2.20 mmol) was added *via* syringe, the reaction mixture cooled to 0 °C and *n*-butyllithium (0.60 mL, 0.09 g, 1.50 mmol, 2.5 M solution in hexane) added dropwise *via* syringe. The reaction mixture was allowed to warm to room temperature and stirred under a nitrogen atmosphere for 2 hours. After cooling the reaction mixture to 0 °C, *p*-toluenesulfonyl azide (0.50 mL, 0.63 g, 3.20 mmol) was added dropwise *via* syringe and the reaction mixture stirred at 0 °C under a nitrogen atmosphere for 1 hour. The reaction mixture was allowed to warm to room temperature and stirred for a further 16 hours. Water (10 mL) was added and the mixture transferred to a separating funnel. The organic components were extracted with dichloromethane (3 × 10 mL) and the combined organic layers dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (dichloromethane / ethyl acetate / petroleum ether 1 : 2 : 30), followed by recrystallisation from ethyl acetate and *n*-hexane (1 : 10), afforded **161** as pale yellow crystals (0.10 g, 0.20 mmol, 40% yield) with the following physicochemical characteristics.

$R_f = 0.55$ (silica gel, diethyl ether / *n*-hexane 4 : 6); ¹H-NMR (CDCl₃, 500 MHz) δ 7.81 (d, $J = 8.2$ Hz, 2H, H_{Ar}), 7.69 (s, 2H, H_{Ar}), 7.45 – 7.41 (m, 2H, H_{Ar}), 7.25 – 7.22 (m, 2H, H_{Ar}), 7.15 (d, $J = 8.6$ Hz, 2H, H_{Ar}), 4.86 (d, $J = 5.9$ Hz, 2H, OCH₂O), 4.75 (d, $J = 5.9$ Hz, 2H, OCH₂O), 2.65 (s, 6H, CH₃) ppm; ¹³C-NMR (CDCl₃, 125 MHz) δ 145.9, 133.2, 131.5, 130.9, 127.3, 126.8, 126.5, 126.2, 126.1, 117.8, 99.1 (CH₂), 56.5 (CH₃) ppm. The physicochemical analysis data corresponded closely to those reported in the literature by Beckendorf and García Mancheño.¹⁰

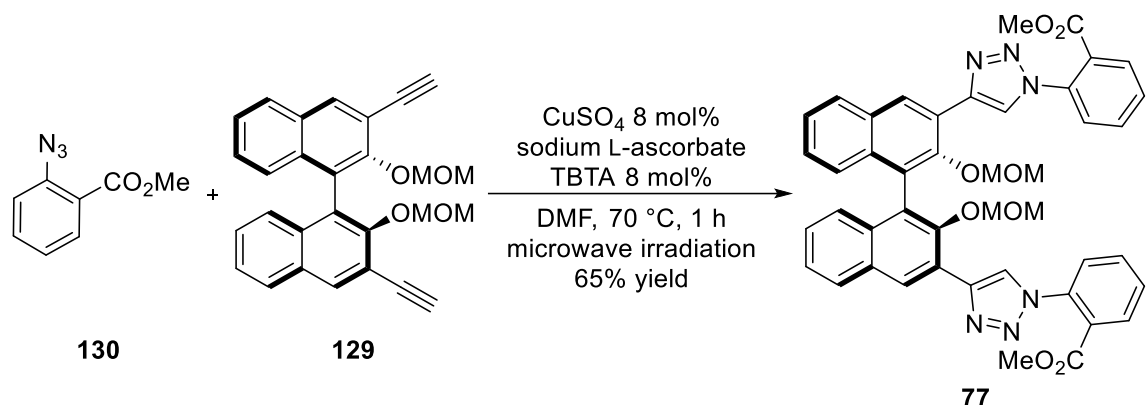
General procedure for the copper(I)-catalysed cycloaddition of azides **130 – 135 with (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**)**



R = 2-CO₂Me, 3-CO₂Me, 4-CO₂Me, 2-CN, 3-CN, 4-CN

A mixture of (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**) (1 equivalent), azide **130 – 135** (2 equivalents), copper(II) sulfate pentahydrate (8 mol%), sodium L-ascorbate (0.8 equivalents), and tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) (8 mol%) in *N,N*-dimethylformamide (4 mL) in a Biotage 5 mL microwave vial sealed with a PTFE crimp cap was submitted to a microwave irradiation (Biotage Emrys Creator synthesiser, 300 W) at 70 °C for 1 hour. After cooling to room temperature, the reaction mixture was transferred to a separating funnel and water (5 mL) added. The organic components were extracted with ethyl acetate (3 × 10 mL) and the combined organic layers washed with water (3 × 30 mL), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel afforded the corresponding (*S*)-BINOL-derived ligand **77 – 82**.

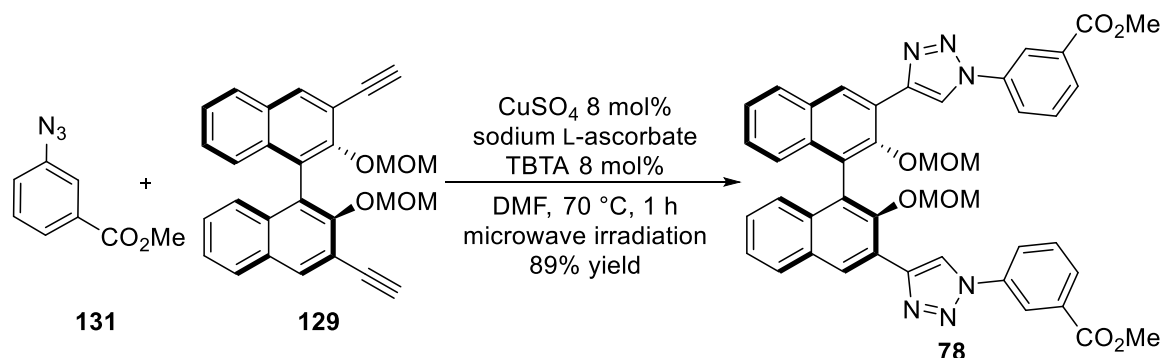
Synthesis of (*S*)-dimethyl 2,2'-(4,4'-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl))dibenzoate (77**)**



77 (0.12 g, 0.20 mmol, 65% yield) pale yellow solid. Purification by flash column chromatography on silica gel (1st column: ethyl acetate / petroleum ether 4 : 6; 2nd column: diethyl ether 100%). *R*_f = 0.16 (ethyl acetate / *n*-hexane 4 : 6); mp 63 – 65 °C; [α]_D²⁰ +168.20 (*c* 1.0, CHCl₃); FT-IR (thin film) 3172, 3067, 2957, 2834, 1731 (C=O),

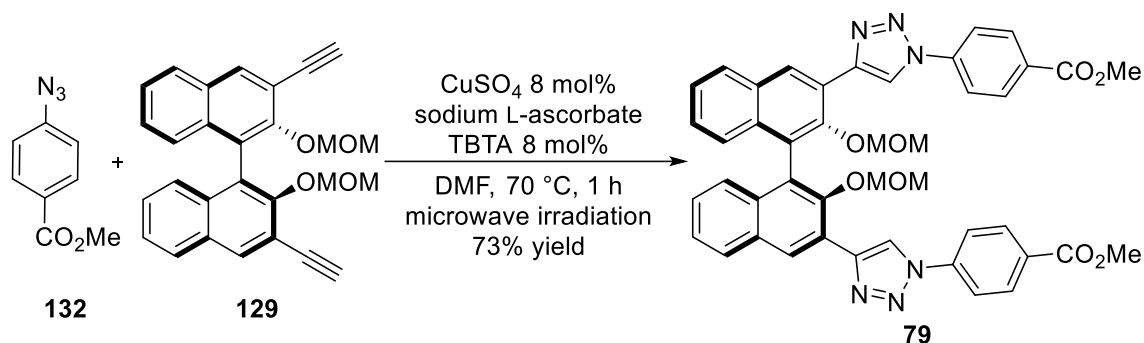
1604, 1505, 1435, 1298, 1270, 1160, 1090, 1041, 975, 911, 731 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 9.05 (s, 2H, H_{Ar}), 8.60 (s, 2H, NCH), 8.07 – 7.99 (m, 4H, H_{Ar}), 7.68 (td, $J = 7.7, 1.5$ Hz, 2H, H_{Ar}), 7.63 – 7.53 (m, 4H, H_{Ar}), 7.50 – 7.46 (m, 2H, H_{Ar}), 7.36 – 7.28 (m, 4H, H_{Ar}), 4.69 (d, $J = 4.9$ Hz, 2H, OCH_2O), 4.44 (d, $J = 4.9$ Hz, 2H, OCH_2O), 3.72 (s, 6H, $\text{CH}_3\text{OC}=\text{O}$), 2.65 (s, 6H, $\text{CH}_3\text{OCH}_2\text{O}$) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ 165.6 ($\text{C}=\text{O}$), 149.8, 143.2, 136.2, 133.8, 132.7, 131.3, 131.0, 129.9, 128.7, 128.7, 127.5, 127.1, 126.6, 126.1, 125.9, 125.7, 125.1, 124.2, 98.6 (CH_2), 56.9 ($\text{CH}_3\text{OCH}_2\text{O}$), 52.6 ($\text{CH}_3\text{OC}=\text{O}$) ppm; MALDI-TOF-MS m/z 815.1 [$\text{M}+\text{K}$]; HRMS (NSI) Calculated for $\text{C}_{44}\text{H}_{37}\text{N}_6\text{O}_8$ [$\text{M}+\text{H}$] 777.2667, found 777.2669.

Synthesis of (*S*)-dimethyl 3,3'-(4,4'-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl)dibenzoate (78)



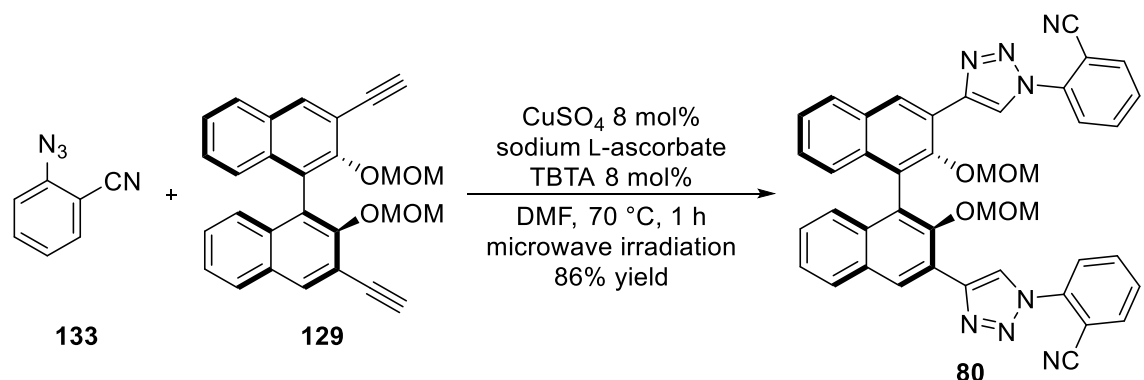
78 (0.16 g, 0.20 mmol, 89% yield) pale yellow solid. Purification by flash column chromatography on silica gel (1st column: ethyl acetate / petroleum ether 4 : 6; 2nd column: diethyl ether / petroleum ether 8 : 2). $R_f = 0.49$ (ethyl acetate / *n*-hexane 1 : 1); mp 82 – 84 °C; $[\alpha]_{\text{D}}^{20} +258.60$ (c 1.0, CHCl_3); FT-IR (thin film) 3172, 3062, 3005, 2952, 2825, 1727 ($\text{C}=\text{O}$), 1599, 1500, 1435, 1297, 1272, 1160, 1090, 1041, 974, 911, 755 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 9.06 (s, 2H, H_{Ar}), 8.91 (s, 2H, H_{Ar}), 8.45 (s, 2H, NCH), 8.13 – 8.06 (m, 6H, H_{Ar}), 7.64 (t, $J = 8.0$ Hz, 2H, H_{Ar}), 7.50 (t, $J = 7.3$ Hz, 2H, H_{Ar}), 7.39 – 7.28 (m, 4H, H_{Ar}), 4.66 (d, $J = 5.0$ Hz, 2H, OCH_2O), 4.43 (d, $J = 5.0$ Hz, 2H, OCH_2O), 3.97 (s, 6H, $\text{CH}_3\text{OC}=\text{O}$), 2.74 (s, 6H, $\text{CH}_3\text{OCH}_2\text{O}$) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ 165.9 ($\text{C}=\text{O}$), 150.1, 144.4, 137.4, 134.0, 132.1, 131.1, 130.2, 129.7, 129.0, 129.0, 127.5, 126.2, 126.0, 125.9, 124.7, 124.0, 121.4, 121.2, 99.1 (CH_2), 57.3 ($\text{CH}_3\text{OCH}_2\text{O}$), 52.7 ($\text{CH}_3\text{OC}=\text{O}$) ppm; MALDI-TOF-MS m/z 815.2 [$\text{M}+\text{K}$]; HRMS (NSI) Calculated for $\text{C}_{44}\text{H}_{37}\text{N}_6\text{O}_8$ [$\text{M}+\text{H}$] 777.2667, found 777.2669.

Synthesis of (*S*)-dimethyl 4,4'-(4,4'-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl)dibenzoate (79)



79 (0.13 g, 0.20 mmol, 73% yield) yellow solid. Purification by flash column chromatography on silica gel (ethyl acetate / petroleum ether 3 : 7). R_f = 0.10 (ethyl acetate / *n*-hexane 2 : 9); mp 216 – 218 °C; $[\alpha]_D^{24} +250.30$ (*c* 1.0, CHCl₃); FT-IR (thin film) 3171, 3058, 3006, 2952, 2823, 1723 (C=O), 1607, 1518, 1437, 1281, 1236, 1160, 1110, 1040, 974, 918, 769 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 9.07 (s, 2H, H_{Ar}), 8.90 (s, 2H, NCH), 8.22 (d, J = 8.7 Hz, 4H, H_{Ar}), 8.07 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.93 (d, J = 8.7 Hz, 4H, H_{Ar}), 7.52 – 7.49 (m, 2H, H_{Ar}), 7.38 – 7.30 (m, 4H, H_{Ar}), 4.65 (d, J = 4.9 Hz, 2H, OCH₂O), 4.42 (d, J = 4.9 Hz, 2H, OCH₂O), 3.96 (s, 6H, CH₃OC=O), 2.74 (s, 6H, CH₃OCH₂O) ppm; ¹³C-NMR (CDCl₃, 100 MHz) δ 166.0 (C=O), 149.9, 144.5, 140.3, 134.0, 131.5, 131.1, 130.3, 129.0, 127.6, 126.1, 126.0, 125.9, 123.9, 121.2, 119.9, 99.0 (CH₂), 57.3 (CH₃OCH₂O), 52.6 (CH₃OC=O) ppm, one ¹³C signal not observed; MALDI-TOF-MS m/z 815.3 [M+K]; HRMS (NSI) Calculated for C₄₄H₃₇N₆O₈ [M+H] 777.2667, found 777.2676.

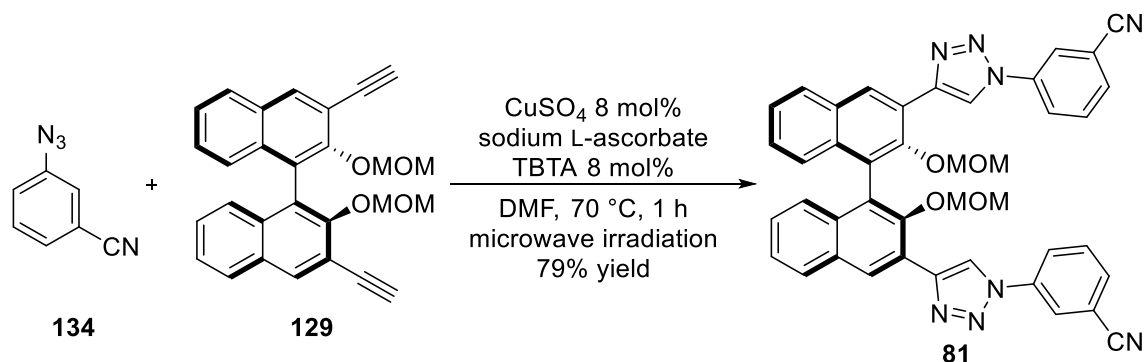
Synthesis of (*S*)-2,2'-(4,4'-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl)dibenzonitrile (80)



80 (0.14 g, 0.20 mmol, 86% yield) pale yellow solid. Purification by flash column chromatography on silica gel (ethyl acetate / petroleum ether 6 : 4). R_f = 0.17 (ethyl acetate / *n*-hexane 1 : 1); mp 220 – 222 °C (decomposition); $[\alpha]_D^{24} +212.50$ (*c* 1.0, CHCl₃); FT-IR (thin film) 3161, 3060, 2954, 2820, 2231 (C≡N), 1601, 1499, 1456, 1281, 1235,

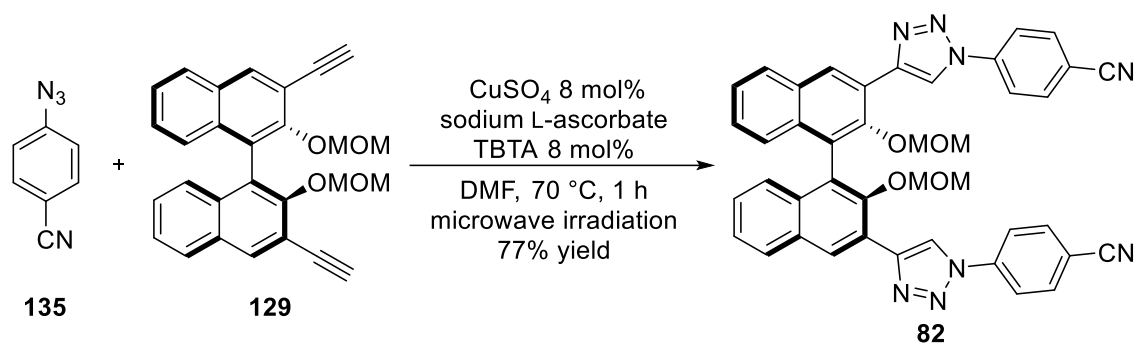
1158, 1038, 908, 764 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 9.05 (s, 2H, H_{Ar}), 8.93 (s, 2H, NCH), 8.06 (d, $J = 8.2$ Hz, 2H, H_{Ar}), 7.90 – 7.86 (m, 4H, H_{Ar}), 7.84 – 7.78 (m, 2H, H_{Ar}), 7.61 (td, $J = 7.7, 1.2$ Hz, 2H, H_{Ar}), 7.51 – 7.47 (m, 2H, H_{Ar}), 7.38 – 7.30 (m, 4H, H_{Ar}), 4.70 (d, $J = 5.1$ Hz, 2H, CH_2), 4.48 (d, $J = 5.1$ Hz, 2H, CH_2), 2.66 (s, 6H, CH_3) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ 150.2, 144.5, 138.8, 134.6, 134.4, 134.1, 131.0, 129.7, 129.1, 128.9, 127.4, 126.3, 126.0, 125.9, 125.6, 123.8, 123.7, 115.7, 107.3, 98.8 (CH_2), 57.0 (CH_3) ppm; MALDI-TOF-MS m/z 733.7 [$\text{M}+\text{Na}$]; HRMS (NSI) Calculated for $\text{C}_{42}\text{H}_{31}\text{N}_8\text{O}_4$ [$\text{M}+\text{H}$] 711.2463, found 711.2471.

Synthesis of (*S*)-3,3'-(4,4'-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl)dibenzonitrile (81)



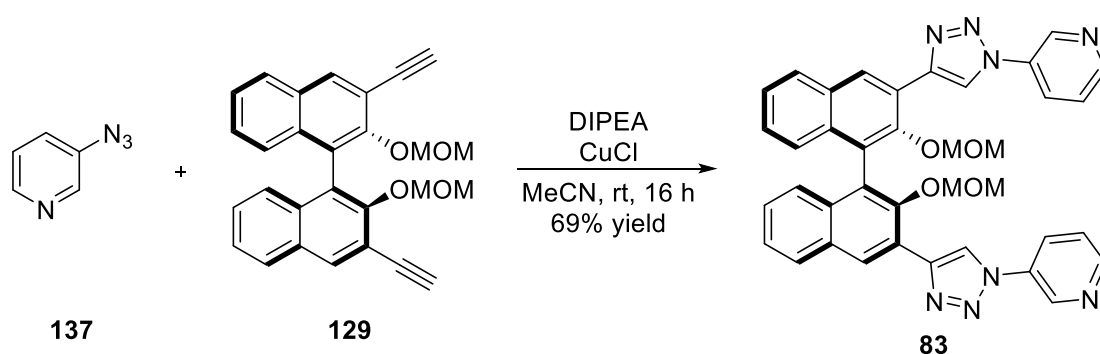
81 (0.13 g, 0.20 mmol, 79% yield) pale yellow solid. Purification by flash column chromatography on silica gel (ethyl acetate / petroleum ether 1 : 1). $R_f = 0.42$ (ethyl acetate / *n*-hexane 1 : 1); mp 89 – 91 $^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{24} +246.70$ (c 1.0, CHCl_3); FT-IR (thin film) 3152, 3058, 2929, 2822, 2233 ($\text{C}\equiv\text{N}$), 1587, 1498, 1451, 1280, 1239, 1158, 1040, 974, 913, 797, 753 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 9.07 (s, 2H, H_{Ar}), 8.87 (s, 2H, NCH), 8.16 (s, 2H, H_{Ar}), 8.11 – 8.06 (m, 4H, H_{Ar}), 7.75 – 7.67 (m, 4H, H_{Ar}), 7.54 – 7.50 (m, 2H, H_{Ar}), 7.39 – 7.29 (m, 4H, H_{Ar}), 4.64 (d, $J = 4.9$ Hz, 2H, CH_2), 4.41 (d, $J = 4.9$ Hz, 2H, CH_2), 2.75 (s, 6H, CH_3) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ 149.8, 144.7, 137.8, 134.0, 132.1, 131.1, 131.1, 129.1, 127.7, 126.1, 126.0, 125.8, 124.3, 123.6, 123.6, 121.0, 117.6, 114.4, 99.0 (CH_2), 57.4 (CH_3) ppm, one ^{13}C signal not observed; MALDI-TOF-MS m/z 711.3 [$\text{M}+\text{H}$]; HRMS (NSI) Calculated for $\text{C}_{42}\text{H}_{31}\text{N}_8\text{O}_4$ [$\text{M}+\text{H}$] 711.2463, found 711.2471.

Synthesis of (*S*)-4,4'-(4,4'-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl)dibenzonitrile (82**)**



82 (0.13 g, 0.20 mmol, 77% yield) pale yellow solid. Purification by flash column chromatography on silica gel (ethyl acetate / petroleum ether 1 : 1). $R_f = 0.62$ (ethyl acetate / *n*-hexane 1 : 1); mp 270 – 272 °C (decomposition); $[\alpha]_D^{24} +324.50$ (c 1.0, CHCl_3); FT-IR (thin film) 3158, 3064, 2959, 2824, 2231 ($\text{C}\equiv\text{N}$), 1607, 1515, 1454, 1235, 1158, 1040, 973, 917, 841, 754 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 9.07 (s, 2H, H_{Ar}), 8.90 (s, 2H, NCH), 8.08 (d, $J = 8.2$ Hz, 2H, H_{Ar}), 8.03 – 7.94 (m, 4H, H_{Ar}), 7.91 – 7.81 (m, 4H, H_{Ar}), 7.54 – 7.50 (m, 2H, H_{Ar}), 7.41 – 7.28 (m, 4H, H_{Ar}), 4.64 (d, $J = 4.9$ Hz, 2H, CH_2), 4.41 (d, $J = 4.9$ Hz, 2H, CH_2), 2.75 (s, 6H, CH_3) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ 148.7, 143.6, 138.8, 133.0, 132.9, 129.9, 127.9, 127.9, 126.6, 125.0, 124.9, 124.7, 122.4, 119.8, 119.4, 116.7, 111.3, 97.8 (CH_2), 56.2 (CH_3) ppm; MALDI-TOF-MS m/z 733.0 [$\text{M}+\text{Na}$]; HRMS (NSI) Calculated for $\text{C}_{42}\text{H}_{31}\text{N}_8\text{O}_4$ [$\text{M}+\text{H}$] 711.2463, found 711.2469.

Synthesis of (*S*)-3,3'-(4,4'-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl)dipyridine (83**)⁹**

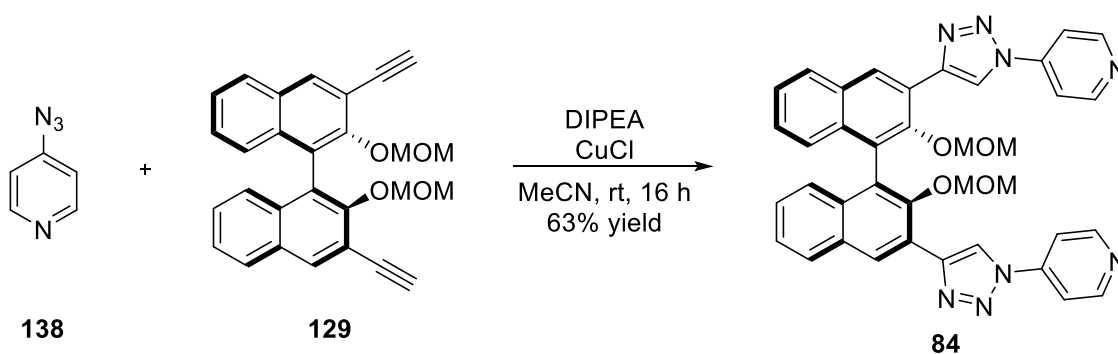


A solution of (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**) (0.03 g, 0.10 mmol) in acetonitrile (2 mL) was stirred in a 10 mL round-bottom flask at room temperature. A solution of 3-azidopyridine (**137**) (0.02 g, 0.20 mmol) in acetonitrile (1 mL) and *N,N*-diisopropylethylamine (0.50 mL, 0.37 g, 2.80 mmol) were successively added *via* syringe and the reaction mixture stirred at room temperature for 15 minutes. Copper(I) chloride (0.01 g, 0.10 mmol) was added and the reaction mixture stirred at room

temperature for 16 hours. Saturated aqueous ammonium chloride solution (5 mL) was added and the mixture transferred to a separating funnel. The organic components were extracted with ethyl acetate (3 × 5 mL) and the combined organic layers dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (methanol / dichloromethane 0.4 : 9.6) afforded **83** as a yellow solid (0.03 g, 0.10 mmol, 69% yield) with the following physicochemical characteristics.

$R_f = 0.25$ (methanol / dichloromethane 0.4 : 9.6); mp 178 – 180 °C; $[\alpha]_D^{20} +215.40$ (c 1.0, CHCl_3); FT-IR (thin film) 3165, 3055, 2934, 2826, 1586, 1497, 1430, 1354, 1236, 1160, 1061, 1041, 974, 918, 734, 701 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 9.10 (s, 2H, H_{Ar}), 9.07 (s, 2H, H_{Ar}), 8.89 (s, 2H, NCH), 8.71 (s, 2H, H_{Ar}), 8.22 – 8.20 (m, 2H, H_{Ar}), 8.07 (d, $J = 8.2$ Hz, 2H, H_{Ar}), 7.54 – 7.48 (m, 4H, H_{Ar}), 7.37 – 7.29 (m, 4H, H_{Ar}), 4.64 (d, $J = 5.0$ Hz, 2H, CH_2), 4.41 (d, $J = 5.0$ Hz, 2H, CH_2), 2.74 (s, 6H, CH_3) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz) δ 150.0, 149.9, 144.6, 141.7, 134.0, 133.8, 131.1, 129.0, 128.0, 127.6, 126.0, 126.0, 125.8, 124.4, 123.8, 121.2, 99.0 (CH_2), 57.3 (CH_3) ppm, one ^{13}C signal not observed; MALDI-TOF-MS m/z 701.2 [$\text{M}+\text{K}$]; HRMS (NSI) Calculated for $\text{C}_{38}\text{H}_{31}\text{N}_8\text{O}_4$ [$\text{M}+\text{H}$] 663.2463, found 663.2461.

Synthesis of (*S*)-4,4'-(4,4'-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl)dipyridine (**84**)⁹

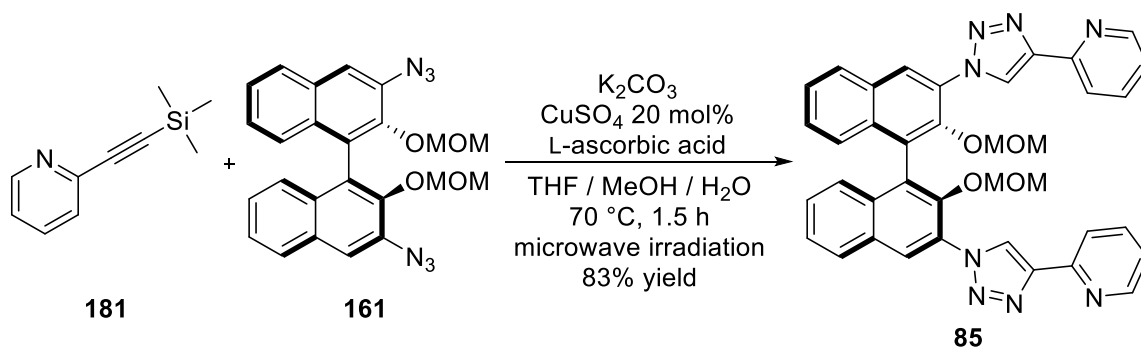


A solution of (*S*)-3,3'-diethynyl-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**129**) (0.10 g, 0.20 mmol) in acetonitrile (7.5 mL) was stirred in a 25 mL round-bottom flask at room temperature. 4-Azidopyridine (**138**) (0.06 g, 0.50 mmol) dissolved in acetonitrile (2.5 mL) and *N,N*-diisopropylethylamine (1.65 mL, 1.22 g, 9.50 mmol) were successively added *via* syringe and the reaction mixture stirred at room temperature for 15 minutes. Copper(I) chloride (0.02 g, 0.20 mmol) was added and the reaction mixture stirred at room temperature for 16 hours. Saturated aqueous ammonium chloride solution (10 mL) was added and the mixture transferred to a separating funnel. The organic components were

extracted with ethyl acetate (3×10 mL) and the combined organic layers dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (methanol / dichloromethane 0.3 : 9.7) afforded **84** as a yellow solid (0.10 g, 0.20 mmol, 63% yield) with the following physicochemical characteristics.

$R_f = 0.18$ (methanol / dichloromethane 0.3 : 9.7); mp 93 – 95 °C; $[\alpha]_D^{20} +255.30$ (c 1.0, CHCl_3); FT-IR (thin film) 3169, 3045, 2935, 2827, 1591, 1508, 1409, 1354, 1236, 1159, 1057, 1040, 973, 918, 821, 754, 734 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 9.07 (s, 2H, H_{Ar}), 8.95 (s, 2H, NCH), 8.80 (s, 4H, H_{Ar}), 8.08 (d, $J = 8.2$ Hz, 2H, H_{Ar}), 7.80 (d, $J = 6.1$ Hz, 4H, H_{Ar}), 7.53 – 7.50 (m, 2H, H_{Ar}), 7.38 – 7.35 (m, 2H, H_{Ar}), 7.31 (d, $J = 8.5$ Hz, 2H, H_{Ar}), 4.63 (d, $J = 5.0$ Hz, 2H, CH_2), 4.41 (d, $J = 5.0$ Hz, 2H, CH_2), 2.76 (s, 6H, CH_3) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz) δ 151.9, 149.9, 144.7, 143.2, 134.0, 131.1, 129.1, 129.0, 127.7, 126.1, 126.0, 125.8, 123.5, 120.5, 113.7, 99.0 (CH_2), 57.4 (CH_3) ppm; MALDI-TOF-MS m/z 701.3 $[\text{M}+\text{K}]$; HRMS (NSI) Calculated for $\text{C}_{38}\text{H}_{31}\text{N}_8\text{O}_4$ $[\text{M}+\text{H}]$ 663.2463, found 663.2461.

Synthesis of (*S*)-2,2'-(1,1'-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl))dipyridine (**85**)¹¹

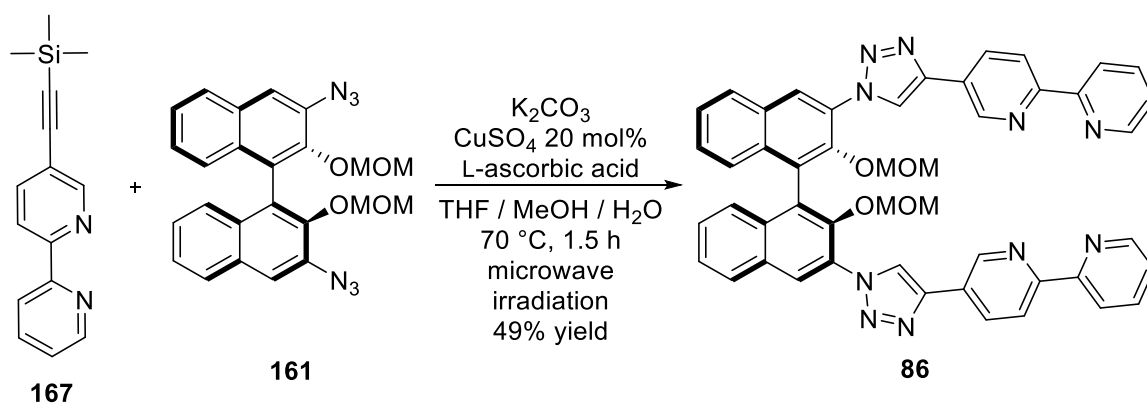


Potassium carbonate (0.05 g, 0.40 mmol), copper(II) sulfate (0.01 g, 0.04 mmol), L-ascorbic acid (0.02 g, 0.10 mmol) and (*S*)-3,3'-diazido-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**161**) (0.05 g, 0.10 mmol) were combined and stirred in a mixture of tetrahydrofuran (0.5 mL), methanol (0.5 mL) and water (0.5 mL) in a Biotage 5 mL microwave vial at room temperature. A solution of 2-((trimethylsilyl)ethynyl)pyridine (**181**) (0.04 g, 0.20 mmol) in a mixture of tetrahydrofuran (0.5 mL), methanol (0.5 mL) and water (0.5 mL) was added *via* syringe, the microwave vial sealed with a PTFE crimp cap and the reaction mixture submitted to a microwave irradiation (Biotage Emrys Creator synthesiser, 300 W) at 70 °C for 1.5 hours. After cooling to room temperature, the reaction mixture was transferred to a separating funnel and saturated aqueous ammonium chloride

solution (5 mL) added. The organic components were extracted with dichloromethane (3 × 10 mL) and the combined organic layers washed with saturated aqueous sodium bicarbonate solution (30 mL), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (methanol / dichloromethane 0.2 : 9.8) afforded **85** as a pale yellow solid (0.06 g, 0.10 mmol, 83% yield) with the following physicochemical characteristics.

$R_f = 0.17$ (methanol / dichloromethane 0.2 : 9.8); mp 58 – 60 °C; $[\alpha]_D^{20} +106.00$ (c 1.0, CHCl_3); FT-IR (thin film) 3162, 3056, 2954, 2827, 1599, 1468, 1427, 1355, 1242, 1160, 1077, 1026, 984, 954, 901, 785, 752 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 8.86 (s, 2H, H_{Ar}), 8.63 (d, $J = 4.7$ Hz, 2H, H_{Ar}), 8.43 (s, 2H, NCH), 8.26 (d, $J = 7.9$ Hz, 2H, H_{Ar}), 8.01 (d, $J = 8.2$ Hz, 2H, H_{Ar}), 7.81 (td, $J = 7.7, 1.5$ Hz, 2H, H_{Ar}), 7.55 (t, $J = 7.5$ Hz, 2H, H_{Ar}), 7.43 (t, $J = 7.7$ Hz, 2H, H_{Ar}), 7.35 (d, $J = 8.5$ Hz, 2H, H_{Ar}), 7.27 – 7.24 (m, 2H, H_{Ar}), 4.48 (d, $J = 5.9$ Hz, 2H, CH_2), 4.42 (d, $J = 6.0$ Hz, 2H, CH_2), 2.52 (s, 6H, CH_3) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz) δ 150.2, 149.8, 148.8, 146.7, 137.0, 133.7, 131.0, 130.4, 128.7, 128.3, 127.0, 126.8, 126.3, 124.7, 123.1, 120.5, 99.6 (CH_2), 56.6 (CH_3) ppm, one ^{13}C signal not observed; MALDI-TOF-MS m/z 701.2 [$\text{M}+\text{K}$]; HRMS (NSI) Calculated for $\text{C}_{38}\text{H}_{31}\text{N}_8\text{O}_4$ [$\text{M}+\text{H}$] 663.2463, found 663.2460.

Synthesis of (*S*)-5,5'-(1,1'-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl))di-2,2'-bipyridine (**86**)¹¹



Potassium carbonate (0.05 g, 0.40 mmol), copper(II) sulfate (0.01 g, 0.04 mmol), L-ascorbic acid (0.02 g, 0.10 mmol) and (*S*)-3,3'-diazido-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**161**) (0.05 g, 0.10 mmol) were combined and stirred in a mixture of tetrahydrofuran (0.5 mL), methanol (0.5 mL) and water (0.5 mL) in a Biotage 5 mL microwave vial at room temperature. A solution of 5-((trimethylsilyl)ethynyl)-2,2'-bipyridine (**167**) (0.06 g, 0.20 mmol) in a mixture of tetrahydrofuran (0.5 mL), methanol (0.5 mL) and water (0.5 mL) was added *via* syringe, the microwave vial sealed with

a PTFE crimp cap, and the reaction mixture submitted to a microwave irradiation (Biotage Emrys Creator synthesiser, 300 W) at 70 °C for 1.5 hours. After cooling to room temperature, the reaction mixture was transferred to a separating funnel and saturated aqueous ammonium chloride solution (5 mL) added. The organic components were extracted with dichloromethane (3 × 10 mL) and the combined organic layers washed with saturated aqueous sodium bicarbonate solution (30 mL), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (1st column: methanol / dichloromethane 0.4 : 9.6; 2nd column: methanol / dichloromethane 0.2 : 9.8) afforded **86** as a pale yellow solid (0.04 g, 0.10 mmol, 49% yield) with the following physicochemical characteristics.

$R_f = 0.16$ (methanol / dichloromethane 0.4 : 9.6); mp 112 – 114 °C; $[\alpha]_D^{20} +203.90$ (c 1.0, CHCl₃); FT-IR (thin film) 3145, 3053, 2955, 2827, 1574, 1455, 1354, 1243, 1161, 1078, 1037, 985, 901, 797, 749 cm⁻¹; ¹H-NMR (CDCl₃, 500 MHz) δ 9.22 (s, 2H, H_{Ar}), 8.70 (s, 2H, H_{Ar}), 8.66 (s, 2H, NCH), 8.56 – 8.38 (m, 8H, H_{Ar}), 8.04 (d, $J = 8.2$ Hz, 2H, H_{Ar}), 7.83 (t, $J = 7.7$ Hz, 2H, H_{Ar}), 7.59 – 7.56 (m, 2H, H_{Ar}), 7.47 – 7.44 (m, 2H, H_{Ar}), 7.35 – 7.30 (m, 4H, H_{Ar}), 4.53 (d, $J = 5.8$ Hz, 2H, CH₂), 4.43 (d, $J = 5.8$ Hz, 2H, CH₂), 2.61 (s, 6H, CH₃) ppm; ¹³C-NMR (CDCl₃, 125 MHz) δ 156.0, 155.8, 149.3, 146.6, 146.5, 145.2, 137.1, 134.0, 133.8, 130.4, 130.3, 128.9, 128.6, 127.0, 126.9, 126.5, 126.2, 124.0, 122.7, 121.3, 99.8 (CH₂), 56.8 (CH₃) ppm, two ¹³C signals not observed; MALDI-TOF-MS m/z 834.3 [M+NH₄]; HRMS (NSI) Calculated for C₄₈H₃₇N₁₀O₄ [M+H] 817.2994, found 817.2994.

3.4. References

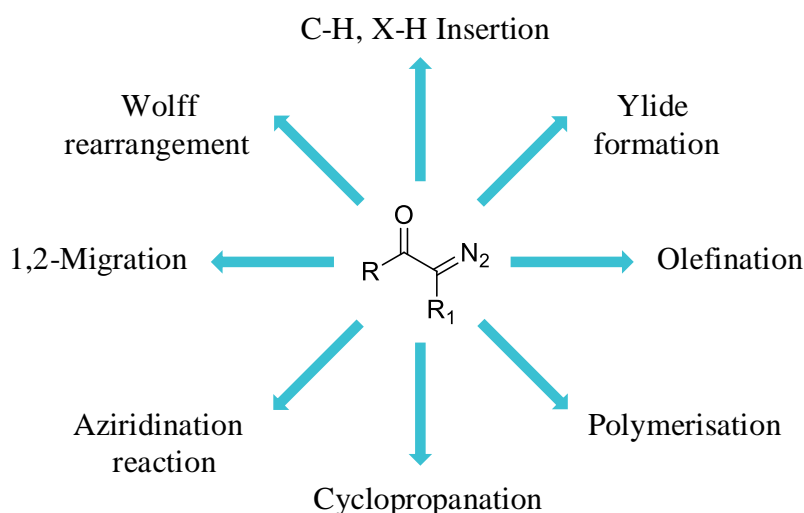
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Chapter 4
Introduction

4.1. Introduction to α -diazocarbonyl compounds

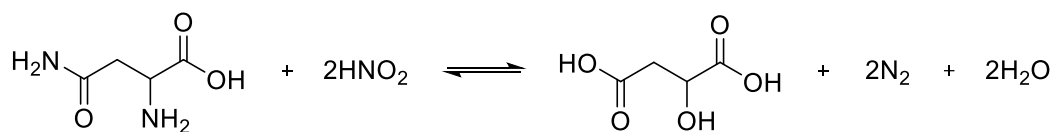
Owing to the ease of preparation and ability to undergo various chemical transformations, such as C-H and X-H bond insertion, ylide formation, cyclopropanation, aziridination reaction, 1,2-migration, and Wolff rearrangement (**Scheme 4.1**), α -diazocarbonyl compounds are exceedingly interesting to chemists.^{1,2} New applications of α -diazocarbonyl compounds could arise due to their recent employment in polymerisation and olefination.³



Scheme 4.1 Representation of various reactions of α -diazocarbonyl compounds.

4.2. Historical background of α -diazocarbonyl compounds

The chemistry of α -diazocarbonyl compounds dates back to 1858 and the discovery of a diazotization method for aromatic amines (by treating them with nitrous acid) made by Johann Peter Griess.^{4,5} Prior to this work, in 1849, Piria had already witnessed a transformation of asparagine into malic acid in the presence of nitrous acid *via* substitution of an amino group by hydroxyl group (**Scheme 4.2**).⁶



Scheme 4.2 Reaction of asparagine with nitrous acid reported by Piria.⁶

In the same year, Hunt and Hofmann made a similar observation in a reaction of aniline with nitrous acid to yield phenol.⁵ Few years later, in 1853, Gerland synthesised hydroxybenzoic acid from aminobenzoic acid.⁷ Additionally, he observed the generation of a red intermediate, the amount of which increased when the experiment was performed in dilute and cold solution.⁸ Further investigations of the aforementioned process were conducted by Griess himself and led to the isolation of diazo- derivative of an

aminobenzoic acid. Interested in this new chemistry, Griess expanded his research, which resulted in the discovery of a new class of compounds, to which the term ‘diazo’ was assigned.⁸

Several years later, in 1883, Curtius published research on the diazotization of natural α -amino acids and discovered the first aliphatic diazocarbonyl compound, ethyl α -diazooacetate (**60**) (Figure 4.1), which was prepared from glycine.^{2,9} In 1890, he also discovered a new gaseous compound built from hydrogen and nitrogen atoms and had given it the name of ‘Stickstoffwasser-stoffsäure’ with the English equivalent ‘hydrazoic acid’ (**182**) (Figure 4.1).¹⁰ The next milestone in the diazocarbonyl chemistry took place in 1902 with the discovery of diazocarbonyl rearrangement bearing the name of the author and known as the Wolff rearrangement.^{2,11}

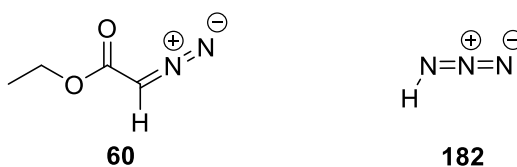


Figure 4.1 The structures of ethyl α -diazooacetate (**60**) and hydrazoic acid (**182**) discovered by Curtius.

Although α -diazocarbonyl compounds have a long history, simple diazocarbonyl compounds became readily available only in the late 1920s with the synthesis of diazoketones *via* acylation of diazomethane (see further) reported by Arndt *et al.*^{2,12} Despite the hazardous and toxic nature of diazomethane, this method, together with the diazo transfer reaction, remains one of the most frequently used methods for the synthesis of α -diazocarbonyl compounds.

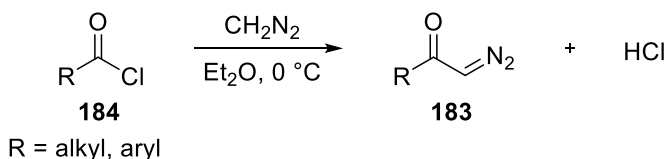
4.3. Synthesis of α -diazocarbonyl compounds

Since 1883 and the first synthesis of ethyl α -diazooacetate, there have been extensive studies carried out in search of new synthetic routes to α -diazocarbonyl compounds. Although various procedures have been successfully established over the years, acylation of diazomethane and diazo transfer reaction continue to be the main approaches to α -diazocarbonyl compounds.

4.3.1. Acylation of diazomethane

Arndt *et al.*^{2,12} were the first to report a preparation of α -diazoketones **183** *via* acylation of diazomethane. This method involves a treatment of diazomethane in diethyl ether with acid chloride **184** at 0 °C or a lower temperature (Scheme 4.3). Excess of diazomethane is

required as hydrogen chloride generated as by-product of this transformation could subsequently undergo a reaction with the desired α -diazocarbonyl compound **183** to form α -chlorocarbonyl compound.



Scheme 4.3 General scheme for the synthesis of α -diazoketones **183** *via* acylation method.

To avoid the use of an excess of diazomethane, utilisation of a tertiary amine to remove the hydrogen chloride produced in the reaction was proposed by Newman and Beal.¹³ This approach yielded the α -diazoketones in excellent yields while consuming only one equivalent of diazomethane, but was restricted to aromatic acid chlorides.

The use of anhydrides as acylating agents for diazomethane is also well known and may be utilised when the conventional procedure with acid chlorides fails. For application of this method a carboxylic acid is usually first treated with *N,N'*-dicyclohexylcarbodiimide to generate an acid anhydride intermediate, which is thereafter allowed to react with diazomethane to afford the α -diazoketone.¹⁴

In cases of acid-sensitive starting materials, mixed anhydrides can also be employed as precursors of α -diazoketones. Generated *in situ* in a reaction of carboxylic acid with chloroformate, *e.g.*, methyl, ethyl, or isobutyl chloroformate, the intermediate anhydride is treated with diazomethane to afford the desired α -diazocarbonyl compound.

Acylation of diazomethane with acyl chlorides or anhydrides has been successfully applied over the past years. Syntheses of such compounds as the anticancer bisdiazoketone azotomycin **185**¹⁵ and an antibiotic 6-diazo-5-oxo-L-norleucine (**186**),¹⁶ commonly known as DON (**Figure 4.2**), had been performed *via* this method and were described in the literature.

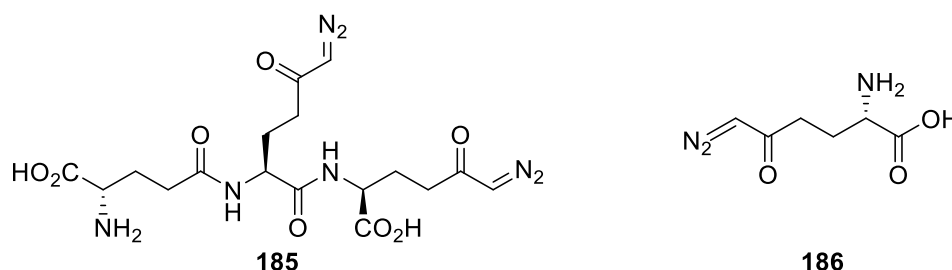


Figure 4.2 Structures of azotomycin **185** and 6-diazo-5-oxo-L-norleucine (**186**) reported by Pettit and Nelson¹⁵ and DeWald and Moore¹⁶ respectively.

Furthermore, this approach has been also employed in the preparation of chiral non-racemic α -diazoketones **187** and **188** from *N*-protected L-proline and L-phenylalanine (Figure 4.3).

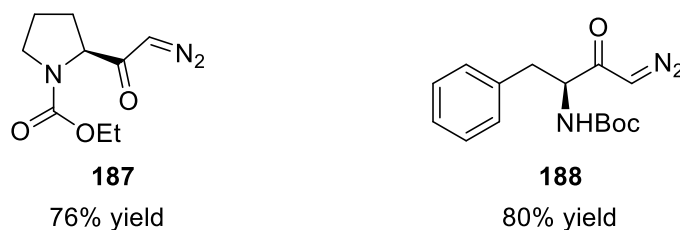
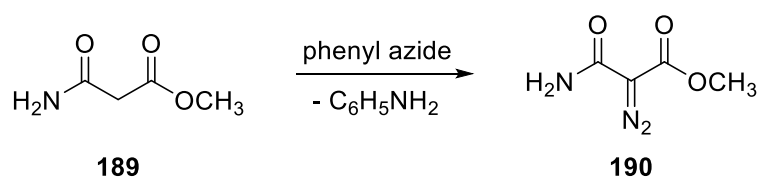


Figure 4.3 Chiral non-racemic α -diazoketones **187** and **188** reported by Ye and McKervey.¹⁷

The protocol for the acylation of diazomethane, first published in 1927,¹² contributed towards the growth in utility of α -diazocarbonyl compounds in synthetic transformations. Acetylation of diazomethane is a powerful method but it cannot be used if the carbonyl group is embedded in a cyclic system or is, for example, part of a 1,3-dicarbonyl system.

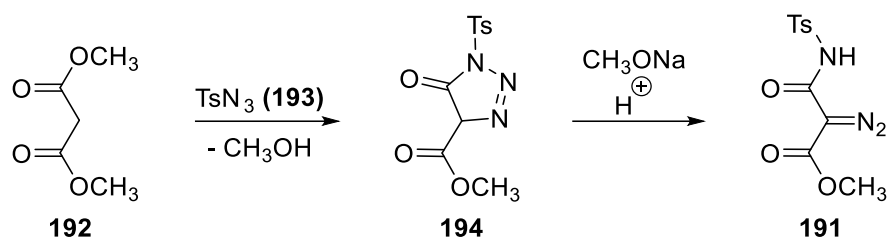
4.3.2. Diazo transfer reaction

A method of choice for the synthesis of α -diazoketones not derivable from activated acids with diazomethane is the diazo group transfer reaction. The diazo group is transferred from a donor molecule (sulfonyl azide) to an acceptor molecule (a derivative of an acid or ketone) in exchange for two protons.² The first use of this approach was described by Dimroth¹⁸ in 1910. Reaction of malonic ester amide **189** with phenyl azide afforded diazomalonic ester amide **190** (Scheme 4.4).



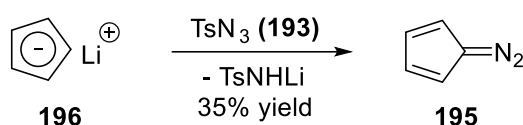
Scheme 4.4 Synthesis of **190** reported by Dimroth.¹⁸

In 1926 Curtius and Klavehn¹⁹ reported the synthesis of methyl diazomalonate amide **191** employing dimethyl malonate (**192**) and *p*-toluenesulfonyl azide (**193**) as starting materials. The authors proposed triazolone **194** as the intermediate of the reaction (Scheme 4.5).



Scheme 4.5 Preparation of **191** reported by Curtius and Klavehn.¹⁹

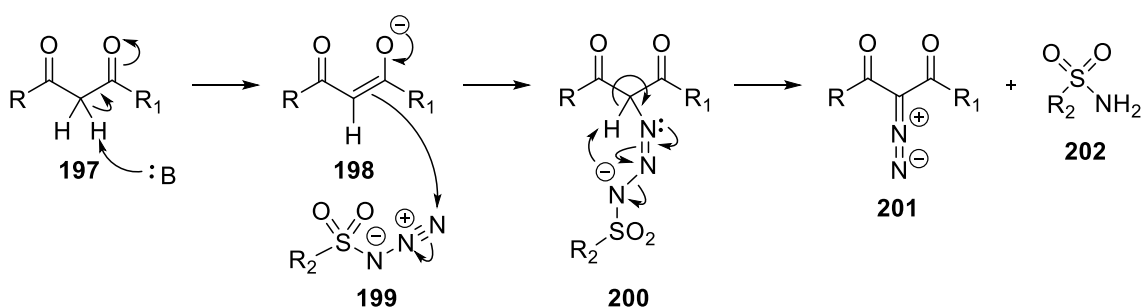
Less than three decades later, Doering and DePuy,²⁰ described the preparation of diazocyclopentadiene (**195**). Reaction of cyclopentadienyllithium (**196**) with *p*-toluenesulfonyl azide (**193**) resulted in a generation of diazocyclopentadiene (**195**) (**Scheme 4.6**).



Scheme 4.6 Synthesis of diazocyclopentadiene (**195**) reported by Doering and DePuy.²⁰

Influenced by the work of Doering and DePuy, Regitz²¹ began extensive studies of the diazo transfer reaction and was the first to develop protocols for the preparation of diazo derivatives from a variety of substrates using *p*-toluenesulfonyl azide (**193**) in the presence of a base.²¹ By this means, 1,3-dicarbonyl compounds such as malonic ester, β -ketoester, β -diketone and β -ketoamide, were straightforwardly transformed into α -diazo-1,3-dicarbonyl products in a reaction with *p*-toluenesulfonyl azide and a base.

The proposed mechanistic pathway for the Regitz diazo transfer reactions reported by Li and Corey²² is outlined in **Scheme 4.7**.



Scheme 4.7 Mechanistic pathway for the synthesis of α -diazo-1,3-dicarbonyl compound **201** via Regitz diazo transfer reaction reported by Li and Corey.²²

Removal of the α -hydrogen atom in **197** by a base leads to an enolate **198**, which attacks the terminal nitrogen atom in sulfonyl azide **199** to afford the intermediate tosyl derivative **200**. Proton transfer reaction followed by loss of the sulfonamide **202** generates the anticipated α -diazo-1,3-dicarbonyl compound **201**.

Various α -diazocarbonyl compounds have been synthesised employing the Regitz diazo transfer reaction, such as α -diazoketone **203**,²³ α -diazooester **204**,²⁴ α -diazamide **205**,²⁵ α -diazoketosulfonate **206**,²⁶ or α -diazoketophosphonate **207**²⁷ (Figure 4.4).

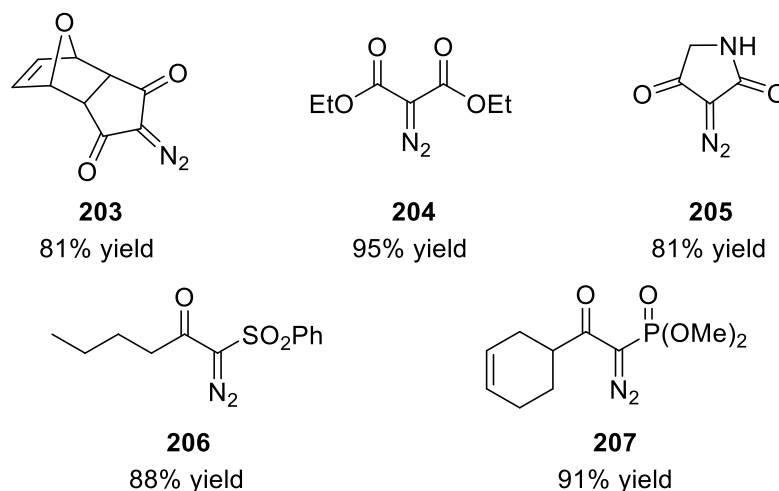
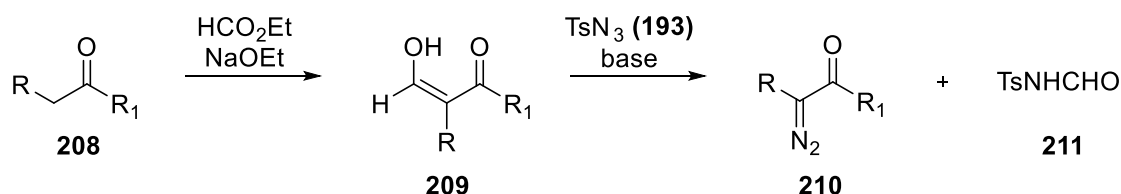


Figure 4.4 Examples of α -diazocarbonyl compounds **203** – **207** synthesised *via* the Regitz diazo transfer reaction.

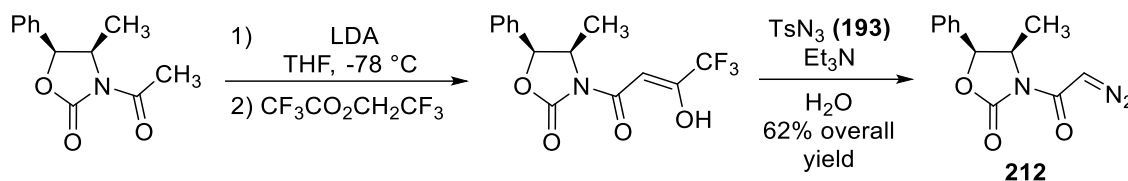
Although successfully applied for the preparation of α -diazocarbonyl compounds bearing two carbonyl groups and thus possessing α -hydrogen atoms acidic enough to be removed by a base, this diazo transfer method fails to produce the desired diazo compounds when the methylene group is activated by a single carbonyl function only. Further activation is required.² This can be achieved by conversion of the starting materials into acyl aldehydes *via* formylation prior to the diazo group transfer. This technique, known as the Regitz deformylating diazo transfer, was first introduced in 1967 and involves Claisen condensation of a ketone **208** with ethyl formate to introduce the strongly activating formyl group at the α -position of a carbonyl compound **209**.²¹ Deformylation takes place during the diazo group transfer reaction and results in a generation of the desired α -diazocarbonyl compound **210** and sulfonamide **211** (Scheme 4.8).²



Scheme 4.8 Synthesis of α -diazocarbonyl compounds *via* the Regitz deformylating diazo transfer.²

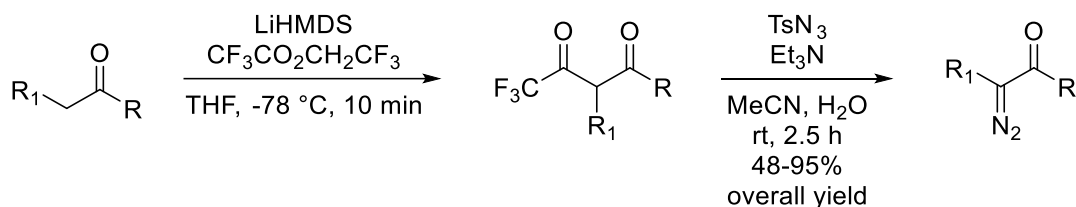
The aforementioned method is not suitable for base-sensitive substrates as the Claisen condensation generally requires harsh conditions therefore delivering products in low yields. In 1985, Doyle *et al.*²⁸ modified the Regitz deformylating diazo transfer technique

and introduced a trifluoroacetyl group in place of the formyl group to improve the diazo transfer reaction of a base-sensitive *N*-acyl-oxazolidone derivative **212** (Scheme 4.9).



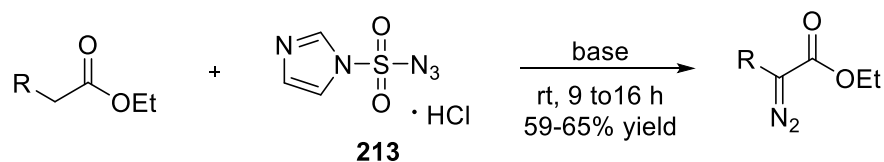
Scheme 4.9 Modification of the Regitz deformylating diazo transfer method and synthesis of **212** reported by Doyle *et al.*²⁸

Five years later, Danheiser *et al.*²⁹ based on the Doyle's experiment, introduced the activation of a ketone by conversion to the corresponding α -trifluoroacetyl derivative prior to the diazo group transfer reaction. For majority of starting materials this modification resulted in better yields in comparison to the Regitz deformylating diazo transfer technique (Scheme 4.10).



Scheme 4.10 Synthesis of a series of α -diazoketones *via* trifluoroacetylation prior to the diazo transfer reaction reported by Danheiser *et al.*²⁹

The most recent reagent for the diazo transfer reaction was developed by Goddard-Borger and Stick³⁰ in 2007. Imidazole-1-sulfonyl azide hydrochloride (**213**) was designed and straightforwardly synthesised to act as a donor molecule in the diazo group transfer reaction. It proved to be efficient for substrates such as malonic esters, β -ketoesters and cyanoacetates (Scheme 4.11).

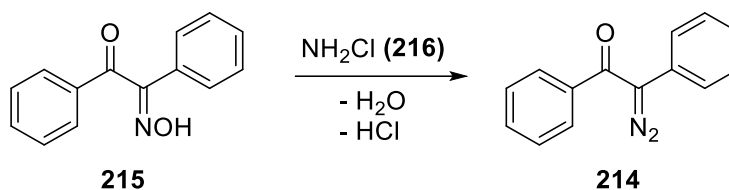


Scheme 4.11 Imidazole-1-sulfonyl azide hydrochloride (**213**) as a diazo group transfer reagent reported by Goddard-Borger and Stick.³⁰

4.3.3. Alternative synthetic routes to α -diazocarbonyl compounds

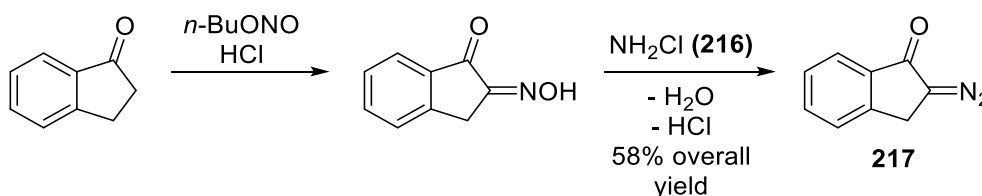
Although the acylation of diazomethane and diazo transfer reaction remain the two most commonly utilised methods, other alternative routes for the synthesis of α -diazocarbonyl compounds that have proved their usefulness were developed over the past years.

In 1915, Forster³¹ reported a preparation of α -diazoketone **214** in a reaction of α -keto oxime **215** with chloroamine (**216**) (Scheme 4.12).



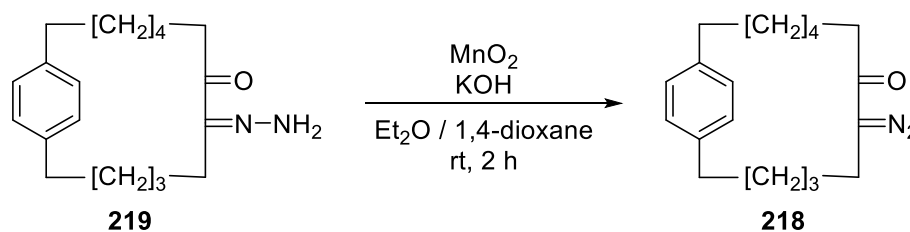
Scheme 4.12 Synthesis of **214** via Forster reaction reported by Forster.³¹

Cava *et al.*³² in 1958 have successfully applied the Forster reaction for the synthesis of cyclic α -diazoketones. Benefiting from a slight modification of the Forster's protocol and by generating chloroamine (**216**) *in situ*, α -diazo-1-indanone (**217**) was prepared in 58% yield (Scheme 4.13).



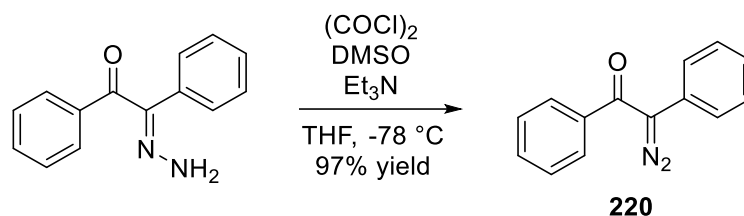
Scheme 4.13 Synthesis of **217** by utilisation of modified Forster's protocol reported by Cava *et al.*³²

Dehydrogenation of hydrazones can be performed with a number of oxidising reagents such as mercury oxide, manganese dioxide, silver(I) oxide, or lead tetraacetate.³³ Reported by Allinger and Freiberg³⁴ in 1962, this method was applied for the preparation of α -diazocarbonyl paracyclophane derivative **218** by a treatment of monohydrazone derivative **219** with manganese dioxide and potassium hydroxide in a mixture of diethyl ether and 1,4-dioxane at room temperature for 2 hours (Scheme 4.14).



Scheme 4.14 Synthesis of **218** reported by Allinger and Freiberg.³⁴

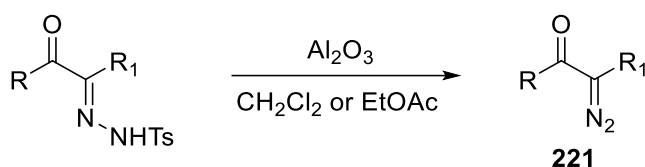
Heavy-metal-based oxidants are favourable for the dehydrogenation of hydrazones. However, a new metal-free modification of this method surfaced in 2007 when Javed and Brewer³⁵ reported the use of chlorodimethylsulfonium chloride (Swern reagent), generated *in situ* from dimethyl sulfoxide and oxalyl chloride in the presence of triethylamine, for the synthesis of α -diazo-1,2-diphenylethanone (**220**) (Scheme 4.15).



Scheme 4.15 Metal-free dehydrogenation of hydrazones reported by Javed and Brewer.³⁵

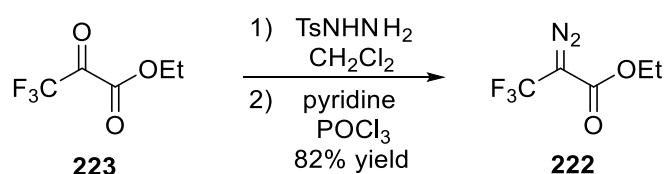
Bamford-Stevens tosylhydrazone decomposition³⁶ is another synthetic route to α -diazocarbonyl compounds within which the desired α -diazocarbonyl product is obtained upon treatment of tosylhydrazone with a strong base.

In 1966, Muchowski³⁷ reported a modified procedure of this method using a suspension of alumina in dichloromethane or ethyl acetate instead of a strong base for the elimination of *p*-toluenesulfinate ion and generation of α -diazocarbonyl compound **221** (**Scheme 4.16**).



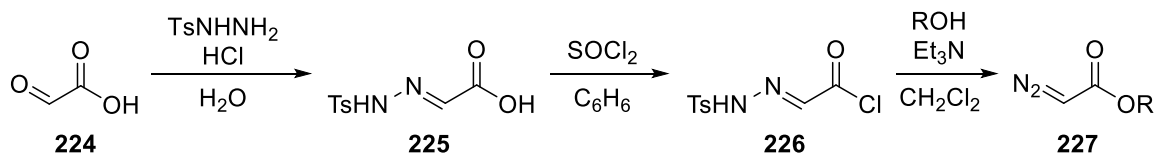
Scheme 4.16 Modified Bamford-Stevens tosylhydrazone decomposition reported by Muchowski.³⁷

Another modification of the Bamford-Stevens reaction was reported by Shi and Xu³⁸ in 1989. The desired ethyl α -diazo-3-trifluoropropanoate (**222**) was prepared by a conversion of **223** into corresponding tosylhydrazone and subsequent treatment with pyridine and phosphoryl chloride in 82% yield (**Scheme 4.17**).



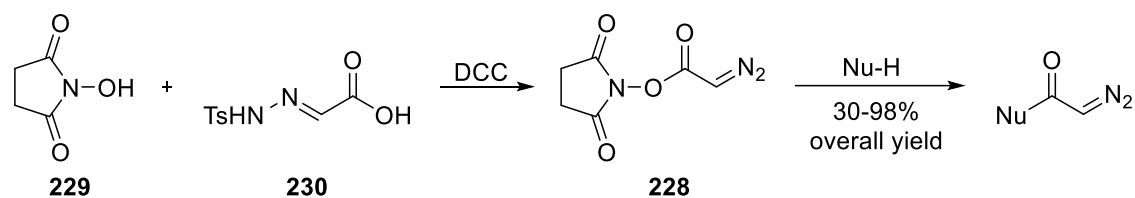
Scheme 4.17 Synthesis of **222** reported by Shi and Xu.³⁸

In 1968, House and Blankley³⁹ reported a protocol for the synthesis of α -diazoesters *via* diazoacetylation of alcohols. Glyoxylic acid (**224**) was chosen for exploration of this method. Conversion of the acid **224** into tosylhydrazone **225** and treatment with thionyl chloride afforded the corresponding acid chloride **226**, which was consecutively reacted with an alcohol and treated with triethylamine to generate the anticipated α -diazoester **227** (**Scheme 4.18**).



Scheme 4.18 Preparation of α -diazoesters *via* diazoacetylation of alcohols reported by House and Blankley.³⁹

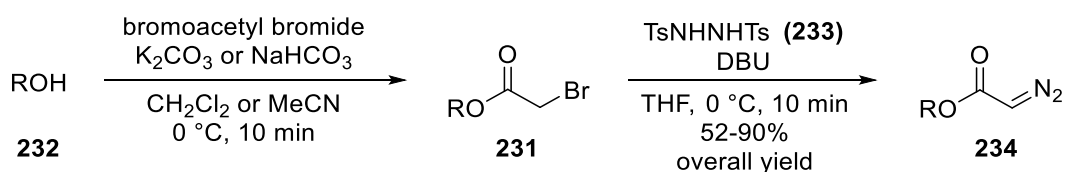
A modification of the House's method for a direct diazoacetylation of aromatic or aliphatic amines, phenols, thiophenol, and peptides under mild conditions was reported by Badet *et al.*⁴⁰ in 1993. This synthetic approach relies on the use of an easily obtainable and stable succinimidyl diazoacetate (**228**) (synthesised in a reaction of *N*-hydroxysuccinimide (**229**) with glyoxylic acid tosylhydrazone **230** in the presence of *N,N'*-dicyclohexylcarbodiimide), which allows the diazoacetylation to proceed in a single step (**Scheme 4.19**).



Scheme 4.19 Succinimidyl diazoacetate (**228**) as a convenient reagent for the direct diazoacetylation reported by Badet *et al.*⁴⁰

Badet's method was a great improvement in the synthetic methodology for the preparation of α -diazocarbonyl compounds as it allowed not only for the preparation of acid-sensitive α -diazoacetyl compounds but also functionalisation of esterified α -amino acids and diazoacetylation of aliphatic and aromatic thiols and alcohols.⁴⁰

Fukuyama *et al.*⁴¹ in 2007 reported an alternative method for a two-step diazoacetylation of alcohols to corresponding α -diazoacetic acid esters. In the first step α -bromoacetate **231** is generated in a reaction of an alcohol **232** with bromoacetyl bromide in the presence of a base; in the second step α -bromoacetate **231** reacts with 4-methyl-*N'*-tosylbenzenesulfonylhydrazide (**233**) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford the corresponding α -diazoacetic acid ester **234** (**Scheme 4.20**, **Table 4.1**).



Scheme 4.20 Two-step synthesis of α -diazoacetic acid ester **234** from corresponding alcohol reported by Fukuyama *et al.*⁴¹


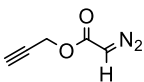
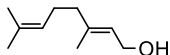
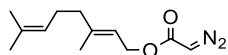

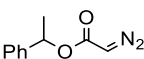
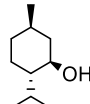
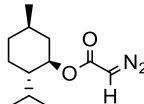

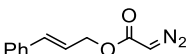
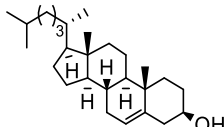
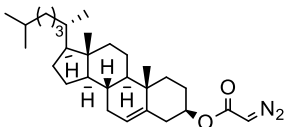
Substrate	Product	Yield (%)	Substrate	Product	Yield (%)
		67			52
		64			52
		78			79

Table 4.1 A series of α -diazoacetic acid esters reported by Fukuyama *et al.*⁴¹

Due to the ease of this technique and the ability to employ primary and secondary saturated and unsaturated alcohols, Fukuyama's protocol was the method of choice within this research project for the synthesis of a series of α -diazoacetic acid esters and will be discussed further on within this thesis; Chapter 5 Results and Discussion; section 5.2.

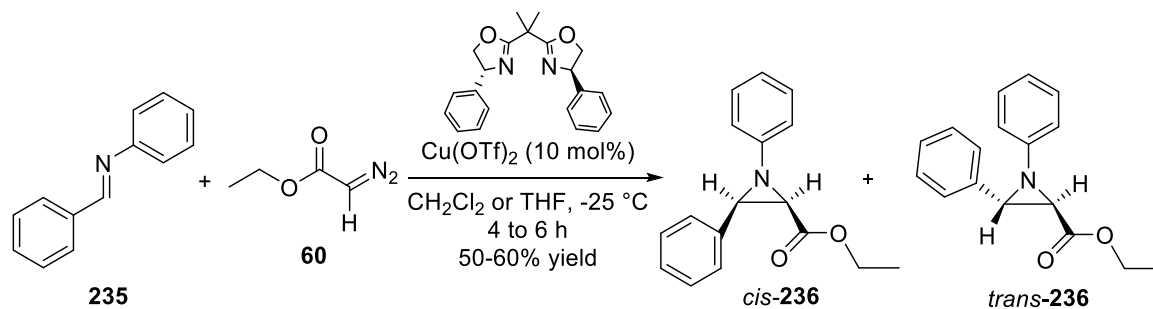
4.4. α -Diazocarbonyl compounds in the catalytic asymmetric synthesis of aziridines

α -Diazocarbonyl compounds are versatile intermediates that can undergo a wide range of chemical transformations. As mentioned numerous reports illustrating their chemistry could be found in the literature. A full description of the utilisation of α -diazocarbonyl compounds lies beyond the scope of this PhD thesis. Their application in the catalytic synthesis of enantiomerically pure aziridines, an area of study within the Bew research group, will be restricted to this aspect and presented in more detail.

Aziridines are useful saturated three-membered heterocycles that can easily undergo ring-opening reactions due to the strain incorporated into their skeletons.⁴² Chiral aziridines are especially valuable compounds as they are precursors to enantiomerically pure α -amino acids.⁴³ One of the synthetic methods for the preparation of chiral non-racemic aziridines that has gained interest over the last 20 years is the catalytic asymmetric aziridination of imines with α -diazocarbonyl compounds.⁴⁴

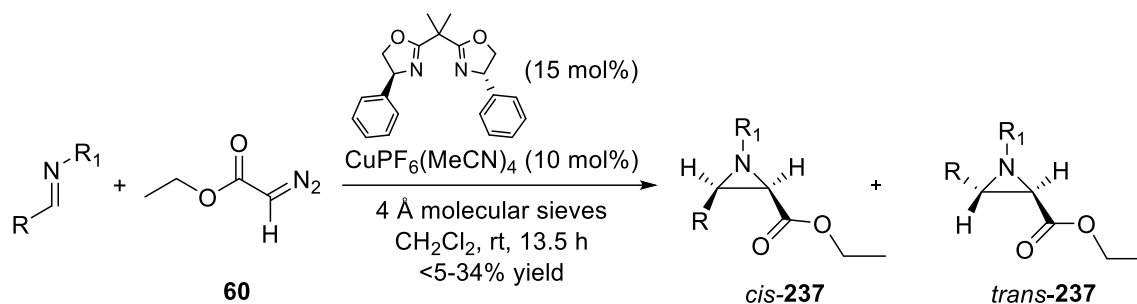
In 1995, Jørgensen and Rasmussen⁴⁵ attempted a synthesis of a chiral non-racemic aziridine from an imine and α -diazoacetic acid ester utilising copper(II) trifluoromethanesulfonate as the catalyst. Reaction of (*E*)-*N*-benzylideneaniline (**235**) with ethyl α -diazoacetate (**60**) in the presence of copper(II) trifluoromethanesulfonate (10 mol%) and (4*R*,4'*R*)-2,2'-(propane-2,2-diyl)bis(4-phenyl-4,5-dihydrooxazole) as

a chiral ligand afforded the corresponding aziridines *cis*-**236** and *trans*-**236** in 50 to 60% yield depending on the solvent used (dichloromethane or tetrahydrofuran) (**Scheme 4.21**). Although *cis*-**236** and *trans*-**236** were obtained in moderate yields and with diastereomeric ratios of 1.7 : 1 and 6 : 1 (*cis* : *trans*) in dichloromethane and tetrahydrofuran respectively, the enantiomeric excess values (not indicated by the authors) were low despite the utilisation of a chiral ligand in the reaction.



Scheme 4.21 Synthesis of *cis*-**236** and *trans*-**236** reported by Jørgensen and Rasmussen.⁴⁵

In the same year, Jacobsen *et al.*⁴⁶ attempted the catalytic synthesis of enantiomerically pure aziridines from imines and ethyl α -diazoacetate (**60**). Treatment of imine with ethyl α -diazoacetate (**60**) in the presence of tetrakis(acetonitrile)copper(I) hexafluorophosphate (10 mol%), chiral ligand (15 mol%) and 4 Å molecular sieves led to the corresponding enantiomerically enriched aziridines as a mixture of two diastereomers *cis*-**237** and *trans*-**237** (**Scheme 4.22**, **Table 4.2**).



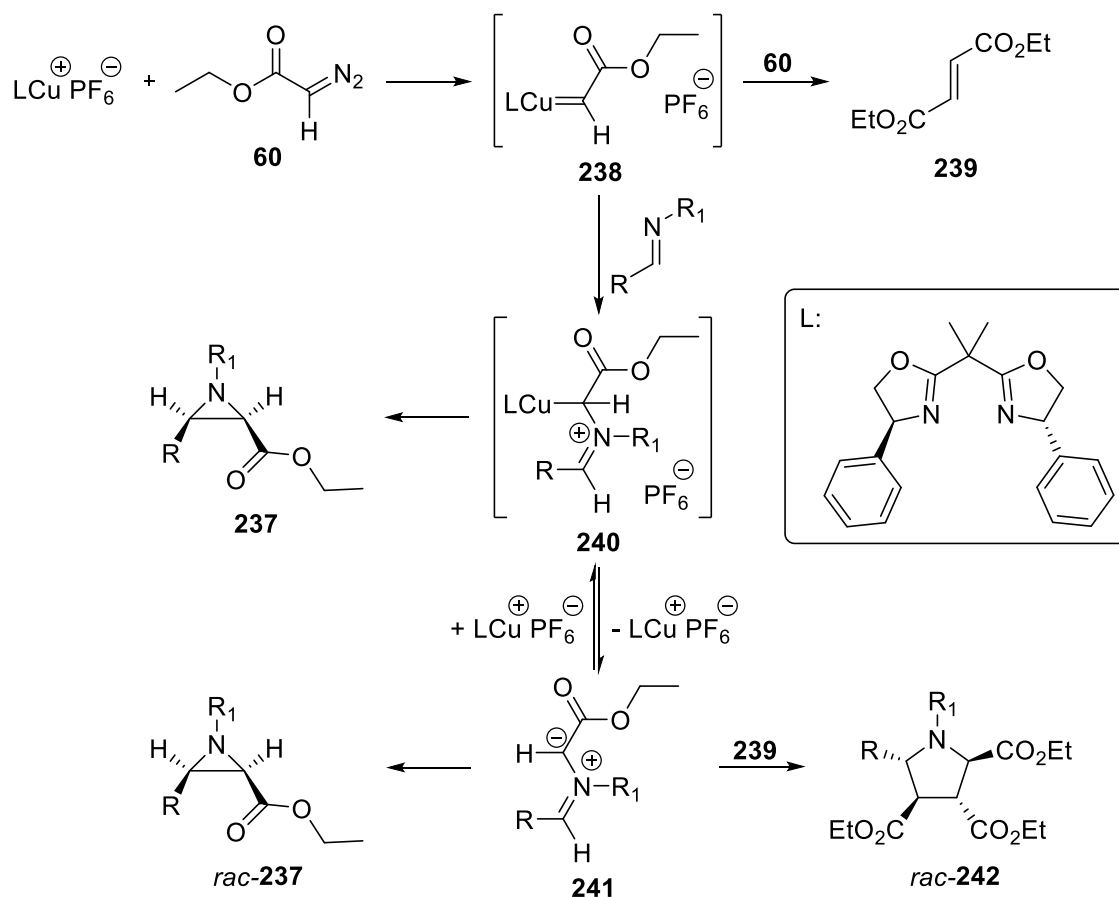
Scheme 4.22 Catalytic asymmetric synthesis of *cis*-**237** and *trans*-**237** reported by Jacobsen *et al.*⁴⁶

R	R₁	<i>cis</i> / <i>trans</i>	<i>e.e.</i> (<i>cis</i>) / <i>e.e.</i> (<i>trans</i>) (%)	Yield (%)
4-MePh	Ph	9 / 1	44 / 26	17
4-ClPh	Ph	-	-	<5
Ph	4-MeOPh	9 / 1	67 / 32	23
Ph	4-ClPh	4 / 1	49 / 22	34

Table 4.2 Enantioselective synthesis of *cis*-**237** and *trans*-**237** reported by Jacobsen *et al.*⁴⁶

Despite the low yields and moderate enantiomeric excess values (22% to 67%), it was the first example of catalytic synthesis of enantiomerically enriched aziridines from imine and α -diazocarbonyl compound.

The mechanistic pathway for this transformation reported by Jacobsen *et al.*⁴⁶ is outlined in **Scheme 4.23**.

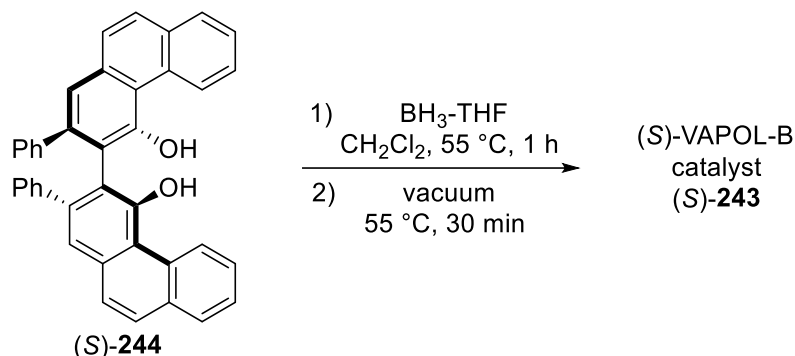


Scheme 4.23 Mechanistic pathway for the synthesis of optically active **237** reported by Jacobsen *et al.*⁴⁶

Reaction of ethyl α -diazooacetate (**60**) with tetrakis(acetonitrile)copper(I)hexafluorophosphate affords bis(dihydrooxazole)copper(I) carbene complex **238**, which subsequently reacts either with ethyl α -diazooacetate (**60**) to afford dimethyl (*E*)-butenedioate (**239**), or with imine to yield copper(I)-complexed azomethine ylide **240**. The complexed ylide **240** can undergo ring closure to generate enantiomerically enriched aziridine **237** or dissociate from the metal-ligand complex to free azomethine ylide **241**. The ylide **241** can then undergo either cyclisation to furnish racemic aziridine *rac*-**237** or cycloaddition with **239** to yield racemic pyrrolidine *rac*-**242**.

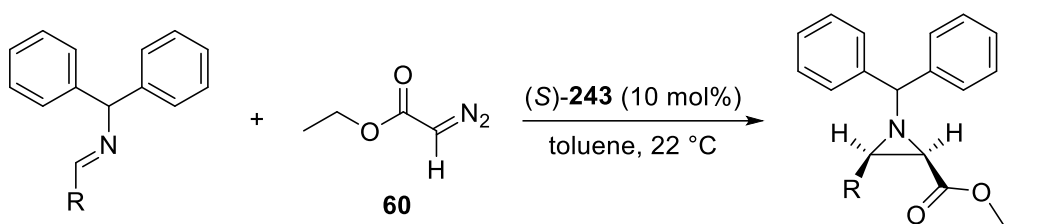
A breakthrough took place in 1999, when Wulff and Antilla⁴⁷ achieved outstanding enantioselectivities in the Lewis acid-catalysed aziridinations of various benzhydryl imines with ethyl α -diazooacetate (**60**). The chiral boron catalyst (*S*)-**243** derived from vaulted

biaryl ligand (*S*)-VAPOL (*S*)-**244** was prepared by treatment of (*S*)-**244** with borane-tetrahydrofuran complex (**Scheme 4.24**). However, the structure of the catalyst (*S*)-**243** was not clarified by the authors.



Scheme 4.24 Synthesis of (*S*)-**243** reported by Wulff and Antilla.⁴⁷

Despite the unknown structure, (*S*)-**243** successively catalysed the reaction of imines with **60** to afford aziridines with very high *cis*-diastereoselectivity and enantiomeric excess values >91%, and in yields up to 77% (**Scheme 4.25**, **Table 4.3**).



Scheme 4.25 Catalytic asymmetric aziridination reaction reported by Wulff and Antilla.⁴⁷

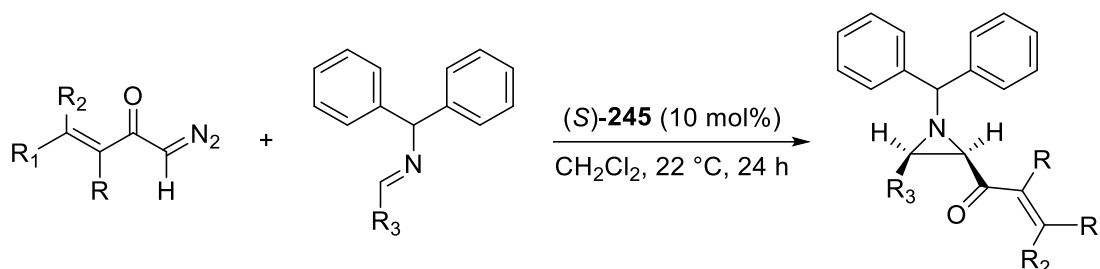
R	Time (h)	<i>cis</i> / <i>trans</i>	Yield (%)	<i>e.e.</i> (<i>cis</i>) (%)
Ph	5	>50 : 1	77	97
4-BrPh	4	16 : 1	64	97
4-NO ₂ Ph	24	11 : 1	68	91
4-AcOPh	16	40 : 1	67	96
2-Me	24	3 : 1	51	98
2-Naphthyl	4	30 : 1	70	97
2-Furyl	8	16 : 1	55	94
<i>n</i> -Propyl	7	>50 : 1	54	91

Table 4.3 Enantioselective aziridination reaction catalysed by Lewis acid (*S*)-**243** reported by Wulff and Antilla.⁴⁷

Since that report, much improvement has been achieved within Wulff's methodology. It has been recognised that the initial borane-tetrahydrofuran complex utilised for the synthesis of the catalyst could be replaced by borate esters such as triphenyl borate which proved to be a more reliable technique for the preparation of the chiral non-racemic

VANOL and VAPOL-derived catalysts.⁴⁸ Although the scope of Wulff's methodology was expanded over the next years to a wider range of imines as starting materials for the asymmetric aziridination reaction, ethyl α -diazacetate **60** remained the compound of choice for the majority of studies, most probably due to the commercial availability.

It was not until 2007, when Wulff *et al.*⁴⁹ reported the first catalytic enantioselective aziridination reaction using vinyl α -diazoketones with benzhydryl imines and (*S*)-VAPOL-derived catalyst (*S*)-**245** (Scheme 4.26, Figure 4.5, Table 4.4).



Scheme 4.26 Utilisation of vinyl α -diazoketones in catalytic asymmetric aziridination reaction reported by Wulff *et al.*⁴⁹

Vinyl α -diazoketone	R ₃	<i>cis</i> / <i>trans</i>	Yield (%)	<i>e.e.</i> (<i>cis</i>) (%)
	Ph	>50 : 1	79	95
	4-MePh	>50 : 1	71	99.7
	4-BrPh	14 : 1	51	96
	4-NO ₂ Ph	>50 : 1	80	95
	<i>c</i> -C ₆ H ₁₁	5 : 1	90	93
	Ph	15 : 1	76	98.1
	4-MePh	>50 : 1	83	96.1
	4-BrPh	20 : 1	76	98.5
	4-NO ₂ Ph	7 : 1	67	95.7
	<i>c</i> -C ₆ H ₁₁	10 : 1	75	94.4
	Ph	25 : 1	85	95.7

Table 4.4 Examples of the reaction of vinyl α -diazoketones with imines catalysed by (*S*)-**245** reported by Wulff *et al.*⁴⁹

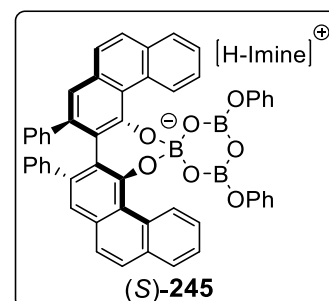
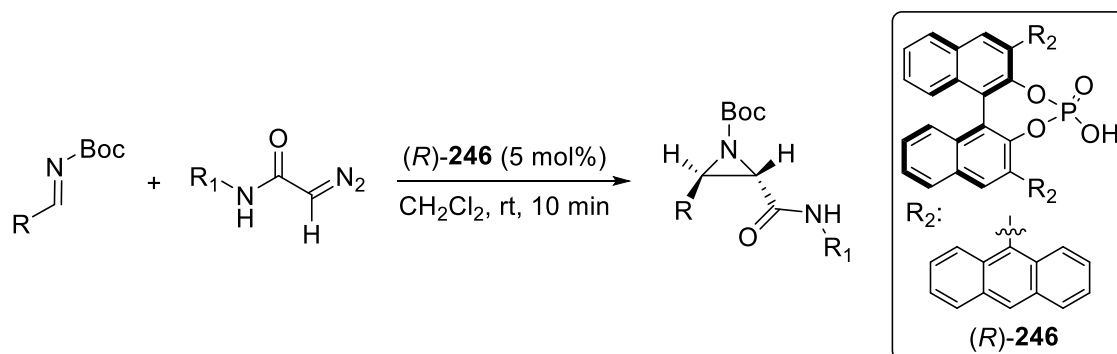


Figure 4.5 Structure of (*S*)-**245** reported by Wulff *et al.*⁴⁹

Wulff *et al.*⁴⁹ had successfully shown in this report that the family of α -diazocarbonyl compounds for the aziridination reaction can be extended to the vinyl α -diazoketones. The desired aziridines were obtained with moderate to high diastereoselectivity for the *cis*-isomer, in yields up to 90% and with enantiomeric excess values >93%. Furthermore, the authors presented the possibility of stereoselective conversion of the aziridines into

chiral five-carbon amine units *via* reduction of the ketone moiety and subsequent opening of the aziridine ring.⁴⁹

In 2009, Zhong *et al.*⁵⁰ reported the use of another class of α -diazocarbonyl compounds, α -diazooacetamides, which provided aziridines in excellent yields (81% to 97%) and with high diastereo- and enantioselectivity (88% to 98%) (**Table 4.5**). Reaction of an array of α -diazooacetamides with a series of *N*-Boc protected imines was catalysed by a chiral BINOL-derived phosphoric acid (*R*)-**246** at room temperature to furnish the desired aziridines within 10 minutes (**Scheme 4.27**).



Scheme 4.27 Catalytic asymmetric aziridination reaction of α -diazooacetamides with *N*-Boc-protected imines reported by Zhong *et al.*⁵⁰

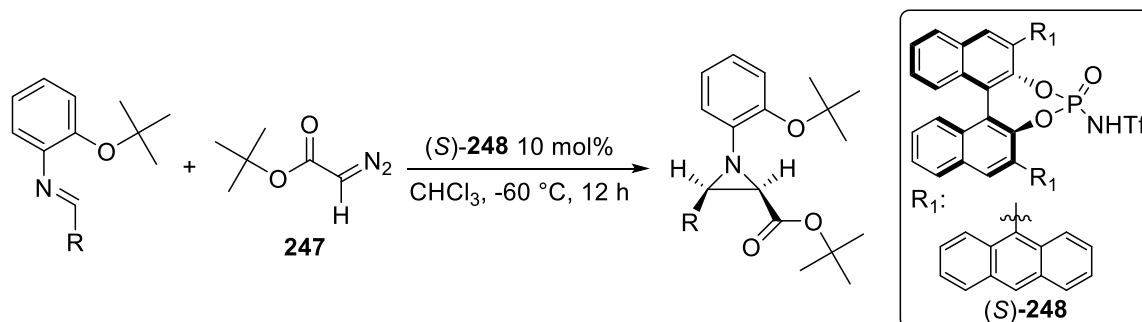
R	R ₁	Yield (%)	<i>e.e.</i> (<i>trans</i>) (%)	R	R ₁	Yield (%)	<i>e.e.</i> (<i>trans</i>) (%)
Ph	4-MeOPh	97	93	4-BrPh	3,5-ClPh	89	98
4-FPh	4-MeOPh	91	94	Ph	Ph	95	92
3-MeOPh	4-MeOPh	96	96	Ph	2-ClPh	95	94
4-MePh	4-MeOPh	90	88	Ph	4-ClPh	96	88
4-BrPh	4-MeOPh	95	90	Ph	2-MeOPh	93	92
3-MePh	4-MeOPh	96	90	Ph	3-MeOPh	94	96
2-Naphthyl	4-MeOPh	91	88	Ph	3,5-ClPh	81	95

Table 4.5 Utilisation of α -diazooacetamides for the synthesis of asymmetric aziridines reported by Zhong *et al.*⁵⁰

The diastereoselectivity of this reaction was a surprise to the authors as the aziridines obtained were *trans*-isomers with the diastereomeric ratio >50 : 1. Furthermore, no significant difference had been observed in the results depending on the substitution of the α -diazooacetamide.

The catalytic synthesis of enantiomerically pure aziridines employing *t*-butyl α -diazooacetate (**247**) and *N*-aryl imines has been one of the focal points within the Bew

research group. Utilisation of (*S*)-BINOL-derived catalyst (*S*)-**248** (10 mol%) (synthesised by a former PhD student in the research laboratory⁵¹ and thereafter published independently by Rueping *et al.*⁵²) in a reaction of *t*-butyl α -diazoacetate (**247**) with *N*-aryl imines resulted in the preparation of enantiomerically enriched aziridines in excellent yields, with high enantiomeric excess values and diastereoselectivity towards the *cis*-isomer (**Scheme 4.28, Table 4.6**).



R	Yield (%)	Enantiomeric excess (%)
Ph	91	90
4-ClPh	97	93
4-BrPh	96	93
4-IPh	96	92
4-FmocOPh	91	90

Table 4.6 Examples of enantiomerically pure aziridines synthesised by P. Pesce.⁵¹

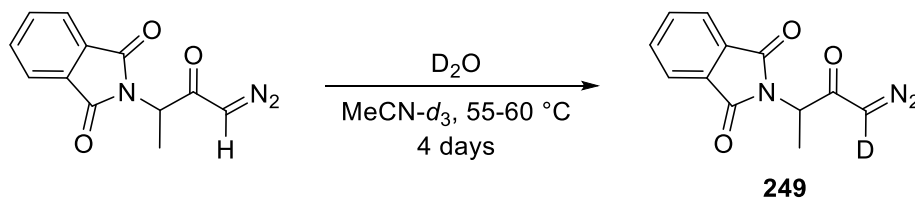
An ongoing study of the catalytic enantioselective aziridination reaction within the Bew research group is currently being expanded further. In search of new starting materials a series of α -diazoacetic acid esters and α -diazoketone has been prepared and a protocol for the hydrogen / deuterium exchange reaction at the α -carbon atom in these compounds has been successfully established, both of which are the subject of discussion and will be presented further on in this PhD thesis (Chapter 5 Results and Discussion). Furthermore, additional research is being conducted by a present PhD student in the Bew research group. This focuses on the preparation of α -diazoacetamides and their utilisation in the catalytic synthesis of non-racemic aziridines with excellent diastereomeric ratios (99 : 1) towards the *trans*-isomer.

4.5. Deuterium labelled α -diazocarbonyl compounds

α -Diazocarbonyl compounds are highly desirable molecules due to the vast array of transformations to which they can be subjected. With the recently growing demand for isotopically labelled compounds and increasing interest and developments in the hydrogen / deuterium exchange reaction,⁵³ α -diazocarbonyl compounds appear to be ideal target molecules for the introduction of deuterium into their structures. However, only a limited number of reports describing their synthesis or utilisation are available in the literature.

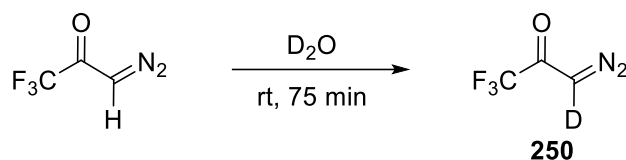
The first report referring to a hydrogen / deuterium exchange reaction at the α -carbon atom in α -diazocarbonyl compound surfaced in 1969. Peterson and Indelicato⁵⁴ mentioned the synthesis of ethyl α -deutero- α -diazoacetate in a reaction of ethyl α -diazoacetate in a biphasic mixture of deuterium oxide and diethyl ether with utilisation of potassium carbonate as a catalyst. However, neither a protocol nor any information about the yield of the reaction or deuterium incorporation level was supplied by the authors.

In 1973, Paul and Korytnyk⁵⁵ reported a preparation of α -deutero- α -diazoketone **249** (Scheme 4.29) for mechanistic studies and to substantiate the belief that the hydrogen atom at the diazo-bearing carbon is the most acidic one. The authors did not provide information about the amounts of reagents used. The deuterium incorporation was determined based on the $^1\text{H-NMR}$ spectroscopic evidence.



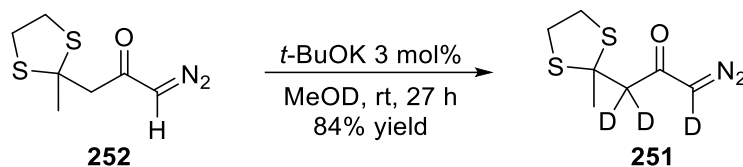
Scheme 4.29 Hydrogen / deuterium exchange reaction reported by Paul and Korytnyk.⁵⁵

More than twenty years later, Strazzolini *et al.*⁵⁶ straightforwardly synthesised α -deutero- α -diazoketone **250** under catalyst-free conditions by continuous exchange of deuterium oxide containing sodium chloride at room temperature (five cycles of deuterium oxide, 15 minutes each) (Scheme 4.30). Almost complete hydrogen / deuterium exchange was reported based on the $^1\text{H-NMR}$ spectroscopic evidence with the use of diiodomethane as internal proton standard. The synthesised **250** was utilised in a GC-MS experiment to determine the fragmentation of the molecule. These studies were subsequently applied towards better understanding of the mechanistic pathway of Wolff rearrangement.



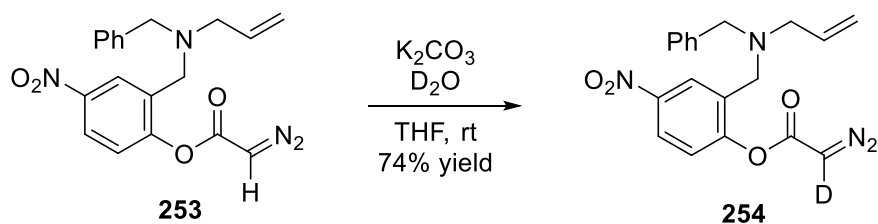
Scheme 4.30 α -Deutero- α -diazoacetone **250** reported by Strazzolini *et al.*⁵⁶

Another example of the synthesis of a deuterium labelled α -diazoacetone **251** for mechanistic studies was reported by Mori *et al.*⁵⁷ in 2000. The hydrogen / deuterium exchange reaction of **252** was performed in methanol- d_1 in the presence of a strong base, potassium *t*-butoxide (3 mol%), at room temperature to afford after 27 hours deuterium labelled α -diazo-3-(2-methyl-1,3-dithiolan-2-yl)propan-2-one **251** in 84% yield with 95% and 88% of deuterium incorporation at the methylene group and at the α -position adjacent to diazo group respectively (based on the $^1\text{H-NMR}$ spectroscopic evidence) (**Scheme 4.31**).



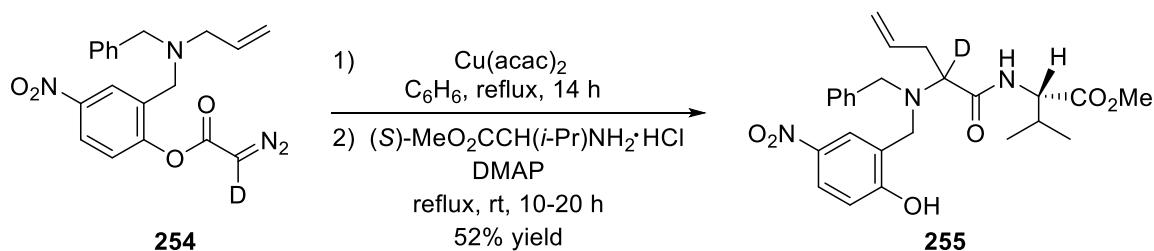
Scheme 4.31 Synthesis of **251** reported by Mori *et al.*⁵⁷

In 2003, utilisation of α -deutero- α -diazoacetic acid ester as a precursor for the preparation of α -deutero- α -amino acid derivative was illustrated by Clark and Middleton.⁵⁸ Reaction of **253** in a mixture of deuterium oxide and tetrahydrofuran in the presence of potassium carbonate at room temperature afforded the desired **254** in 74% yield with >95% deuterium incorporation (no protocol for this reaction was described) (**Scheme 4.32**).



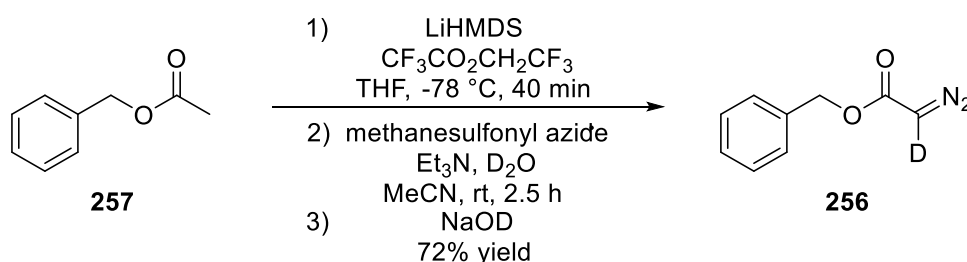
Scheme 4.32 Hydrogen /deuterium exchange reaction of **253** reported by Clark and Middleton.⁵⁸

α -Deutero- α -diazoacetic acid ester **254** was subsequently utilised as a starting material for the synthesis of a novel α -deutero- α -amino acid derivative **255** (**Scheme 4.33**).



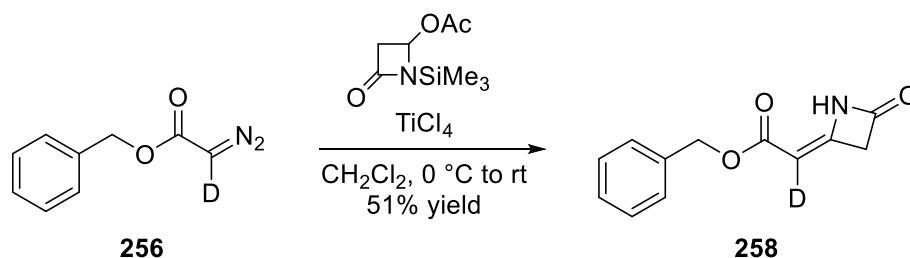
Scheme 4.33 Preparation of a novel α -deuterio- α -amino acid derivative **255** reported by Clark and Middleton.⁵⁸

Galletti *et al.*⁵⁹ successfully synthesised a deuterium labelled (4-oxoazetidin-2-yliden)acetate belonging to the family of β -lactams, compounds that display promising biological activity as antibiotics and enzyme inhibitors, utilising benzyl- α -deuterodiazoacetate (**256**) as an intermediate.⁵⁹ Reaction of benzyl acetate (**257**) with lithium bis(trimethylsilyl)amide (LiHMDS) in tetrahydrofuran at -78°C and consecutive treatment with trifluoroethyl trifluoroacetate at -78°C afforded α -trifluoroacetyl ketone, which was subsequently allowed to react with methanesulfonyl azide in the presence of triethylamine in a mixture of acetonitrile and deuterium oxide to furnish, after quenching the reaction mixture with a solution of sodium deuterioxide in deuterium oxide, the desired benzyl- α -deuterodiazoacetate (**256**) in 72% yield (**Scheme 4.34**).



Scheme 4.34 Synthesis of **256** reported by Galletti *et al.*⁵⁹

Benzyl- α -deuterodiazoacetate (**256**) was subsequently treated with 4-acetoxyazetidin-2-one in the presence of titanium tetrachloride in dichloromethane at 0°C followed by warming to room temperature to afford 4-(1-deutero-alkyliden)azetidin-2-one (**258**) in 51% yield (**Scheme 4.35**). The degree of deuterium incorporation was not indicated in the report.



Scheme 4.35 Benzyl- α -deuterodiazoacetate (**256**) as a starting material for the synthesis of **258** reported by Galletti *et al.*⁵⁹

The most recent use of a deuterium labelled α -diazocarbonyl compound had been described by Johnson and O'Bryan⁶⁰ in 2012. The deuterium labelled **259** was one of the intermediates in the 11-step synthesis of γ -cyhalothrin **260**, a synthetic pyrethroid insecticide (**Figure 4.6**).

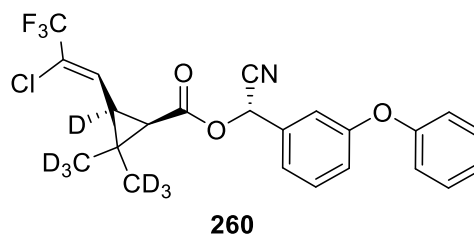
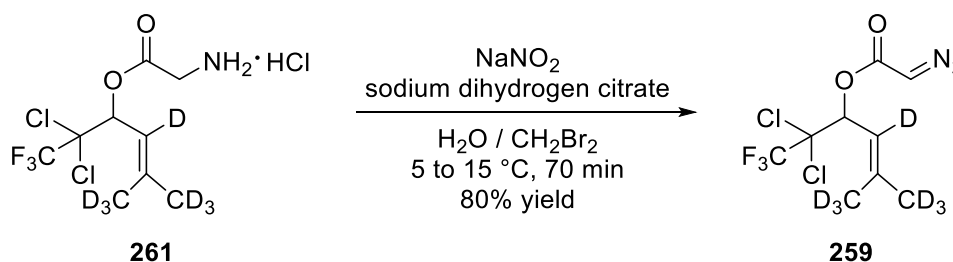


Figure 4.6 Structure of γ -cyhalothrin **260** reported by Johnson and O'Bryan.⁶⁰

The introduction of a diazo moiety into a deuterium labelled **259** was achieved *via* diazotization of **261** with sodium nitrite in the presence of sodium dihydrogen citrate in a mixture of water and dibromomethane at 5 to 15 °C within 70 minutes (80% yield) (**Scheme 4.36**).



Scheme 4.36 Deuterium labelled **259** as an intermediate for the synthesis of γ -cyhalothrin reported by Johnson and O'Bryan.⁶⁰

4.6. Conclusion

Since the first isolation of diazo- derivative of an aminobenzoic acid in 1858 various synthetic methods for the preparation of α -diazocarbonyl compounds had been successfully established, some of which have been briefly summarised in the preceding pages. As versatile intermediates, α -diazocarbonyl compounds can undergo a vast array of transformations. It was intended within this PhD thesis to emphasise chiefly their utilisation in the catalytic asymmetric aziridination reaction as this is the area of study to which they have been subjected to within the Bew research group. With the growing interest and search for deuterium labelled molecules, α -diazocarbonyl compounds appear to be excellent candidates due to the versatile nature and potential applications. However, only a few reports of deuterium labelled α -diazocarbonyl compounds are available in the literature. A part of the research presented herein will focus on the synthesis of

α -deutero- α -diazocarbonyl compounds as starting materials for the catalytic synthesis of enantiomerically pure aziridines.

4.7. References

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Chapter 5
Results and Discussion

5.1. Aim of the project

The aim of this research project was to synthesise a range of α -deuterated (aldehyde proton replaced by deuterium) aromatic aldehydes and α -deutero- α -diazoacetic acid esters as starting materials for the preparation of novel deuterated *N*-aryl-*cis*-aziridine-2-carboxylates. This is an ongoing research project in the Bew research group.

α -Diazocarbonyl compounds are useful intermediates in organic synthesis.¹ They participate in a wide variety of chemical transformations, *i.e.*, addition,² cycloaddition³ and insertion reactions,⁴ as well as thermal, photochemical and metal-catalysed rearrangements.⁵ Owing to this broad spectrum of reactivity they have attracted the attention of researchers and have been extensively studied over the past decades.^{1,6} A number of diazocarbonyl compounds also occur in nature,⁷ *e.g.*, kinamycin F⁸ **262** and lomaiviticin B⁹ **263**, or the α -amino acid derivative azaserine¹⁰ **264** (Figure 5.1).

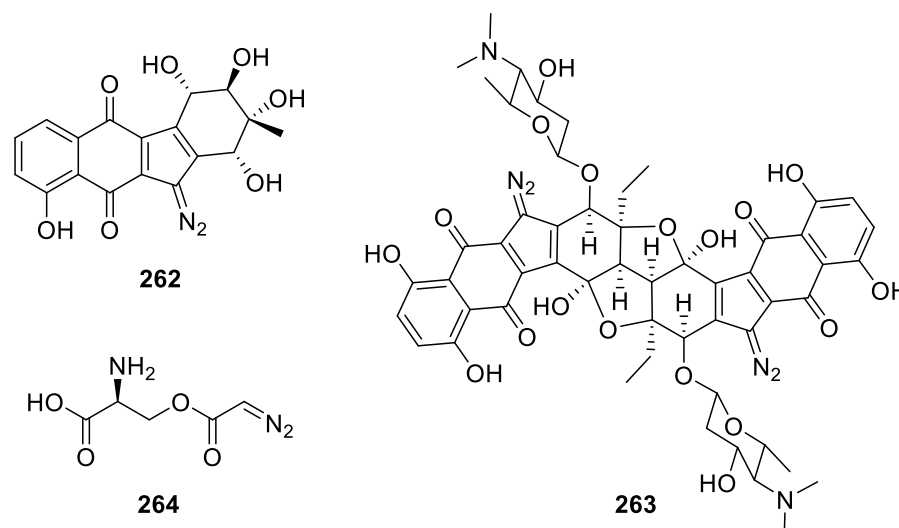


Figure 5.1 Structures of kinamycin F **262**, lomaiviticin B **263**, and azaserine **264**.

Deuterium-labelled compounds have been broadly utilised in numerous scientific fields since the first isolation of deuterium in 1932.^{11,12} Chemists have applied deuterium widely, *e.g.*, for elucidation of reaction mechanistic pathways,¹³ simplification of NMR spectra for the analysis of complex chemical structures¹⁴ such as proteins, sugars and peptides, or metabolic studies of drugs¹⁵ and biologically active molecules.¹⁶ Furthermore, deuterated compounds have also recently attracted the attention of scientists as new drug candidates (heavy drugs).¹⁷ All this has led to an increase in the demand for the preparation of commercially unavailable deuterated compounds.^{12,16}

The synthetic approaches for the preparation of deuterated molecules can be classified into four most frequently employed methods: a) multi-step synthetic routes starting from small

deuterated synthons, *e.g.*, total synthesis of polyunsaturated deuterated isoprostanes;¹⁸ b) functional group reductions using deuterated reducing agents such as deuterium gas or lithium aluminium deuteride, *e.g.*, reduction of phenylalanine to a labelled aminoalcohol as one of the steps towards the synthesis of labelled 2-amino-1-phenylpropane;¹⁹ c) radical reduction using agents such as tributyltin deuteride, *e.g.*, reduction of carboxylic acid to a deuterated aldehyde as one of the steps in the synthesis of deuterated L-lysine;²⁰ and d) hydrogen / deuterium exchange reactions²¹ within which three different types can be distinguished, namely catalysis by a base, *e.g.*, sodium hydroxide utilised in the synthesis of deuterated analogues of various anti-inflammatory 2-arylpropionic acids,²² an acid, *e.g.*, deuterium chloride used in the synthesis of the deuterated tricyclic antidepressant imipramine,²³ or transition metal catalysis, *e.g.*, employment of palladium on carbon for deuterium incorporation into the base moiety of nucleic acids.^{12,21,24}

For this research project reliable protocols were needed for the hydrogen / deuterium exchange reaction at the aldehyde group of a range of aromatic aldehydes and at the α -carbon atom of α -diazoacetic acid esters that would afford high and consistent levels of deuterium incorporation.

It was envisaged that the synthesis of a range of α -deuterated aromatic aldehydes **265 – 270** and α -deutero- α -diazoacetic acid esters **271 – 281** would allow the preparation of novel deuterated *N*-aryl-*cis*-aziridine-2-carboxylates, a research project conducted by former and present PhD students in the Bew research group. Target molecules chosen are outlined in **Figure 5.2**. Within this research project not only was it possible to develop successful syntheses of the aforementioned deuterated compounds but also to broaden application to certain amino acids described later.

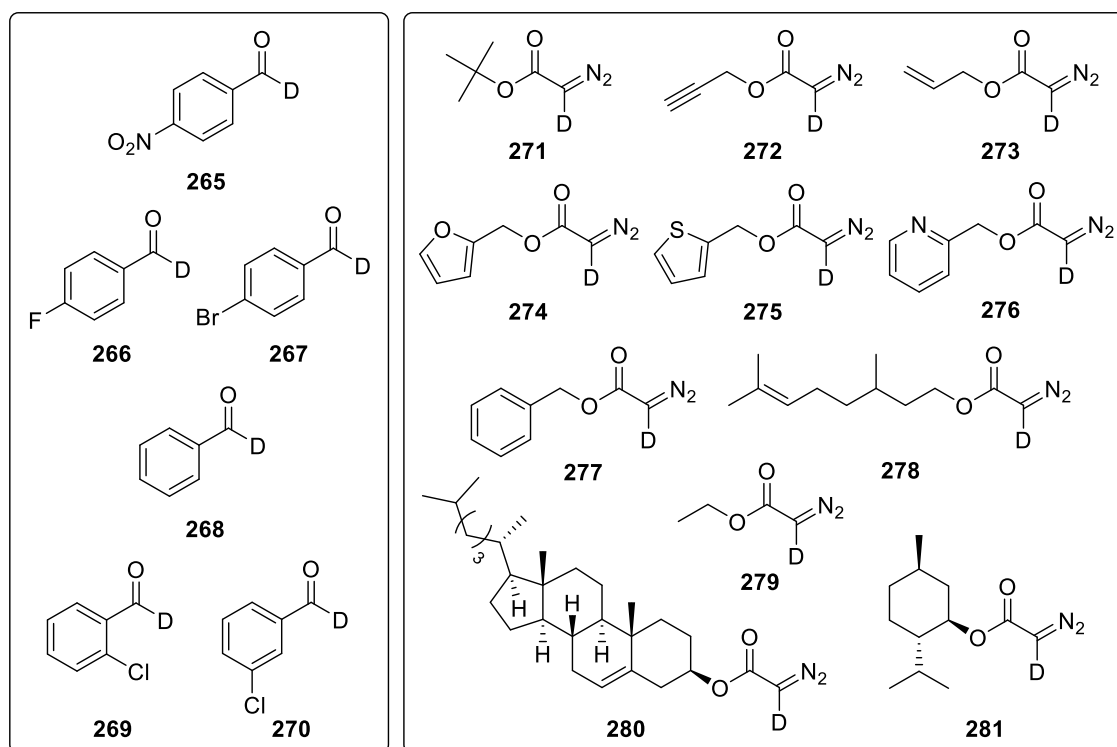
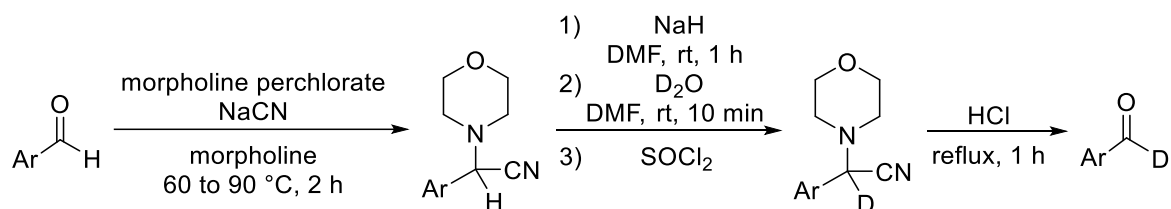


Figure 5.2 α -Deuterated aromatic aldehydes **265** – **270** and α -deutero- α -diazoacetic acid esters **271** – **281** as synthetic targets for the synthesis of deuterated *N*-aryl-*cis*-aziridine-2-carboxylates.

5.2. Synthesis of a range of α -deuterated aromatic aldehydes **265** – **270**

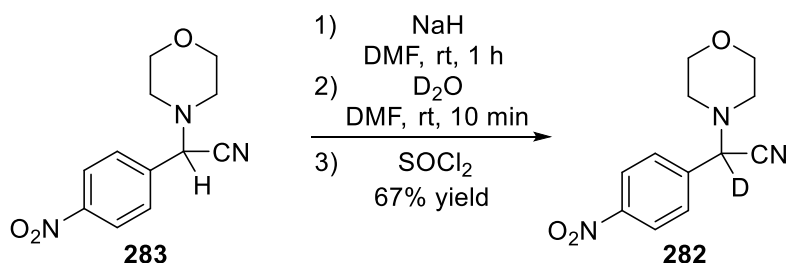
In order to investigate the potential of **265** – **270** as deuterated intermediates for organocatalytic aziridine synthesis, a reliable protocol for the hydrogen / deuterium exchange reaction at the aldehyde group needed to be established. A literature survey revealed a protocol reported by Bennett *et al.*²⁵ who described the α -deuteration of aryl aldehydes with deuterium incorporation levels between 68% and 99% and in yields above 80% (**Scheme 5.1**). The deuterium source, deuterium oxide, is fairly inexpensive.



Scheme 5.1 α -Deuteration of aryl aldehydes published by Bennett *et al.*²⁵

Adopting the aforementioned synthetic route the preparation of α -deutero-4-nitrobenzaldehyde (**265**) was explored. The synthesis of **282** was initiated from 2-morpholino-2-(4-nitrophenyl)acetonitrile (**283**) as it was readily available in the research laboratory (prepared by a former PhD student according to the procedure reported by Bennett *et al.*²⁵).

A reaction of **283** with excess of sodium hydride (3 equivalents) and thereafter with excess of deuterium oxide (5.5 equivalents) and thionyl chloride in *N,N*-dimethylformamide at room temperature afforded, after 1 hour, the anticipated 2-deutero-2-morpholino-2-(4-nitrophenyl)acetonitrile (**282**) in 67% yield (**Scheme 5.2**).



Scheme 5.2 Synthesis of **282** following the protocol reported by Bennett *et al.*²⁵

Deuterium incorporation of **282** occurred selectively adjacent to the nitrile group and was determined to be 94% complete. This was calculated based on the loss of intensity of a signal at δ 4.91 ppm in comparison to the non-labelled material **283**. The signal at δ 4.91 ppm for the residual proton was integrated against a signal at δ 7.77 ppm for two aromatic protons used as an internal standard (**Figure 5.3**).

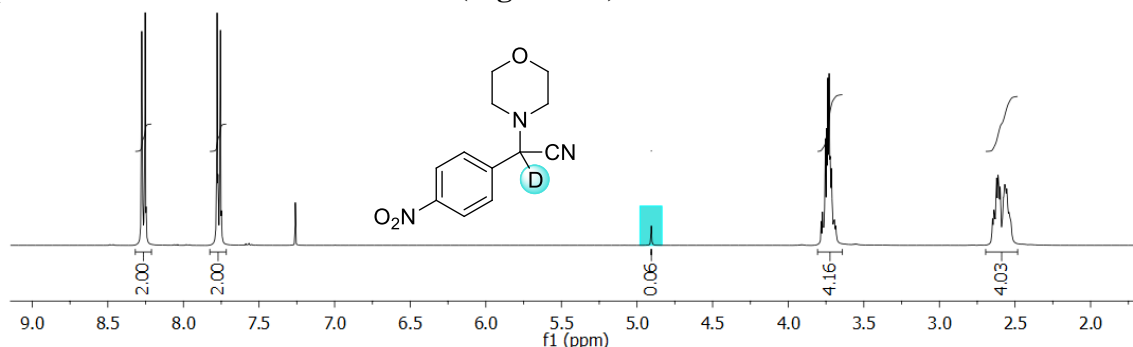
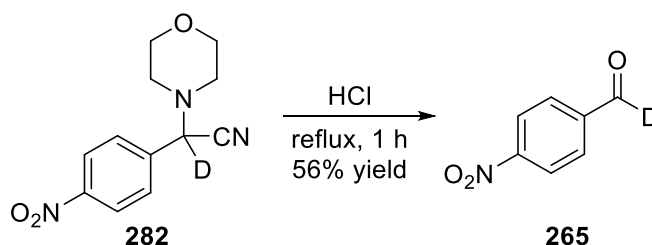


Figure 5.3 The ¹H-NMR (CDCl₃) spectrum of **282**.

With **282** in hand, its conversion into the corresponding α -deutero-4-nitrobenzaldehyde (**265**) was examined (**Scheme 5.3**).

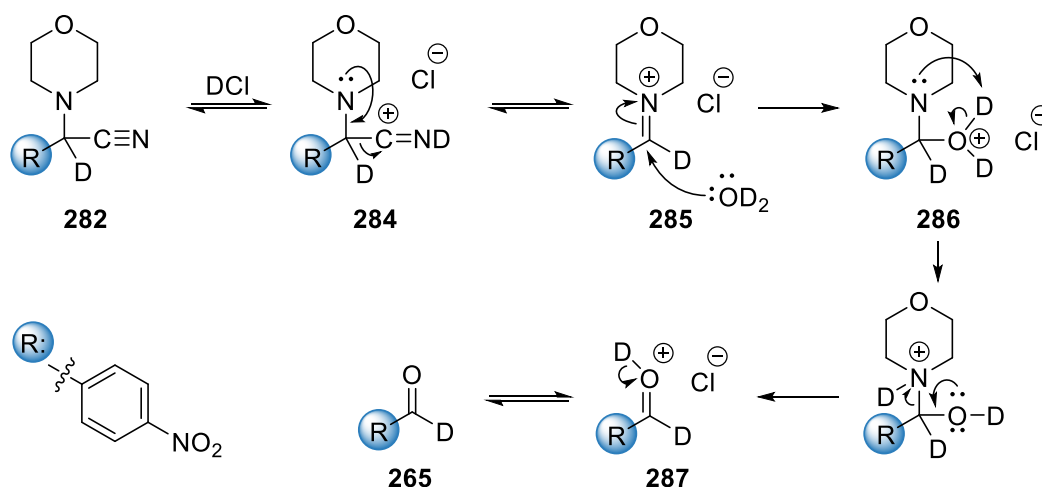


Scheme 5.3 Synthesis of **265** following the procedure reported by Bennett *et al.*²⁵

Refluxing 2-deutero-2-morpholino-2-(4-nitrophenyl)acetonitrile (**282**) in 2 M aqueous hydrochloric acid solution generated, after 1 hour, the corresponding α -deuterated aldehyde **265** in 56% yield. However, the deuterium incorporation decreased from 94% in **282** to only 32% in the desired aldehyde **265** (based on ¹H-NMR spectroscopic evidence).

It was thought that the loss of deuterium was caused by the presence of an aqueous hydrochloric acid solution, which served as the source of protons. To test this hypothesis, the reaction was repeated using deuterium chloride (35 wt.% solution in deuterium oxide) instead of aqueous hydrochloric acid solution. The desired α -deutero-4-nitrobenzaldehyde (**265**) was obtained with a high 98% deuterium incorporation (based on $^1\text{H-NMR}$ spectroscopic evidence) and in a reasonable 52% yield. The structure of **265** was verified by the physicochemical analysis data that corresponded closely to those reported in the literature.²⁶

The proposed mechanistic pathway for the conversion of **282** into **265** is outlined in **Scheme 5.4**.

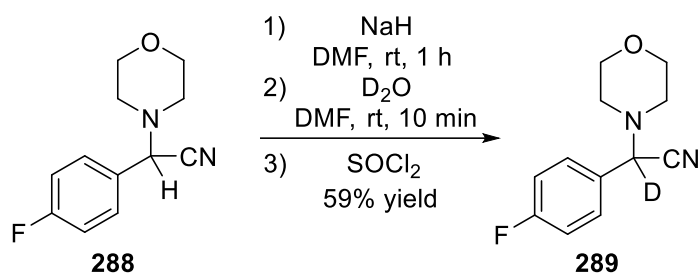


Scheme 5.4 The proposed mechanistic pathway for the transformation of **282** into **265**.

Protonation of the nitrogen atom of the nitrile **282** followed by donation of a lone pair by the nitrogen of the intermediate **284** generates iminium ion **285**, which undergoes nucleophilic addition of deuterium oxide affording **286**. A proton transfer reaction followed by removal of morpholine leads to oxonium ion **287**, which after deprotonation affords the α -deuterated aldehyde **265**.

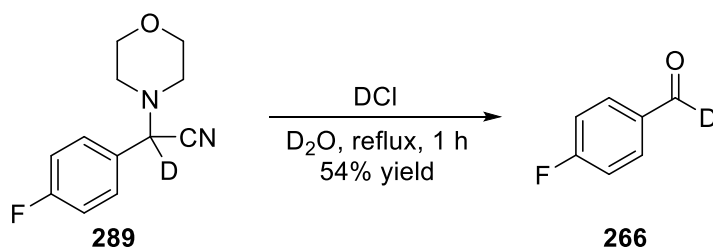
Having successfully prepared α -deutero-4-nitrobenzaldehyde (**265**), the conversion of 2-(4-fluorophenyl)-2-morpholinoacetonitrile (**288**) (readily available in the research laboratory; prepared by a former PhD student according to a procedure reported by Bennett *et al.*²⁵) into α -deutero-4-fluorobenzaldehyde (**266**) was investigated.

Adopting the protocol reported by Bennett *et al.*²⁵ (**Scheme 5.5**), the desired 2-deutero-2-morpholino-2-(4-fluorophenyl)acetonitrile (**289**) was prepared in 59% yield and with 96% deuterium incorporation (based on $^1\text{H-NMR}$ spectroscopic evidence).



Scheme 5.5 Synthesis of **289** according to a procedure reported by Bennett *et al.*²⁵

With **289** in hand and with an established protocol for the transformation of 2-deutero-2-morpholinoacetonitriles into the corresponding α -deuterated aromatic aldehydes, **266** was synthesised in 54% yield (**Scheme 5.6**) and with 97% deuterium incorporation. This was calculated based on the loss of intensity of a signal at δ 9.96 ppm in comparison to the commercially available non-labelled 4-fluorobenzaldehyde. The signal at δ 9.96 ppm for the residual proton was integrated against a signal at δ 7.91 ppm for two aromatic protons used as an internal standard (**Figure 5.4**).



Scheme 5.6 Synthesis of **266** employing the modified procedure reported by Bennett *et al.*²⁵

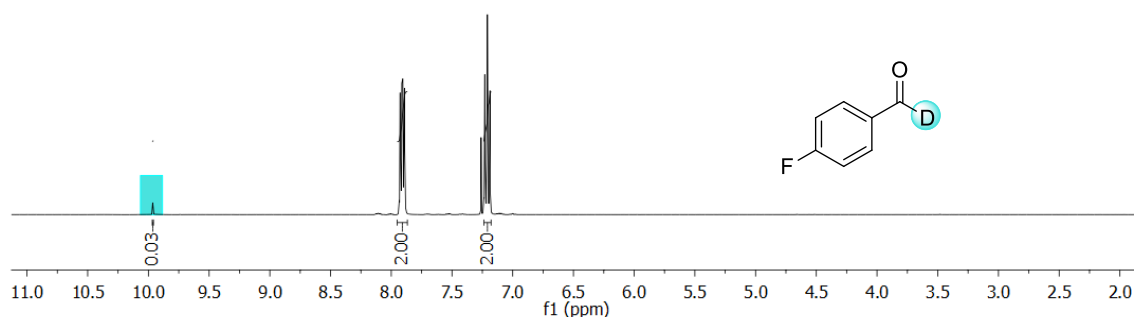
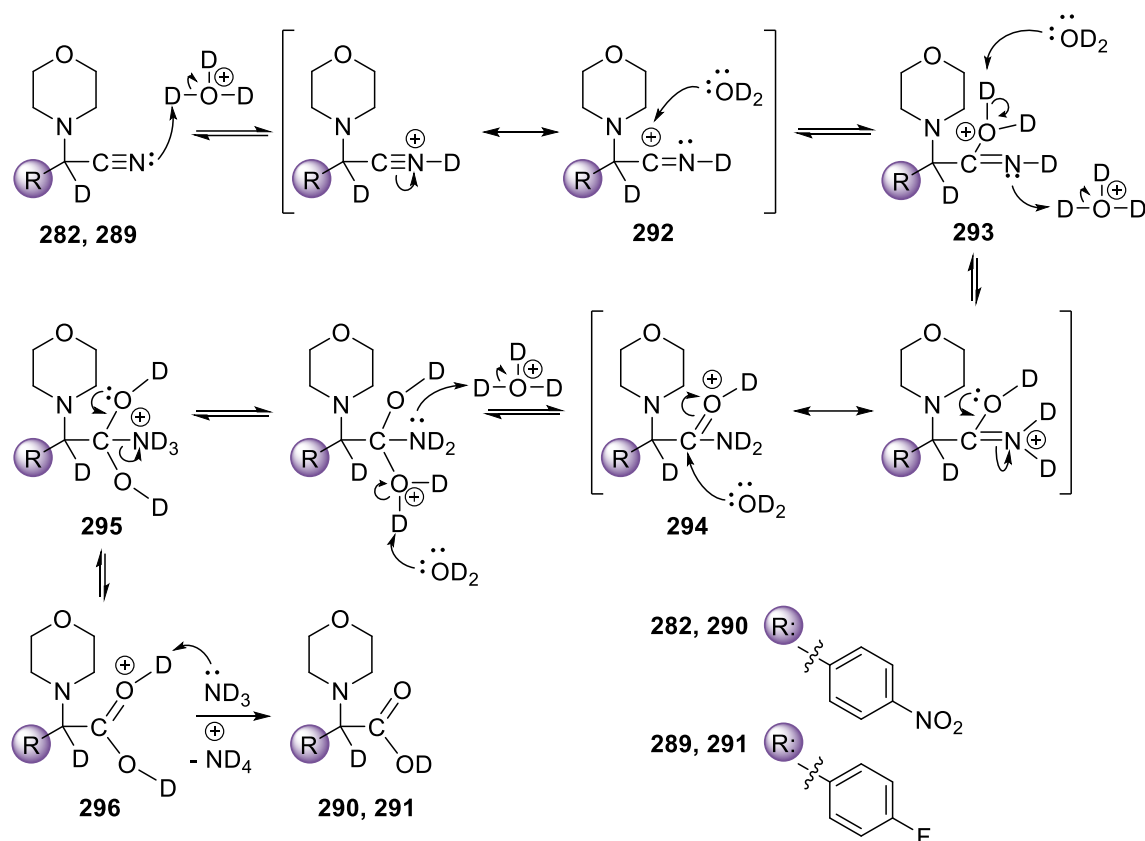


Figure 5.4 The ¹H-NMR (CDCl₃) spectrum of **266**.

The moderate yields (52% and 54%) of the reactions to convert 2-deutero-2-morpholinoacetonitriles **282** and **289** into the corresponding α -deuterated aromatic aldehydes **265** and **266** could be attributed to a side reaction that can take place during the aldehyde generation. In this mechanism 2-deutero-2-morpholinoacetonitriles **282** and **289** undergo partial hydrolysis to **290** and **291** according to a mechanistic pathway proposed by Solomons and Fryhle²⁷ (**Scheme 5.7**).

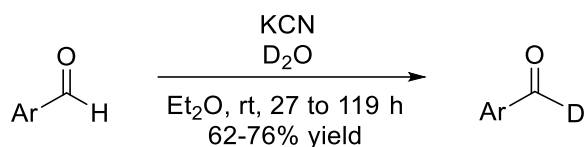


Scheme 5.7 Mechanistic pathway for the generation of **290** and **291** proposed by Solomons and Fryhle.²⁷

Protonation of the nitrogen atom of the nitrile **282** or **289** and consecutive nucleophilic attack on the carbocation **292** by deuterium oxide generates the *N*-deuterium imine **293**. Proton transfer reaction affords the protonated amide **294**. Further attack by deuterium oxide at the protonated carbonyl of **294** and subsequent proton transfer reaction yield intermediate **295**. Loss of deuterated ammonia affords the protonated **296**. Deprotonation of **296** by the deuterated ammonia generates **290** or **291** and deuterated ammonium ion.

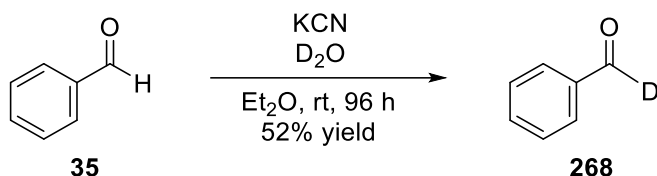
Although a protocol to obtain high levels of deuterium incorporation (>94%) at the aldehyde group of the aromatic aldehydes had been established, an alternative route for the preparation of α -deuterated aromatic aldehydes was sought due to the unsatisfactory yields of the reactions and time-consuming three-step synthesis.

A literature survey revealed a one-step protocol reported by Chancellor *et al.*²⁸ who described deuterium incorporation (50% to 98%) at the aldehyde group of aromatic aldehydes using potassium cyanide (1 or 2 equivalents) in a biphasic solvent system (diethyl ether / deuterium oxide) (**Scheme 5.8**).



Scheme 5.8 The hydrogen / deuterium exchange reaction at the aldehyde group of aromatic aldehydes reported by Chancellor *et al.*²⁸

Adopting the aforementioned protocol, the deuterium incorporation at the aldehyde group of benzaldehyde (**35**) was investigated (**Scheme 5.9**).

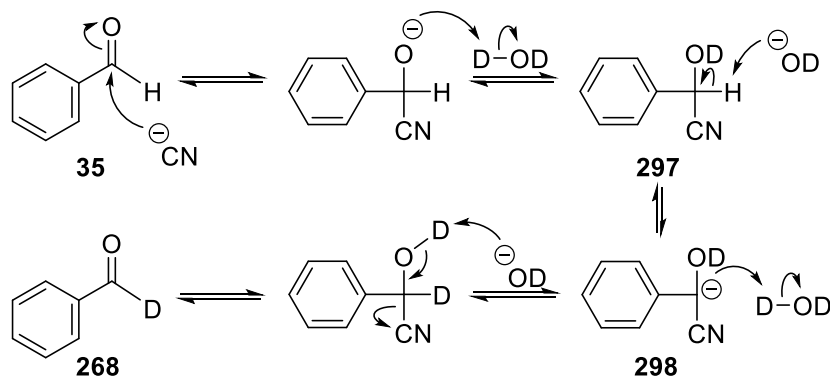


Scheme 5.9 Synthesis of **268** employing a procedure reported by Chancellor *et al.*²⁸

Reaction of **35** with potassium cyanide (2 equivalents) in a mixture of deuterium oxide (38 equivalents) and diethyl ether at room temperature afforded, after 48 hours, the desired α -deuterobenzaldehyde (**268**) with 84% deuterium incorporation (based on $^1\text{H-NMR}$ spectroscopic evidence). It was thought that an additional cycle of the obtained **268** with fresh potassium cyanide (2 equivalents) and deuterium oxide (38 equivalents) in diethyl ether under the above conditions could increase the level of deuterium incorporation of **268**. Indeed, the anticipated **268** was generated in 52% yield and with high 98% deuterium incorporation (based on $^1\text{H-NMR}$ spectroscopic evidence). Analysis of the physicochemical data, which corresponded closely to those reported in the literature,²⁹ verified the structure of **268**.

Chancellor *et al.*²⁸ in their report from 1978 indicated that the generation of α -deuterated aromatic aldehydes using potassium cyanide in a biphasic solvent system (diethyl ether / deuterium oxide) is likely to proceed *via* formation of an acyl anion equivalent.

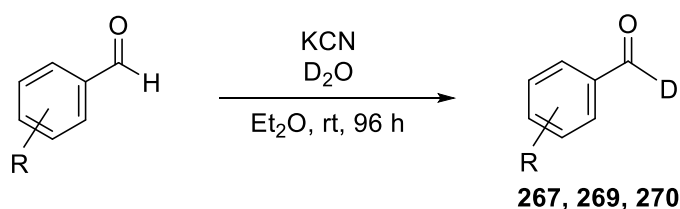
On the basis of the above hypothesis a mechanistic pathway for the hydrogen / deuterium exchange reaction of **35** has been proposed and is outlined in **Scheme 5.10**.



Scheme 5.10 Proposed mechanistic pathway for the hydrogen / deuterium exchange reaction of **35**.

Nucleophilic attack of the cyanide ion at the carbonyl carbon of **35** and consecutive protonation generates the cyanohydrin **297**. Deprotonation of **297** affords the acyl anion equivalent **298**. Protonation of **298** and subsequent elimination of cyano group yields the desired α -deuterobenzaldehyde (**268**). **Scheme 5.10** also represents the starting point of the mechanism for the classical benzoin condensation. However, proton exchange is much faster than carbon-carbon bond formation allowing deuterium exchange to occur before significant amounts of benzoin accumulate.

Employing the protocol reported by Chancellor *et al.*²⁸ for the hydrogen / deuterium exchange reaction at the aldehyde group of aromatic aldehydes (**Scheme 5.11**), three additional α -deuterated aromatic aldehydes **267**, **269**, **270** were synthesised with high levels of deuterium incorporation, *i.e.*, 97% to 98%, and in moderate yields (39% to 45%) (**Table 5.1**).

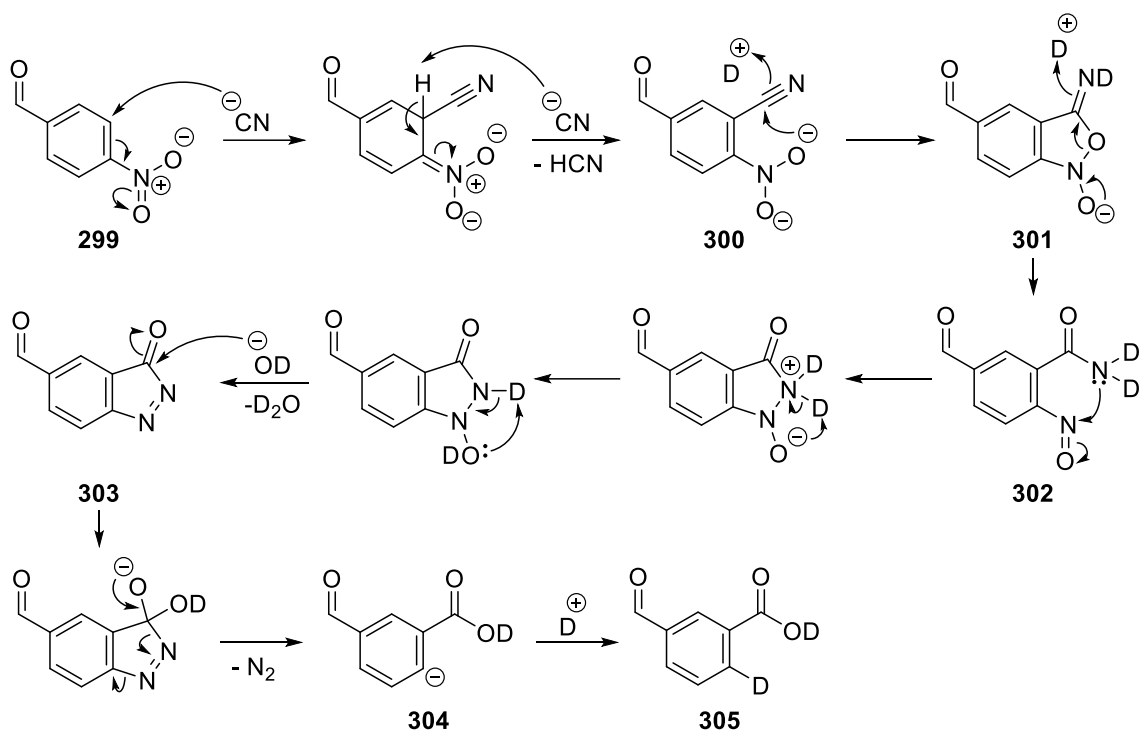


Scheme 5.11 Synthesis of α -deuterated aromatic aldehydes **267**, **269**, **270**.

Compound number	R	Solvent	Temperature (°C)	Deuterium incorporation (%)	Yield (%)
267	4-Br	Et ₂ O / D ₂ O	rt	98	43
269	2-Cl	Et ₂ O / D ₂ O	rt	98	45
270	3-Cl	Et ₂ O / D ₂ O	rt	97	39

Table 5.1 Preparation of **267**, **269**, **270** employing the protocol reported by Chancellor *et al.*²⁸

Encouraged by the high levels of deuterium incorporation and experimental simplicity of the aforementioned protocol, it was decided to explore its application for the synthesis of previously prepared α -deutero-4-fluorobenzaldehyde (**266**) and α -deutero-4-nitrobenzaldehyde (**265**). In fact, **266** was generated in 48% yield and with 97% deuterium incorporation (based on ¹H-NMR spectroscopic evidence) in a one-step synthesis. In an attempt to prepare **265** from 4-nitrobenzaldehyde (**299**) the desired reaction failed and the starting material **299** was quickly consumed. Although not experimentally confirmed, it is postulated that a von Richter reaction took place according to a mechanistic pathway described by Smith and March³⁰ and outlined in **Scheme 5.12**.



Scheme 5.12 The mechanistic pathway for the von Richter reaction to generate **305** published by Smith and March.³⁰

Addition of the cyano group to **299** at the *ortho*-position to the nitro group followed by a deprotonation generates the intermediate **300**. An intramolecular attack by the oxygen of the nitro group at the cyano carbon yields the bicyclic intermediate **301**, which undergoes ring opening affording the aryl nitroso amide **302**. Loss of a deuterium oxide leads to indazolone **303** that loses nitrogen gas to provide carbanion **304** and ultimately the *cine*-substituted benzoic acid **305**.

5.3. Synthesis of a range of α -deutero- α -diazoacetic acid esters **271** – **281**

Before initiating studies towards the hydrogen / deuterium exchange reaction at the α -carbon atom of α -diazoacetic acid esters **306** – **314** (Figure 5.5), a reliable procedure for their synthesis was required.

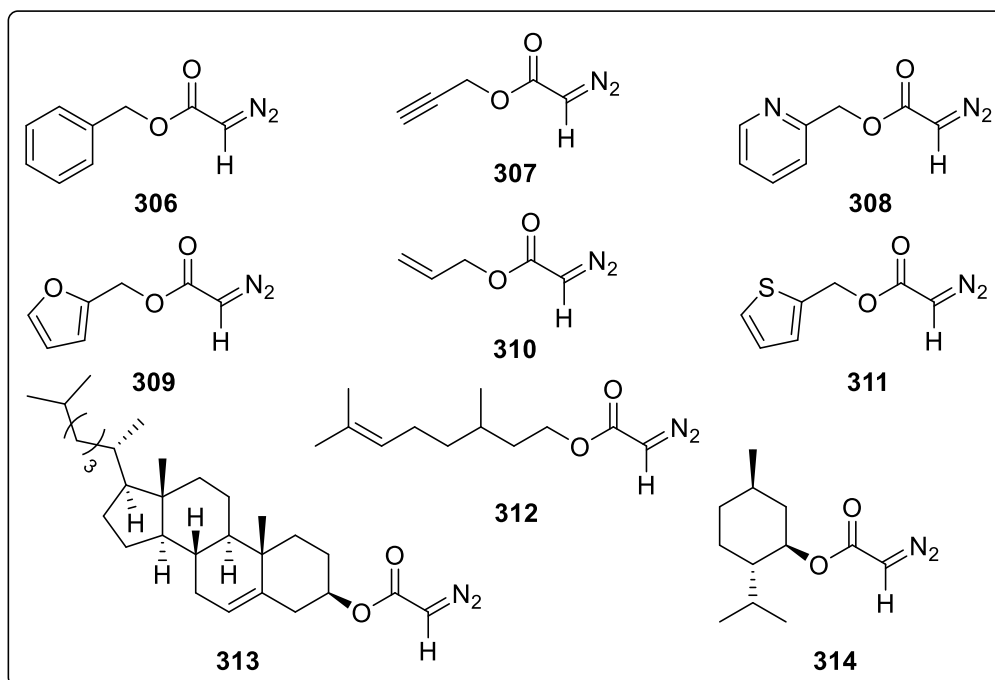
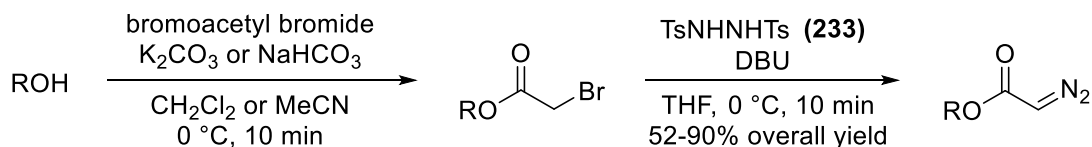


Figure 5.5 A range of α -diazoacetic acid esters **306** – **314**.

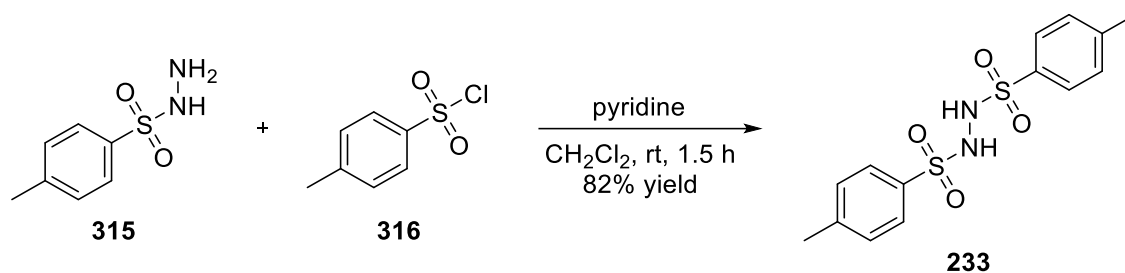
Fukuyama *et al.*³¹ have used 4-methyl-*N'*-tosylbenzenesulfonylhydrazide (**233**) as a reagent for the preparation of a variety of α -diazoacetic acid esters from corresponding alcohols in a two-step procedure and in moderate to high yields (52% to 90%) (**Scheme 5.13**). This procedure was tested.



R = aliphatic, aryl, monoterpene, steroid

Scheme 5.13 Synthesis of α -diazoacetic acid esters according to a procedure reported by Fukuyama *et al.*³¹

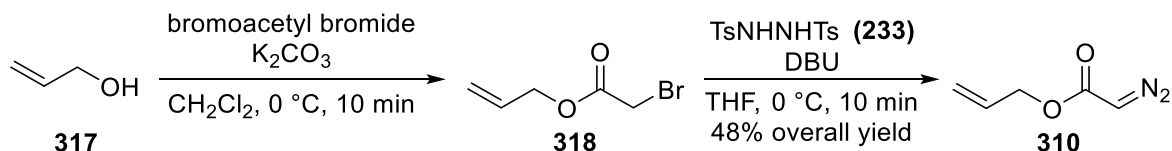
In the first instance, 4-methyl-*N'*-tosylbenzenesulfonylhydrazide (**233**) was prepared in multigram quantities adopting the protocol described by Fukuyama *et al.*³¹ (**Scheme 5.14**).



Scheme 5.14 Synthesis of **233** described in a protocol reported by Fukuyama *et al.*³¹

Reaction of *p*-toluenesulfonyl hydrazide (**315**) with *p*-toluenesulfonyl chloride (**316**) in the presence of pyridine in dichloromethane at room temperature afforded, after 1.5 hours, the anticipated **233** in 82% yield.

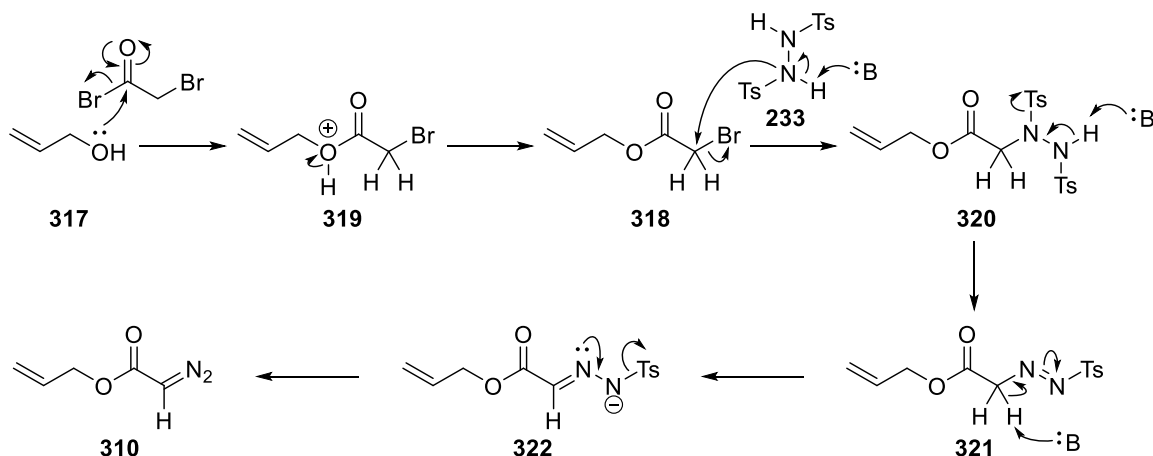
With **233** in hand, the generation of a range of α -diazoacetic acid esters **306** – **314** via the two-step procedure reported by Fukuyama *et al.*³¹ was investigated. To begin with, allyl alcohol (**317**) was employed in the aforementioned protocol (**Scheme 5.15**).



Scheme 5.15 Synthesis of **310** according to a protocol reported by Fukuyama *et al.*³¹

Reaction of **317** with excess of potassium carbonate (5 equivalents) and subsequent treatment with excess of bromoacetyl bromide (3 equivalents) in dichloromethane at 0 °C afforded after 10 minutes allyl bromoacetate (**318**). Consecutive reaction of **318** with excess of 4-methyl-*N'*-tosylbenzenesulfonylhydrazide (**233**) (2 equivalents) and thereafter excess of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (5 equivalents) in tetrahydrofuran at 0 °C generated, after 10 minutes, the desired allyl α -diazoacetate (**310**) in an overall 48% yield after two steps.

The mechanistic pathway for the synthesis of **310** proposed by Ragnarsson and Grehn³² is outlined in **Scheme 5.16**.



B = 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)

Scheme 5.16 The proposed mechanistic pathway for the synthesis of **310** reported by Ragnarsson and Grehn.³²

Nucleophilic attack of the alcohol **317** on the carbonyl carbon of bromoacetyl bromide and subsequent deprotonation of **319** generates allyl bromoacetate **318**. Nucleophilic attack of the deprotonated **233** on the α -carbon atom of **318** affords the intermediate **320**, which undergoes further deprotonation with the release of one tosyl group yielding **321**. Removal

of the α -hydrogen atom of **321** and consecutive donation of a lone pair by a nitrogen of **322** eliminates second tosyl group and affords the anticipated **310**.

The structure of **310** was verified by analysis of the physicochemical data. The FT-IR spectrum revealed the characteristic peak for the carbonyl group at 1682 cm^{-1} and a peak at 2107 cm^{-1} corresponding to the $\text{C}=\text{N}=\text{N}$ stretch of a diazo group. The $^1\text{H-NMR}$ spectrum (**Figure 5.6**) displayed two multiplets at $\delta\ 5.98 - 5.95$ and $5.35 - 5.21$ ppm for the alkenyl protons, a singlet at $\delta\ 4.77$ ppm for the α -hydrogen atom, and a multiplet at $\delta\ 4.66 - 4.64$ ppm for the protons of the methylene group.

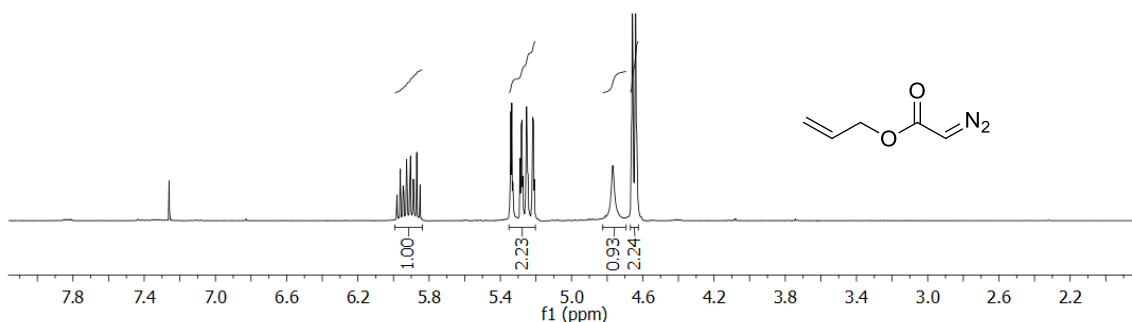


Figure 5.6 The $^1\text{H-NMR}$ (CDCl_3) spectrum of **310**.

Furthermore the $^{13}\text{C-NMR}$ (**Figure 5.7**) revealed peaks at $\delta\ 132.3$ and 118.5 ppm for the alkenyl carbons, a peak at $\delta\ 65.6$ ppm for the carbon of the methylene group, and a peak at $\delta\ 46.4$ ppm for the α -carbon atom adjacent to the diazo group (a $^{13}\text{C}=\text{O}$ signal was not observed). High-resolution mass spectrometry (EI) displayed m/z at 126.0423 (calculated for $\text{C}_5\text{H}_6\text{O}_2\text{N}_2$ [M] 126.0424) confirming the identity of **310**.

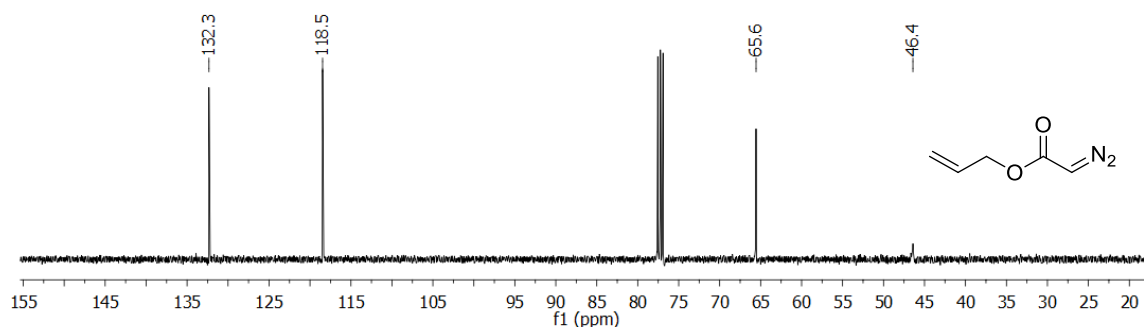
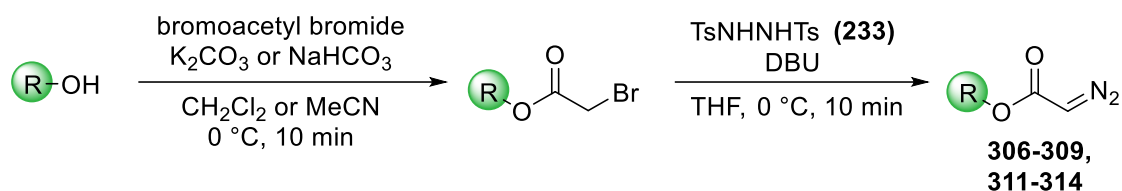


Figure 5.7 The $^{13}\text{C-NMR}$ (CDCl_3) spectrum of **310**.

Employing the aforesaid protocol reported by Fukuyama *et al.*,³¹ a range of alcohols was converted into corresponding α -diazoacetic acid esters **306 - 309**, **311 - 314** (**Scheme 5.17**, **Figure 5.8**, **Table 5.2**).



Scheme 5.17 Synthesis of a series of α -diazoacetic acid esters **306 – 309, 311 – 314** utilising the protocol reported by Fukuyama *et al.*³¹

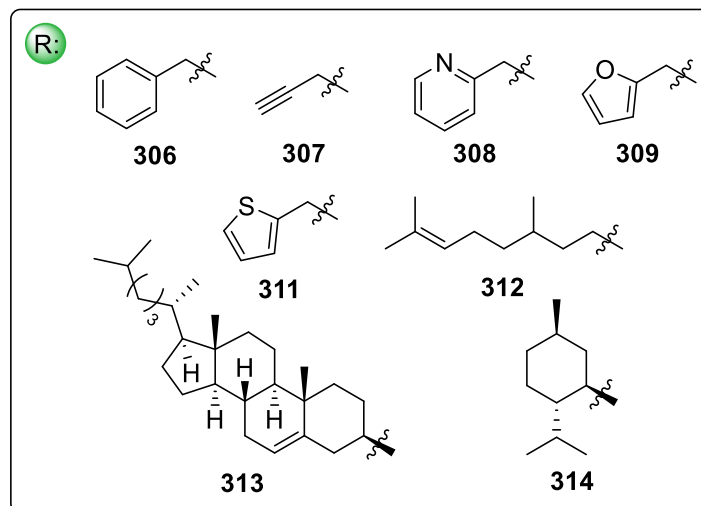


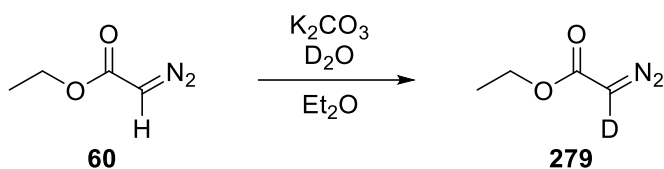
Figure 5.8 Structures of α -diazoacetic acid esters **306 – 309, 311 – 314**.

Compound number	Base	Solvent	Yield (%)	Compound number	Base	Solvent	Yield (%)
306	NaHCO ₃	MeCN	46	311	K ₂ CO ₃	CH ₂ Cl ₂	45
307	K ₂ CO ₃	CH ₂ Cl ₂	25	312	K ₂ CO ₃	CH ₂ Cl ₂	32
308	NaHCO ₃	MeCN	38	313	K ₂ CO ₃	CH ₂ Cl ₂	25
309	K ₂ CO ₃	CH ₂ Cl ₂	51	314	NaHCO ₃	MeCN	50

Table 5.2 Synthesis of **306 – 309, 311 – 314** following a protocol reported by Fukuyama *et al.*³¹

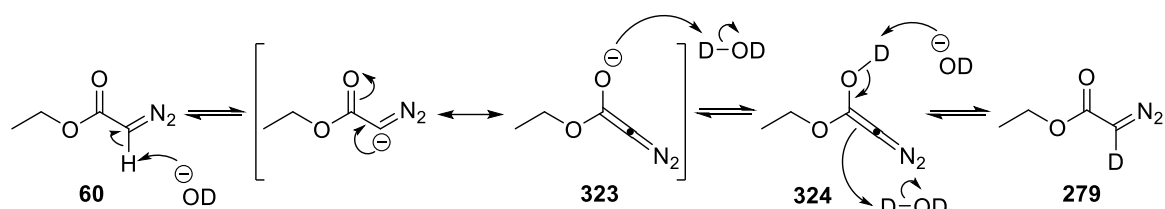
Having successfully synthesised **306 – 314**, the hydrogen / deuterium exchange reaction at the α -carbon atom of α -diazoacetic acid esters **306 – 314** was explored.

A literature survey revealed an article reported by Peterson and Indelicato³³ in which a synthesis of ethyl α -deutero- α -diazoacetate (**279**) in a reaction of ethyl α -diazoacetate (**60**) with potassium carbonate in a biphasic solvent system (diethyl ether / deuterium oxide) was mentioned (**Scheme 5.18**). However, the authors did not describe the amounts of reagents used for this reaction, nor did they provide the yield or the level of deuterium incorporation.



Scheme 5.18 Synthesis of **279** reported by Peterson and Indelicato.³³

The proposed mechanistic pathway for the base-catalysed hydrogen / deuterium exchange reaction at the α -carbon atom of **60** is outlined in **Scheme 5.19**.



Scheme 5.19 The proposed mechanistic pathway for the base-catalysed hydrogen / deuterium exchange reaction at the α -carbon atom of **60**.

Deprotonation at the α -carbon atom of **60** should occur readily owing to the expected acidity of the proton. Generated enolate ion **323** undergoes protonation affording enol **324**. Tautomerisation of **324** yields the desired ethyl α -deutero- α -diazoacetate (**279**).

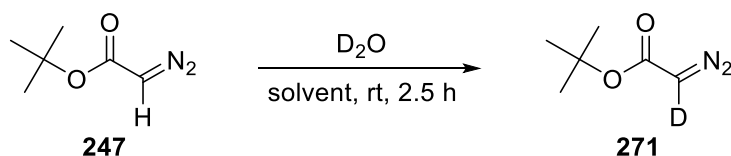
Preliminary studies performed by a former PhD student in the research laboratory led to a reliable protocol for the hydrogen / deuterium exchange reaction at the α -carbon atom of ethyl α -diazoacetate (**60**). A reaction of **60** with potassium carbonate (1 equivalent) and excess of deuterium oxide (100 equivalents) in diethyl ether at room temperature afforded after two cycles of 24 hours (each cycle with fresh potassium carbonate and deuterium oxide) the desired **279** with >93% level of deuterium incorporation (based on ¹H-NMR spectroscopic evidence).

Although the aforementioned protocol was successfully applied for the synthesis of **279**, its utilisation for the synthesis of other α -deutero- α -diazocarbonyl compounds, *i.e.*, benzyl α -deutero- α -diazoacetate (**277**) (73% of deuterium incorporation) and α -deutero- α -diazo-1-phenylethanone (**349**) (36% of deuterium incorporation), did not provide the desired results. Moreover, the long time required for the reaction (48 hours), two-cycle procedure and low yield (less than 50% for the synthesis of **279**) made it inefficient. Further optimisation was necessary.

It was thought important to examine the use of different solvents with deuterium oxide (biphasic solvent system) for the hydrogen / deuterium exchange reaction at the α -carbon atom of α -diazoacetic acid esters as the solubility of a solvent in deuterium oxide could have a significant effect on the level of deuterium incorporation. *t*-Butyl α -diazoacetate (**247**) (readily available in the research laboratory; prepared by a former PhD student) was

chosen for this study. Ethyl α -diazoacetate (**60**) is commercially available as ≤ 85 wt.% solution in dichloromethane but was abandoned as a test compound due to more time-consuming preparation owing to the need to remove dichloromethane *in vacuo* before its utilisation in a reaction.

Making use of the knowledge of miscibility of organic solvents in water,³⁴ the hydrogen / deuterium exchange reaction of **247** (potassium carbonate was excluded from the reaction system) (**Scheme 5.20**) was carried out in various solvent systems (ratio of the solvent to deuterium oxide; 1 : 1 (v / v)) and resulted in the following levels of deuterium incorporation (**Table 5.3**).³⁵



Scheme 5.20 Synthesis of **271** in a mixture of a solvent and deuterium oxide.

Solvent	Solubility in H ₂ O (g / 100 g) ³⁴	D ₂ O (equiv)	Time (h)	Deuterium incorporation (%)
MTBE	4.3	100	2.5	42
Et ₂ O	6.9	100	2.5	51
EtOAc	7.7	100	2.5	46
MEK	26	100	2.5	55
THF	Total	100	2.5	46
1,4-dioxane	Total	100	2.5	47
acetone- <i>d</i> ₆ ^a	Total	100	2.5	80
CD ₃ OD ^a	Total	100	2.5	80
CD ₃ CN ^a	Total	100	2.5	59
DMF	Total	100	2.5	79
DMSO- <i>d</i> ₆ ^a	Total	100	2.5	76

^a The reactions were performed in NMR tubes employing deuterated solvents, which allowed for direct ¹H-NMR spectroscopic monitoring of the hydrogen / deuterium exchange reaction at the α -carbon of **247**.

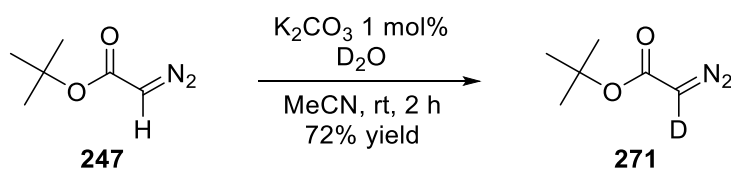
Table 5.3 Study on the level of deuterium incorporation of **271** (based on ¹H-NMR spectroscopic evidence) in a mixture of a solvent and deuterium oxide.³⁵

Low solubility solvents, *i.e.*, *t*-butyl methyl ether, diethyl ether, ethyl acetate, and methyl ethyl ketone, provided moderate levels (42% to 55%) of deuterium incorporation in **271** within a period of 2.5 hours whereas the completely miscible solvents,

i.e., tetrahydrofuran, 1,4-dioxane, acetone- d_6 , methanol- d_4 , acetonitrile- d_3 , *N,N*-dimethylformamide and dimethyl sulfoxide- d_6 , afforded, in general, higher levels (46% to 80%) of deuterium incorporation and therefore became the solvents of further interest. Although the levels of deuterium incorporation in deuterium oxide miscible solvents were reasonable, they were not exceptional and the use of catalytic amount of a weak base in the hydrogen / deuterium exchange reaction was considered. Tetrahydrofuran and 1,4-dioxane were excluded from this study as they provided low levels of deuterium incorporation, 46% and 47% respectively. Acetone- d_6 was abandoned due to the possibility of generating aldol reaction by-products in the presence of a base, and dimethyl sulfoxide- d_6 and *N,N*-dimethylformamide were omitted due to the high boiling points and difficulty in removing them from the α -deutero- α -diazoacetic acid esters. Methanol- d_4 and acetonitrile- d_3 were the preferred choices.

To begin with, the hydrogen / deuterium exchange reaction at the α -carbon atom of *t*-butyl α -diazoacetate (**247**) using 10 mol% of potassium carbonate in a mixture of methanol- d_4 and deuterium oxide at room temperature was performed affording, after 2.5 hours, the desired **271** with 89% deuterium incorporation. The level of deuterium incorporation remained insufficient, albeit higher than the 80% obtained without the use of a base. Repeating the protocol but utilising acetonitrile- d_3 instead of methanol- d_4 had a positive effect on the reaction and the anticipated **271** was generated with impressive $\geq 99\%$ deuterium incorporation. Lower loadings of the catalyst in the mixture of acetonitrile- d_3 and deuterium oxide were also investigated. Employing 0.1 mol% of potassium carbonate afforded **271** with 86% deuterium incorporation after 4 hours, whereas the use of 1 mol% of potassium carbonate led to **271** with $\geq 99\%$ deuterium incorporation within only 2 hours. Reducing the amount of deuterium oxide from the 100 equivalents used originally to 10, 20, and 33 equivalents in the presence of 1 mol% of potassium carbonate afforded **271** with a 79, 90 and 95% deuterium incorporation respectively. To circumvent the use of more expensive acetonitrile- d_3 , acetonitrile dried over 3 Å molecular sieves and HPLC-grade acetonitrile were examined for the hydrogen / deuterium exchange reaction of **247**. Consequently **271** was generated with 91% deuterium incorporation in acetonitrile dried over 3 Å molecular sieves and with $\geq 99\%$ deuterium incorporation in HPLC-grade acetonitrile.

With all the studies complete, the desired *t*-butyl α -deutero- α -diazoacetate (**271**) was ultimately synthesised in 72% yield (**Scheme 5.21**).



Scheme 5.21 Synthesis of *t*-butyl α -deutero- α -diazoacetate (**271**).³⁵

Adding a solution of potassium carbonate (1 mol%) in deuterium oxide (100 equivalents) to a solution of *t*-butyl α -diazoacetate (**247**) in acetonitrile at room temperature afforded, after two hours and one cycle, the anticipated **271** with $\geq 99\%$ deuterium incorporation (based on $^1\text{H-NMR}$ spectroscopic evidence) (**Figure 5.9**).³⁵

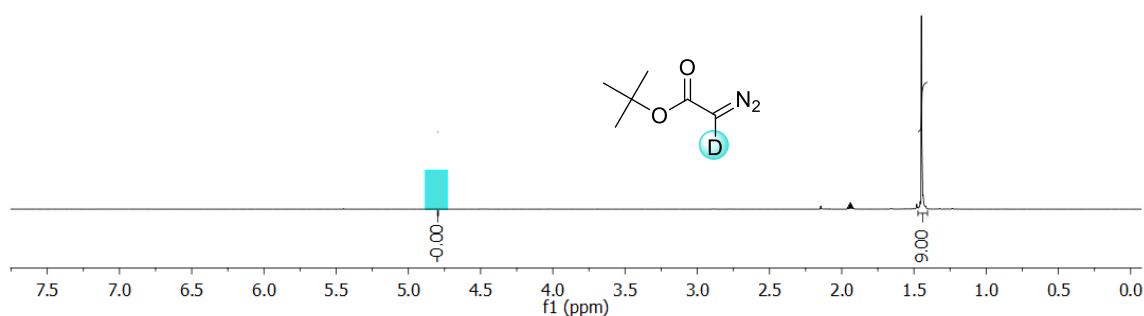


Figure 5.9 The $^1\text{H-NMR}$ (CD_3CN) spectrum of **271**.

The structure of **271** was confirmed by analysis of the physicochemical data. The FT-IR spectrum revealed the characteristic peak for the carbonyl group at 1685 cm^{-1} and a peak at 2105 cm^{-1} corresponding to the $\text{C}=\text{N}=\text{N}$ stretch of a diazo group. The $^1\text{H-NMR}$ spectrum (**Figure 5.9**) displayed a singlet at $\delta 1.45\text{ ppm}$ for the protons of the *t*-butyl group. Furthermore the $^{13}\text{C-NMR}$ (**Figure 5.10**) revealed a peak at $\delta 163.1\text{ ppm}$ for the carbonyl carbon, and peaks at $\delta 82.2$ and 28.8 ppm for the carbons of the *t*-butyl group (a $^{13}\text{C-D}$ signal was not observed).

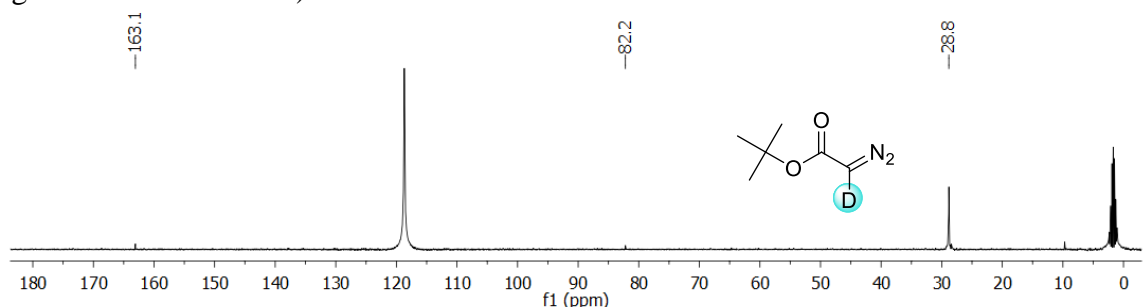
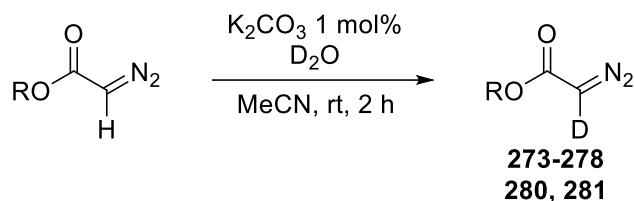


Figure 5.10 The $^{13}\text{C-NMR}$ (CD_3CN) spectrum of **271**.

With an established protocol for the deuterium incorporation at the α -carbon atom of *t*-butyl α -diazoacetate (**247**) in hand, the syntheses of remaining α -deutero- α -diazoacetic acid esters **273 – 278**, **280**, **281** were examined.

Employing the aforementioned protocol, a range of α -diazoacetic acid esters was converted into corresponding α -deutero- α -diazoacetic acid esters **273** – **278**, **280**, **281** with excellent levels of deuterium incorporation (**Scheme 5.22**, **Table 5.4**).³⁵



Scheme 5.22 Synthesis of a series of α -deutero- α -diazoacetic acid esters **273** – **278**, **280**, **281** utilising an optimised protocol for the hydrogen / deuterium exchange reaction at the α -carbon atom.³⁵

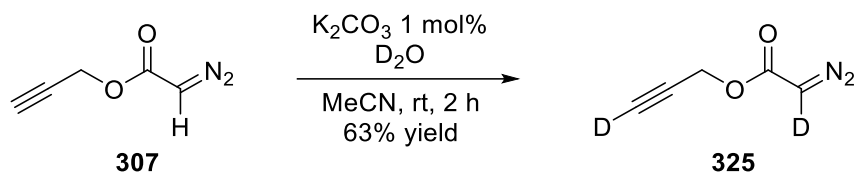
R	Compound number	D ₂ O (equiv)	Yield (%)	Deuterium incorporation (%)
	273	100	— ^a	≥99
	274	100	67	≥98
	275	100	90	≥97
	276	100	82	≥98
	277	100	74	≥99
	278	100	74	≥99
	280	100	83	19
	281	100	89	≥99

^a The yield has not been determined; formation of a by-product was observed.

Table 5.4 Synthesis of **273** – **278**, **280**, **281** employing an optimised protocol for the deuterium incorporation at the α -carbon atom.³⁵

Among the examined α -diazoacetic acid esters only cholesteryl α -diazoacetate (**313**) proved to be problematic during the hydrogen / deuterium exchange reaction. The level of deuterium incorporation was only 19%. This is most likely due to the poor solubility of **313** in the mixture of acetonitrile and deuterium oxide, which leads to a suppression of the hydrogen / deuterium exchange reaction at the α -carbon atom.

Utilisation of propargyl α -diazoacetate (**307**) in the optimised protocol for the hydrogen / deuterium exchange reaction led to an unexpected result. Along with the deuterium incorporation ($\geq 99\%$) at the α -carbon atom, a high level of deuterium incorporation ($\geq 98\%$) at the terminal hydrogen on the alkyne was observed (**Scheme 5.23**, **Figure 5.11**).³⁶



Scheme 5.23 Synthesis of 1-deutero-prop-2-yn-1-yl α -deutero- α -diazoacetate (**325**).

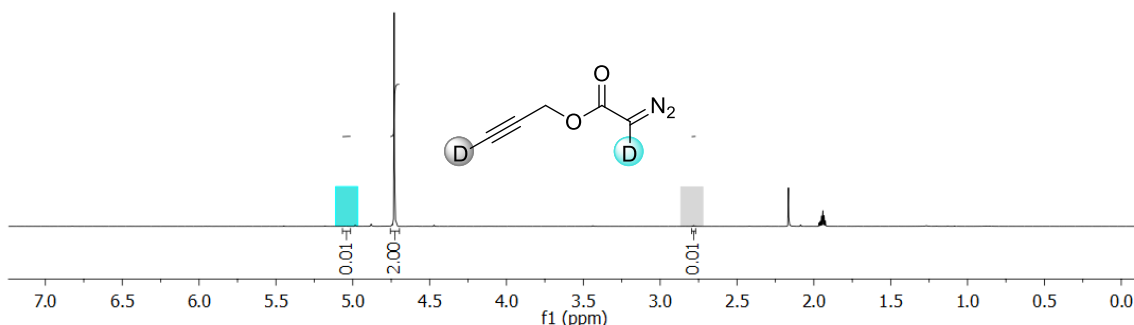


Figure 5.11 The 1H -NMR (CD_3CN) spectrum of **325**.

With a reliable protocol for the base-catalysed hydrogen / deuterium exchange reaction of α -diazoacetic acid esters with excellent levels of deuterium incorporation ($\geq 97\%$) in hand, application to a wider range of α -diazocarbonyl compounds was undertaken. α -Diazoketone **326**, succinimidyl α -diazoacetate **327** (available in the research laboratory and prepared by a PhD student following a protocol reported by Ouhia *et al.*³⁷), α -diazoacetamide-derived α - and β -amino acids **328** – **331** (available in the research laboratory and prepared by a PhD student adopting a protocol reported by Doyle and Kalinin³⁸), α -diazoacetic acid ester-derived α -amino acids **332** and **333**, and the azaserine analogue **334** were chosen as the synthetic targets (**Figure 5.12**).

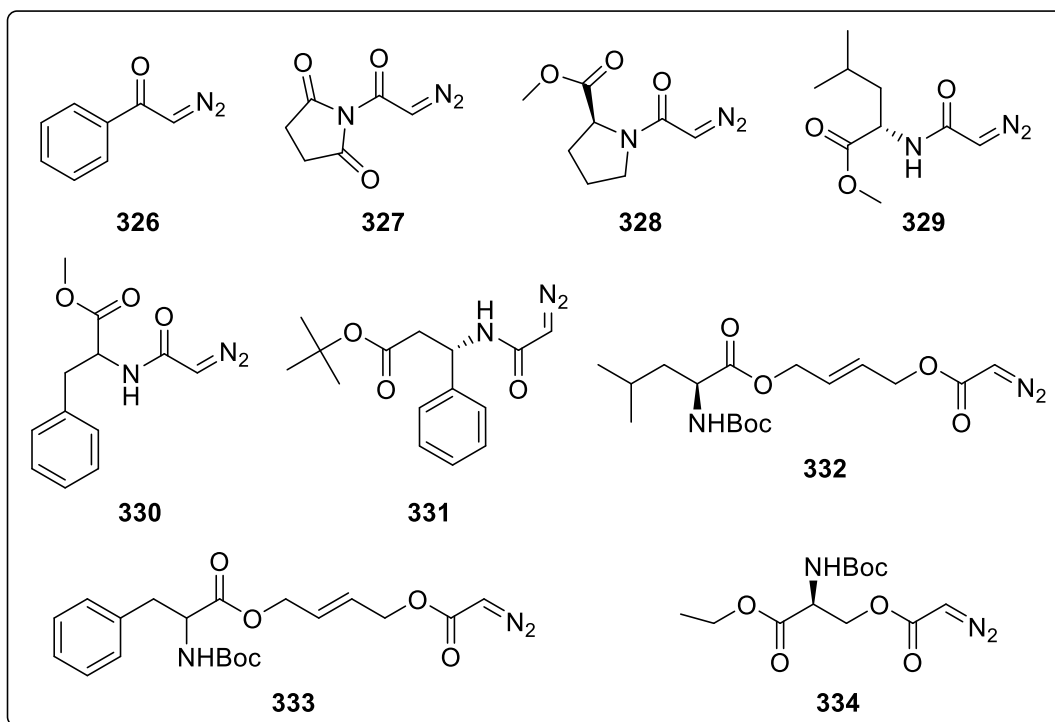
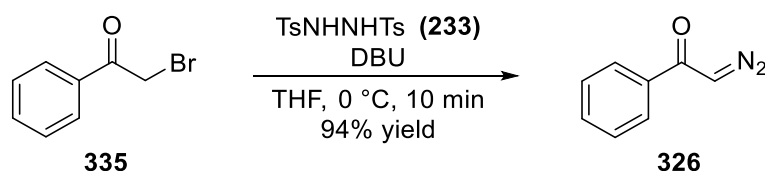


Figure 5.12 A library of α -diazo carbonyl compounds **326** – **334** as synthetic targets for the base-catalysed hydrogen / deuterium exchange reaction.

Before initiating the investigation of a hydrogen / deuterium exchange reaction of the α -diazo carbonyl compounds **326** – **334** chosen, means for their synthesis had to be developed.

The preparation of α -diazo-1-phenylethanone (**326**) was expected to be straightforward as its synthesis had been previously reported by Fukuyama *et al.*³¹ (**Scheme 5.24**).

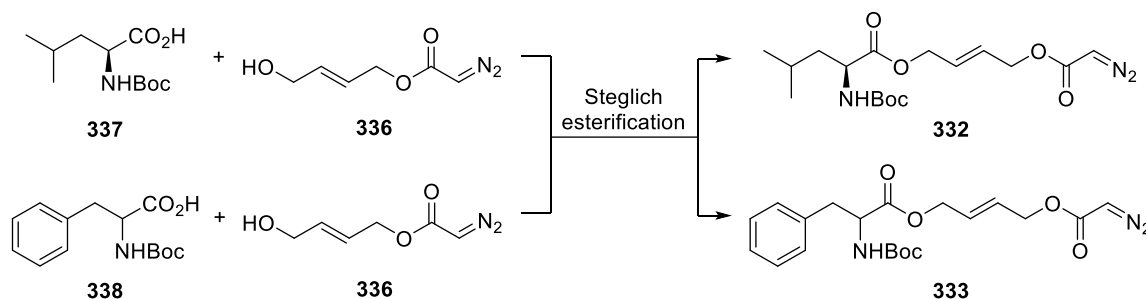


Scheme 5.24 Synthesis of **326** reported by Fukuyama *et al.*³¹

A reaction of 2-bromo-1-phenylethanone (**335**) with excess of 4-methyl-*N'*-tosylbenzenesulfonohydrazide (**233**) (2 equivalents) and thereafter excess of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (5 equivalents) in tetrahydrofuran at 0 °C afforded, after 10 minutes, the desired **326** in 94% yield.

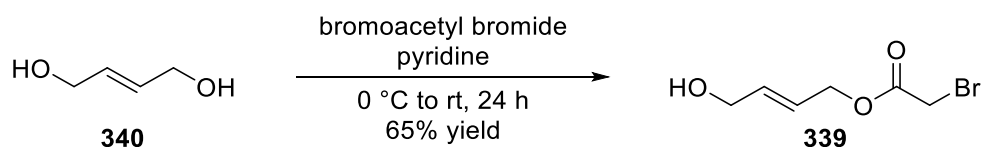
Employing the aforementioned protocol³¹ but using 2-chloro-1-phenylethanone instead of **335**, the anticipated α -diazo-1-phenylethanone (**326**) was prepared in 44% yield. The ¹H- and ¹³C-NMR spectral data of **326** corresponded closely to those reported in the literature.³¹

The synthetic approach to α -diazoacetic acid ester-derived α -amino acids comprised two parts. The first part focused on the preparation of an aliphatic α -diazoacetic acid ester **336** bearing hydroxyl group, and the second on the esterification of the *N*-Boc protected amino acids **337** and **338** via Steglich esterification utilising the synthesised **336** (Scheme 5.25).



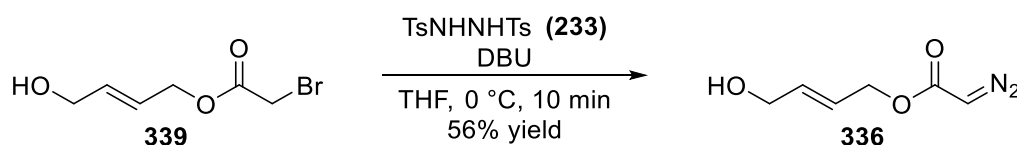
Scheme 5.25 Proposed synthesis of **332** and **333** via a Steglich esterification.

To begin with, (*E*)-4-hydroxybut-2-en-1-yl 2-bromoacetate (**339**) needed to be prepared. Following a protocol reported by Tong *et al.*,³⁹ a reaction of (*E*)-but-2-ene-1,4-diol (**340**) with pyridine and consecutive treatment with bromoacetyl bromide generated, after 24 hours, the anticipated **339** in 65% yield (Scheme 5.26).



Scheme 5.26 Preparation of **339** according to a protocol reported by Tong *et al.*³⁹

With (*E*)-4-hydroxybut-2-en-1-yl 2-bromoacetate (**339**) in hand, its conversion into (*E*)-4-hydroxybut-2-en-1-yl α -diazoacetate (**336**) was achieved following a previously described protocol for the preparation of α -diazoacetic acid esters.⁴⁰ The desired **336** was synthesised in 56% yield (Scheme 5.27).



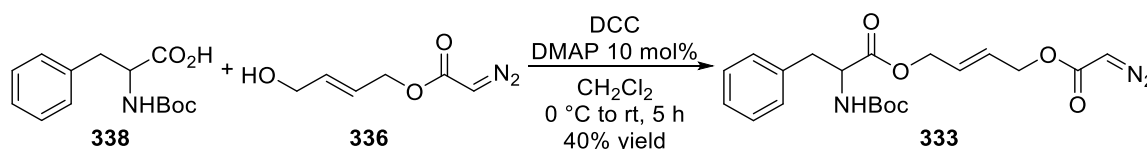
Scheme 5.27 Synthesis of **336** adopting a protocol reported by Fukuyama *et al.*³¹

The analysis of the physicochemical data verified the structure of **336**. The ¹H-NMR spectrum revealed a singlet at δ 4.98 ppm for the α -hydrogen atom confirming the presence of the diazo group in the molecule. Additionally the ¹³C-NMR spectrum displayed a peak at δ 47.3 ppm for the α -carbon atom adjacent to the diazo group.

Having successfully prepared (*E*)-4-hydroxybut-2-en-1-yl α -diazoacetate (**336**), the synthesis of α -diazoacetic acid ester-derived α -amino acids **332** and **333** via a Steglich

esterification with *N,N'*-dicyclohexylcarbodiimide (DCC) as a coupling reagent and 4-dimethylaminopyridine (DMAP) as a catalyst was investigated.

Initially, a protocol reported by Drewe *et al.*⁴¹ was adopted. 4-Dimethylaminopyridine catalysed the esterification of commercially available racemic 2-((*t*-butoxy carbonyl)amino)-3-phenylpropanoic acid (**338**) with (*E*)-4-hydroxybut-2-en-1-yl α -diazoacetate (**336**) in the presence of *N,N'*-dicyclohexylcarbodiimide (1.1 equivalents) in dichloromethane at 0 °C followed by warming to room temperature affording, after 5 hours, the desired **333** in 40% yield (**Scheme 5.28**).



The FT-IR spectrum of **333** displayed the characteristic peak for the carbonyl groups at 1687 cm^{-1} and a peak at 2109 cm^{-1} corresponding to the C=N=N stretch of a diazo group. The ¹H-NMR spectrum (**Figure 5.13**) revealed four multiplets at δ 7.35 – 7.18, 5.85 – 5.61, 4.74 – 4.67 and 4.39 – 4.32 ppm for the aromatic protons, alkenyl protons, protons of the methylene groups adjacent to the alkene moiety, and α -hydrogen atom of the amino acid moiety respectively, a doublet at δ 5.55 ppm for the proton attached to nitrogen atom, two singlets at δ 5.00 and 1.35 ppm for the α -hydrogen atom adjacent to the diazo group and the protons of the methyl groups respectively, and two doublet of doublets at δ 3.10 and 2.91 ppm for the β -hydrogen atoms of the amino acid moiety.

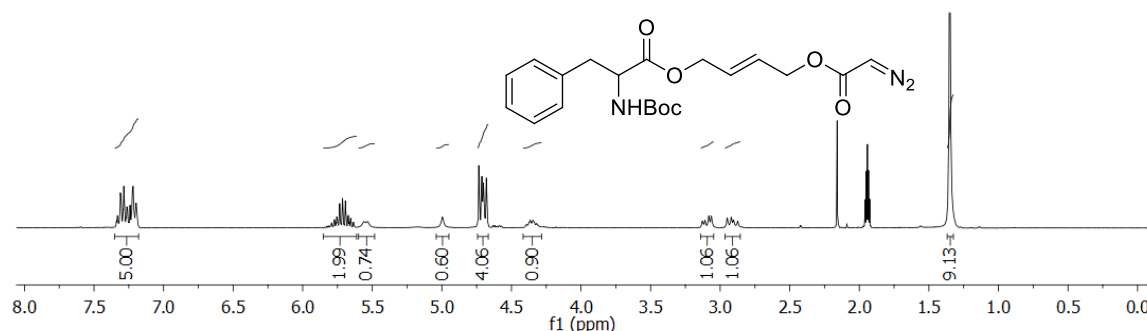


Figure 5.13 The ¹H-NMR (CD_3CN) spectrum of **333**.

Furthermore ¹³C-NMR spectrum (**Figure 5.14**) displayed three peaks at δ 173.2, 163.0 and 156.8 ppm for the carbonyl carbons, four peaks at δ 138.5, 130.7, 129.9 and 128.2 ppm for the aromatic protons, two peaks at δ 129.9 and 129.0 ppm for the alkenyl carbons, a peak at δ 80.4 ppm for the tertiary carbon atom of the *N*-Boc protecting group, two peaks at δ 61.7 and 61.3 ppm for the carbons of the methylene groups adjacent to the alkene moiety,

two peaks at δ 56.4 and 38.4 ppm for the α - and β -carbon atoms of the amino acid moiety respectively, a peak at δ 47.2 ppm for the α -carbon atom of the diazo group, and a peak at δ 28.7 ppm for the carbons of the methyl groups. High-resolution mass spectrometry (NSI) displayed m/z at 426.1639 (calculated for $C_{20}H_{25}N_3O_6Na$ $[M+Na]$ 426.1636) confirming the identity of **333**.

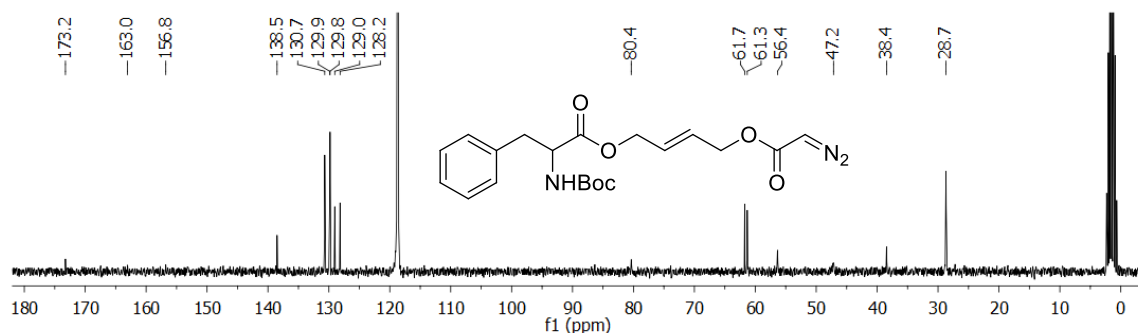
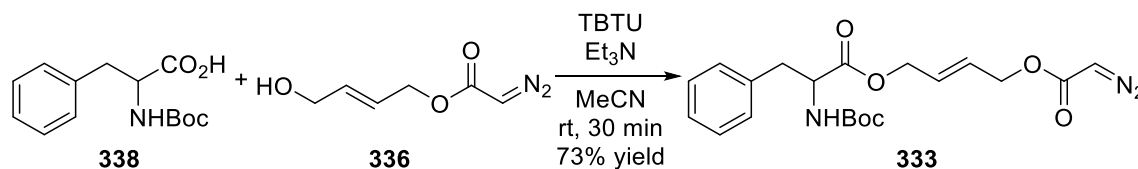


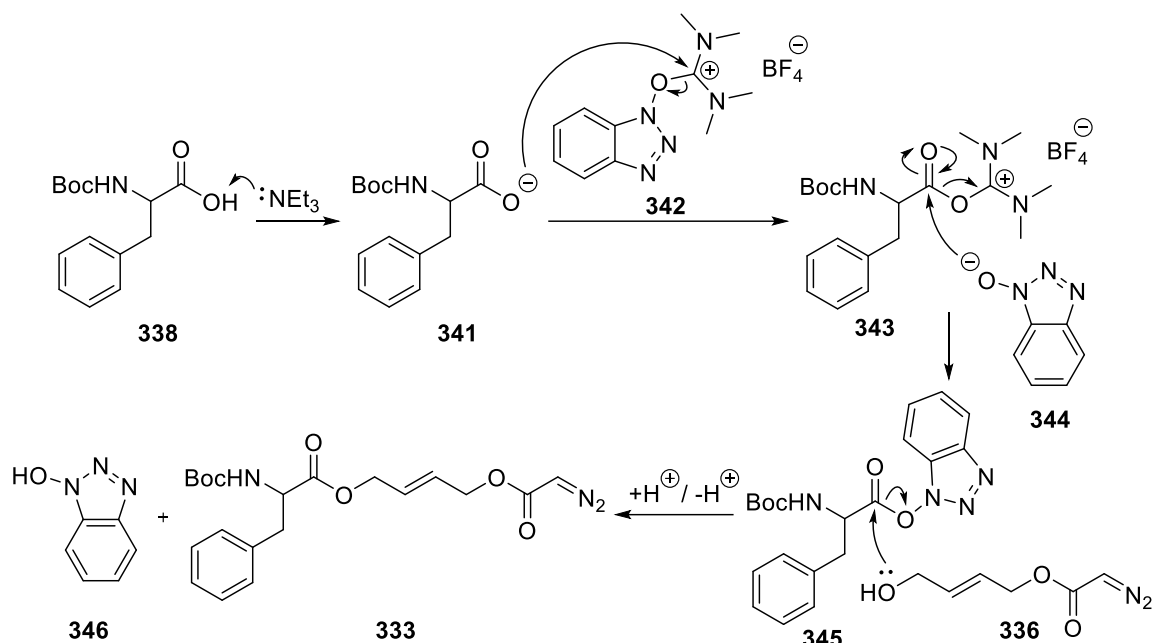
Figure 5.14 The ^{13}C -NMR (CD_3CN) spectrum of **333**.

Although the anticipated **333** had been synthesised, its purification by column chromatography was difficult as the by-product of the reaction, *N,N'*-dicyclohexylurea (DCU), which is soluble in organic solvents and insoluble in water, was difficult to separate from **333**. This purification problem led to a low 40% yield. The use of *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) as coupling reagent was considered as the by-product formed, 1,1,3,3-tetramethylurea (TMU), is water soluble and therefore easily removed during a work-up procedure. Repeating the reaction adopting a protocol reported by Balalaie *et al.*⁴² provided the anticipated **333** in a good 73% yield. Esterification of **338** with **336** in the presence of *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate and excess of triethylamine (2 equivalents) in acetonitrile at room temperature generated, after only 30 minutes, the desired **333** (Scheme 5.29).



Scheme 5.29 Synthesis of **333** using TBTU as a coupling reagent following a protocol reported by Balalaie *et al.*⁴²

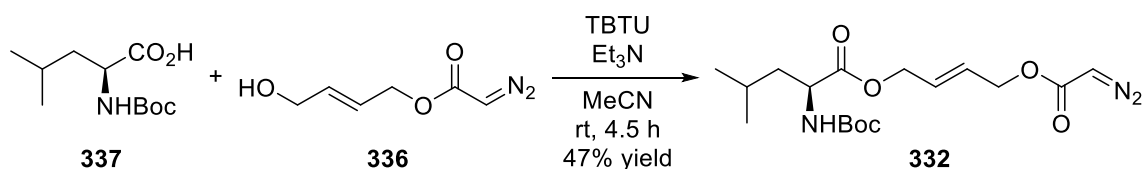
The mechanistic pathway for the esterification of **338** mediated by TBTU reported by Valeur and Bradley⁴³ is outlined in Scheme 5.30.



Scheme 5.30 The mechanistic pathway for the TBTU-mediated esterification of **338** reported by Valeur and Bradley.⁴³

Deprotonation of the α -amino acid **338** by triethylamine generates the carboxylate ion **341**. Nucleophilic attack of **341** at the carbocation **342** and removal of the 1,2,3-benzotriazol-1-olate as a leaving group affords the intermediate **343**. Nucleophilic attack of **344** at the carbonyl carbon of **343** and release of 1,1,3,3-tetramethylurea (TMU) leads to the formation of **345**, which subsequently attacked by **336** at the carbonyl carbon affords the anticipated esterification product **333** and 1-hydroxybenzotriazole (HOBt) **346**.

Encouraged by the effectiveness of this protocol reported by Balalaie *et al.*⁴² its application for the synthesis of (*S,E*)-4-(α -diazoacetoxy)but-2-en-1-yl 2-((*t*-butoxycarbonyl)amino)-4-methylpentanoate (**332**) was examined. Pleasingly the desired **332** was obtained in 47% yield (**Scheme 5.31**). The analysis of the physicochemical data confirmed the structure of **332**.



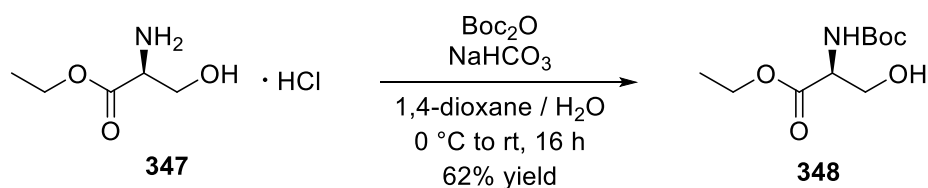
Scheme 5.31 Synthesis of **332** adopting a protocol reported by Balalaie *et al.*⁴²

Although α -diazocarbonyl compounds are versatile intermediates that have found useful applications in synthetic organic chemistry, only a limited number of aforesaid compounds occur naturally.⁴⁴ Azaserine (**264**) (**Figure 5.1**) is the most extensively investigated naturally occurring α -diazocarbonyl compound.⁴⁵ Discovered in 1954 and isolated from

a culture of bacteria *Streptomyces* as a pale yellow-green crystalline solid^{10,46,47} it showed antitumor and antibiotic properties. Over the past few decades intensive studies on the antitumor effects of azaserine have been carried out. However, the compound itself proved to be a potential carcinogen that induced the growth of tumours especially in the pancreas.⁴⁸ In order to conduct further investigations of the carcinogenic effect of azaserine a reliable synthesis of α -deuterated azaserine analogue is highly desirable.

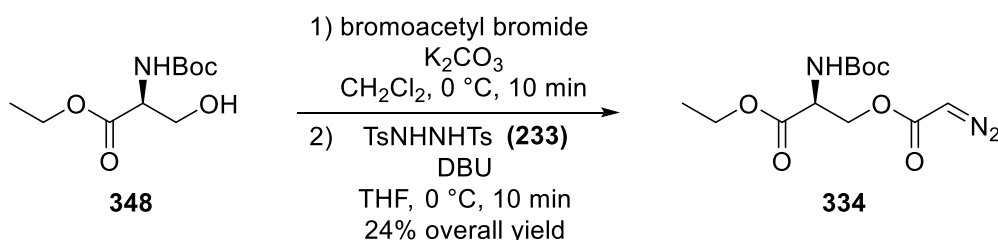
Before initiating the synthesis of (*S*)-ethyl 2-((*t*-butoxycarbonyl)amino)-3-(α -diazoacetoxy)propanoate (**334**), the *N*-Boc protection of the amino moiety of the commercially available (*S*)-ethyl 2-amino-3-hydroxypropanoate hydrochloride (**347**) (ethyl ester of (*S*)-serine) was required.

Employing a procedure reported by You *et al.*⁴⁹ (*S*)-ethyl 2-((*t*-butoxycarbonyl)amino)-3-hydroxypropanoate (**348**) was prepared. Reaction of **347** with sodium bicarbonate and di-*t*-butyl dicarbonate in a mixture of 1,4-dioxane and water afforded, after 16 hours, **348** in 62% yield (Scheme 5.32). The ¹H- and ¹³C-NMR spectral data of **348** corresponded closely to those reported in the literature.⁵⁰



Scheme 5.32 Synthesis of the *N*-Boc-protected **348** following a protocol reported by You *et al.*⁴⁹

The conversion of **348** into (*S*)-ethyl 2-((*t*-butoxycarbonyl)amino)-3-(α -diazoacetoxy)propanoate (**334**) was successfully accomplished using the previously described protocol reported by Fukuyama *et al.*³¹ (Scheme 5.33).



Scheme 5.33 Synthesis of **334** employing a protocol reported by Fukuyama *et al.*³¹

Reaction of **348** with excess of potassium carbonate (5 equivalents) and subsequent treatment with excess of bromoacetyl bromide (3 equivalents) in dichloromethane at 0 °C afforded, after 10 minutes, the corresponding 2-bromoacetate, which was consecutively treated with excess of 4-methyl-*N'*-tosylbenzenesulfonohydrazide (**233**) (2 equivalents) and thereafter excess of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (5 equivalents) in

tetrahydrofuran at 0 °C to afford, after 10 minutes, the desired (*S*)-ethyl 2-((*t*-butoxy carbonyl)amino)-3-(α -diazoacetoxy)propanoate (**334**) in 24% yield.

The specific rotation $[\alpha]_D^{21}$ of **334** was +42.5 (c 1.0, CHCl₃) verifying that the compound was optically active. The FT-IR spectrum of **334** revealed the characteristic peak for the carbonyl groups at 1694 cm⁻¹ and a peak at 2113 cm⁻¹ corresponding to the C=N=N stretch of a diazo group. The ¹H-NMR spectrum (**Figure 5.15**) displayed a doublet at δ 5.30 ppm for the proton attached to a nitrogen atom, a singlet at δ 4.76 ppm for the α -hydrogen atom adjacent to the diazo group and a singlet at δ 1.43 ppm for the protons of the methyl groups, a multiplet at δ 4.59 – 4.36 ppm for the α - and β -hydrogen atoms of the amino acid moiety, and a quartet at δ 4.21 ppm and a triplet at δ 1.26 ppm for the protons of the ethyl ester. Additionally the ¹³C-NMR spectrum (**Figure 5.15**) revealed peaks at δ 169.9 and 155.4 ppm for the carbonyl carbons, a peak at δ 80.4 ppm for the tertiary carbon of the *N*-Boc protecting group, two peaks at δ 64.7 and 53.3 ppm for the β - and α -carbon atoms of the amino acid moiety respectively, two peaks at δ 62.0 and 14.1 ppm for the carbons of the ethyl ester, a peak at δ 46.4 ppm for the α -carbon atom adjacent to the diazo group, and a peak at δ 28.3 ppm for the carbons of the methyl groups of *N*-Boc protecting group (one ¹³C=O signal was not observed). High-resolution mass spectrometry (NSI) displayed m/z at 324.1163 (calculated for C₁₂H₁₉N₃O₆Na [M+Na] 324.1166) confirming the identity of **334**.

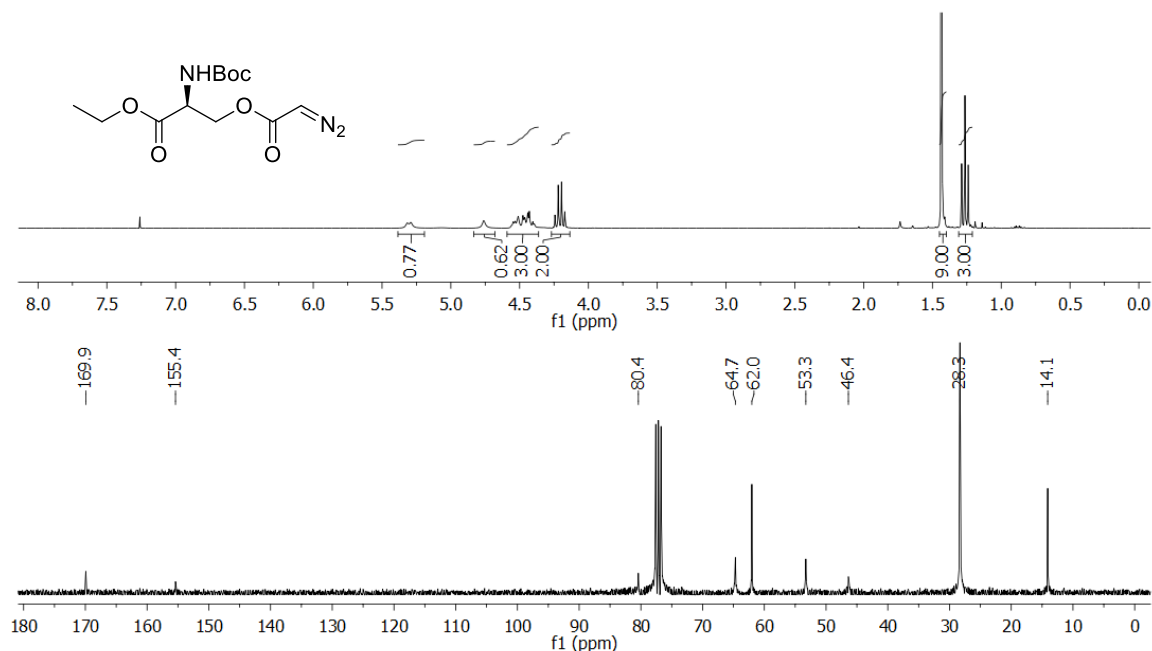
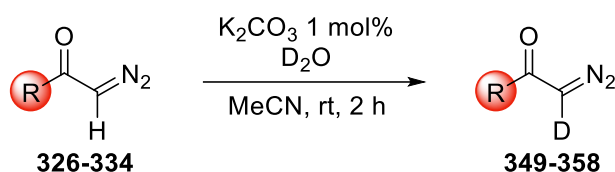


Figure 5.15 The ¹H- and ¹³C-NMR (CDCl₃) spectra of **334**.

Although the yield is only moderate, most likely due to the reaction conditions under which the *N*-Boc protecting group may be partially removed, this is, to the best of

the author's knowledge, the first reported chemical synthesis of an azaserine analogue **334**. With the desired α -diazocarbonyl compounds **326** – **334** in hand, their utilisation in the hydrogen / deuterium exchange reaction was investigated.

Applying the previously established protocol for the synthesis of α -deutero- α -diazocetic acid esters **271** – **281** (Figure 5.2), the desired α -deutero- α -diazocarbonyl compounds **349** – **358** were prepared with excellent levels of deuterium incorporation (Scheme 5.34, Figure 5.16, Table 5.5).



Scheme 5.34 Synthesis of a series of α -deutero- α -diazocarbonyl compounds **349** – **358** utilising an optimised protocol for the base-catalysed hydrogen / deuterium exchange reaction at the α -carbon atom.³⁵

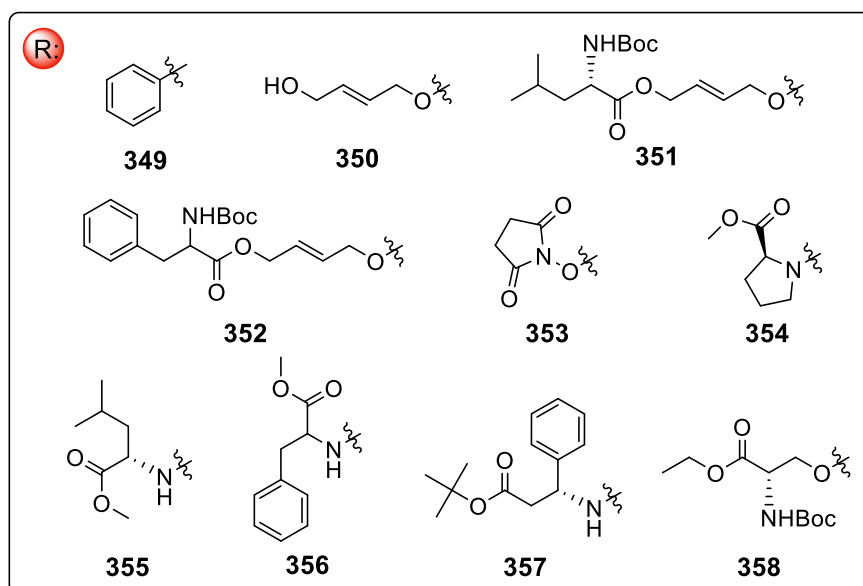


Figure 5.16 Structures of α -deutero- α -diazocarbonyl compounds **349** – **358**.

Compound number	Yield (%)	Deuterium incorporation (%)	Compound number	Yield (%)	Deuterium incorporation (%)
349	85	≥ 99	354	84	≥ 99
350	76	≥ 97	355	78	≥ 99
351	88	≥ 98	356	75	≥ 99
352	78	≥ 99	357	71	≥ 96
353	72	≥ 99	358	85	≥ 99

Table 5.5 Syntheses of **349** – **358** employing an optimised protocol for the hydrogen / deuterium exchange reaction at the α -carbon atom.³⁵

5.4. Conclusion

At the outset of this research project a synthesis of a range of α -deuterated aromatic aldehydes and α -deutero- α -diazoacetic acid esters was proposed. Use of these compounds as starting materials for the preparation of novel deuterated *N*-aryl-*cis*-aziridine-2-carboxylates was envisaged. Several have been prepared by a former PhD student.⁵¹ The first section of this chapter illustrates a synthesis of α -deuterated aromatic aldehydes **265** – **270**. During this part of the research project two different synthetic approaches to the required **265** – **270** were employed; formation of an amino nitrile with subsequent hydrolysis using deuterium chloride in deuterium oxide, and a reaction of an aromatic aldehyde with potassium cyanide in a biphasic diethyl ether / deuterium oxide solvent system. Although within this research project the second approach proved to be more advantageous, *i.e.*, higher yields and less time-consuming, having two protocols in hand for the deuterium incorporation at the α -carbon atom of aromatic aldehydes could only be beneficial as it allows for an introduction of a wider range of functional groups attached to the aromatic ring. In the second section of this chapter the synthesis of a library of α -deutero- α -diazoacetic acid esters **271** – **281**, α -deutero- α -diazoketone **349**, succinimidyl α -deutero- α -diazoacetate **353**, α -deutero- α -diazoacetic acid ester-derived α -amino acids **351** and **352**, and α -diazoacetamide-derived α - and β -amino acids **354** – **357** was described. The first chemical synthesis of an isotope-labelled azaserine analogue **358** was also accomplished. During this part of the research project a series of α -diazocarbonyl compounds was prepared and a quick, efficient, and one-cycle protocol for the base-catalysed hydrogen / deuterium exchange reaction at the α -carbon atom of α -diazocarbonyl compounds with moderate to high yields (63% to 90%) and excellent levels of deuterium incorporation ($\geq 96\%$) was successfully developed.

5.5. References

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Chapter 6
Experimental

6.1. General Methods

All reactions described as being carried out under a nitrogen atmosphere were always performed in flame-dried glassware, which was allowed to cool under an inert atmosphere. All reactions were stirred using a magnetic stirrer plate and a stirrer bar. Reactions carried out at 0 °C were cooled using a water and ice bath. Petroleum ether refers to the fraction that boils in the range 40 – 60 °C. Diethyl ether and tetrahydrofuran were freshly distilled from sodium benzophenone ketyl under an argon atmosphere. Acetonitrile and pyridine were freshly distilled from calcium hydride under an argon atmosphere. Anhydrous *N,N*-dimethylformamide was purchased from Sigma Aldrich. Acetonitrile used for the hydrogen / deuterium exchange reactions was UpS ultra gradient and purchased from ROMIL. Sodium hydride was used as a 60 wt.% dispersion in a mineral oil and washed with *n*-hexane prior to use. All other commercially available reagents were used as supplied unless otherwise specified. Column chromatography was carried out on Fluka silica gel (pore size 60 Å, 70 – 230 mesh). TLC was performed on Merck plates (aluminium coated with 0.2 mm silica gel 60 F₂₅₄). NMR solvents (CDCl₃ and CD₃CN) were dried over type 4 Å and 3 Å molecular sieves respectively prior to use, and CDCl₃ was further filtered through basic aluminium oxide before use.

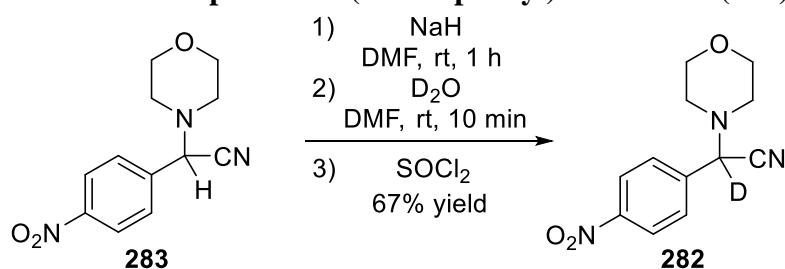
6.2. Characterisation

¹H- and ¹³C-NMR spectra were recorded on Varian Gemini 300 MHz and 400 MHz, Bruker UltraShield 400 MHz and Bruker Ascend 500 MHz spectrometers at the field strength indicated and deuterated solvents were used as specified. Chemical shifts (δ) are reported in parts per million (ppm) and referenced to the residual solvent signal for ¹H-NMR (CDCl₃ = 7.26 ppm, CD₃CN = 1.94 ppm) and ¹³C-NMR (CDCl₃ = 77.16 ppm, CD₃CN = 1.39 and 118.69 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet), coupling constant (reported in Hertz), and integration. FT-IR spectra were recorded on a Perkin-Elmer Spectrum 100 spectrometer. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units and were determined on Shimadzu LCMS and Axima-CFR MALDI-TOF instruments. HRMS was carried out by EPRSC National Mass Spectrometry Service Centre at the Swansea University, Wales. Optical rotation values were measured on a Perkin-Elmer 241 polarimeter. Melting points were recorded using open capillary tubes on melting point apparatus and are uncorrected.

6.3. Caution

Potassium cyanide is extremely toxic. α -Diazoacetic acid esters are generally regarded as potentially explosive compounds. Although during the described preparations no problems were encountered, it is advisable that appropriate handling precautions should be exercised while working with these materials.

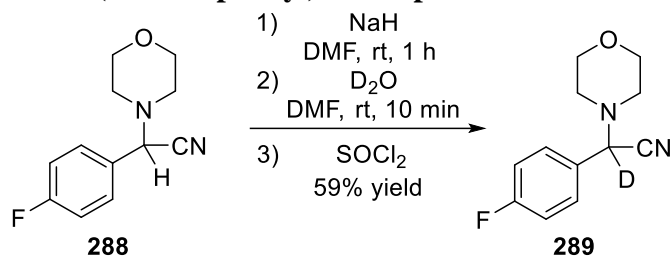
Synthesis of 2-deutero-2-morpholino-2-(4-nitrophenyl)acetonitrile (**282**)¹



A solution of 2-morpholino-2-(4-nitrophenyl)acetonitrile (**283**) (0.86 g, 3.50 mmol) in anhydrous *N,N*-dimethylformamide (5 mL) was stirred in a 50 mL round-bottom flask at room temperature under a nitrogen atmosphere. A suspension of sodium hydride (0.42 g, 11.0 mmol) in anhydrous *N,N*-dimethylformamide (10 mL) was added portionwise and the reaction mixture stirred at room temperature under a nitrogen atmosphere for 1 hour. Deuterium oxide (0.35 mL, 0.38 g, 19.0 mmol) was added dropwise *via* syringe and the reaction mixture stirred at room temperature for 10 minutes. Thionyl chloride (0.28 mL, 0.46 g, 3.80 mmol) was added dropwise *via* syringe to the reaction mixture, followed by addition of water (15 mL). The mixture was transferred to a separating funnel and the organic components extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with water (3 × 50 mL), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Recrystallisation from ethanol afforded **282** as pale yellow crystals (0.58 g, 2.30 mmol, 67% yield) with the following physicochemical characteristics.

¹H-NMR spectroscopic evidence indicated 94% deuterium incorporation; mp 125 – 127 °C; FT-IR (thin film) 3062, 2861, 2820, 1604, 1523 (N=O), 1349 (N=O), 1275, 1113, 1013, 857, 704 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 8.26 (d, *J* = 8.9 Hz, 2H, *H*_{Ar}), 7.77 (d, *J* = 8.9 Hz, 2H, *H*_{Ar}), 3.81 – 3.64 (m, 4H, OCH₂CH₂), 2.69 – 2.48 (m, 4H, OCH₂CH₂) ppm; ¹³C-NMR (CDCl₃, 100 MHz) δ 148.5, 139.6, 129.1, 124.1, 114.2 (C≡N), 66.6 (CH₂CH₂), 61.7 (t, *J* = 22.0 Hz, C-D), 50.1 (CH₂CH₂) ppm; MALDI-TOF-MS *m/z* 249.3 [M+H]; HRMS (APCI) Calculated for C₁₂H₁₃DN₃O₃ [M+H] 249.1092, found 249.1092.

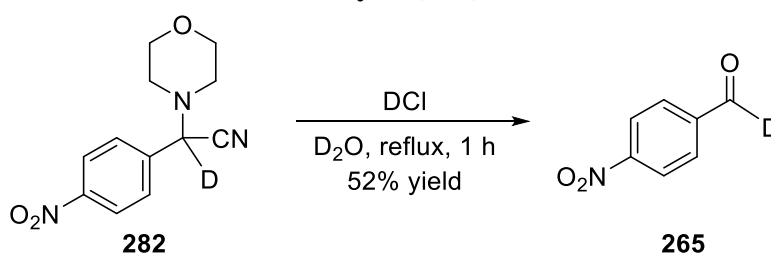
Synthesis of 2-deutero-2-(4-fluorophenyl)-2-morpholinoacetonitrile (**289**)¹



A solution of 2-(4-fluorophenyl)-2-morpholinoacetonitrile (**288**) (1.0 g, 4.50 mmol) in anhydrous *N,N*-dimethylformamide (5 mL) was stirred in a 50 mL round-bottom flask at room temperature under a nitrogen atmosphere. A suspension of sodium hydride (0.54 g, 14.0 mmol) in anhydrous *N,N*-dimethylformamide (10 mL) was added portionwise and the reaction mixture stirred at room temperature under a nitrogen atmosphere for 1 hour. Deuterium oxide (0.45 mL, 0.50 g, 25.0 mmol) was added dropwise *via* syringe and the reaction mixture stirred at room temperature for 10 minutes. Thionyl chloride (0.36 mL, 0.60 g, 5.0 mmol) was added dropwise *via* syringe to the reaction mixture, followed by addition of water (15 mL). The mixture was transferred to a separating funnel and the organic components extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with water (3 × 50 mL), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Recrystallisation from ethanol afforded **289** as white crystals (0.59 g, 2.70 mmol, 59% yield) with the following physicochemical characteristics.

¹H-NMR spectroscopic evidence indicated 96% deuterium incorporation; mp 49 – 51 °C; FT-IR (thin film) 2963, 2860, 2826, 1610, 1509, 1455, 1275, 1231, 1117, 1012, 972, 850, 770 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 7.56 – 7.47 (m, 2H, *H*_{Ar}), 7.13 – 7.05 (m, 2H, *H*_{Ar}), 3.77 – 3.66 (m, 4H, OCH₂CH₂), 2.59 – 2.53 (m, 4H, OCH₂CH₂) ppm; ¹³C-NMR (CDCl₃, 100 MHz) δ 163.1 (d, *J* = 240.0 Hz), 129.9 (d, *J* = 8.0 Hz), 128.4 (d, *J* = 3.0 Hz), 116.0 (d, *J* = 22.0 Hz), 115.1 (C≡N), 66.7 (CH₂CH₂), 61.5 (t, *J* = 22.0 Hz, C-D), 50.0 (CH₂CH₂) ppm; MALDI-TOF-MS *m/z* 222.3 [M+H]; HRMS (APCI) Calculated for C₁₂H₁₃DFN₂O [M+H] 222.1147, found 222.1147.

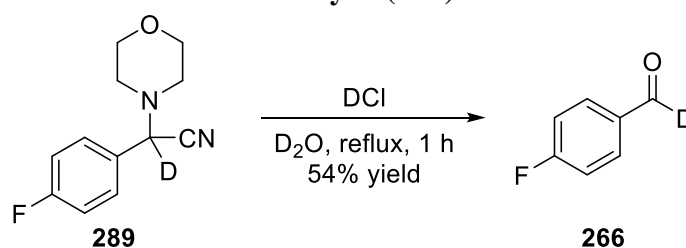
Synthesis of α-deutero-4-nitrobenzaldehyde (**265**)¹



A suspension of 2-deutero-2-morpholino-2-(4-nitrophenyl)acetonitrile (**282**) (0.2 g, 0.80 mmol) in deuterium oxide (2.5 mL) was stirred in a 10 mL round-bottom flask equipped with a condenser at room temperature under a nitrogen atmosphere. Deuterium chloride (0.24 mL, 0.31 g, 2.90 mmol, 35 wt.% solution in deuterium oxide) was added and the reaction mixture heated at reflux for 1 hour. After cooling to room temperature, the mixture was transferred to a separating funnel and the organic components extracted with dichloromethane (3×5 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (dichloromethane 100%) afforded **265** as a pale yellow solid (0.06 g, 0.40 mmol, 52% yield) with the following physicochemical characteristics.

$R_f = 0.61$ (silica gel, dichloromethane 100%); $^1\text{H-NMR}$ spectroscopic evidence indicated 98% deuterium incorporation; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 8.39 (d, $J = 8.8$ Hz, 2H, H_{Ar}), 8.08 (d, $J = 8.9$ Hz, 2H, H_{Ar}) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz) δ 190.1 (t, $J = 27.5$ Hz, C=O), 151.3, 140.1 (t, $J = 3.8$ Hz), 130.6, 124.4 ppm. The physicochemical analysis data corresponded closely to those reported in the literature by Price *et al.*²

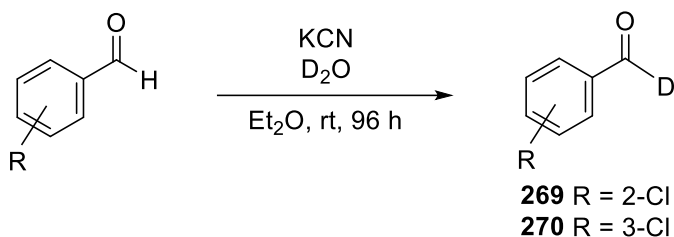
Synthesis of α -deutero-4-fluorobenzaldehyde (**266**)¹



A suspension of 2-deutero-2-(4-fluorophenyl)-2-morpholinoacetonitrile (**289**) (0.56 g, 2.50 mmol) in deuterium oxide (7.5 mL) was stirred in a 25 mL round-bottom flask equipped with a condenser at room temperature under a nitrogen atmosphere. Deuterium chloride (0.75 mL, 0.97 g, 9.0 mmol, 35 wt.% solution in deuterium oxide) was added and the reaction mixture heated at reflux for 1 hour. After cooling to room temperature, the mixture was transferred to a separating funnel and the organic components extracted with dichloromethane (3×10 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (dichloromethane 100%) afforded **266** as a colourless liquid (0.17 g, 1.40 mmol, 54% yield) with the following physicochemical characteristics.

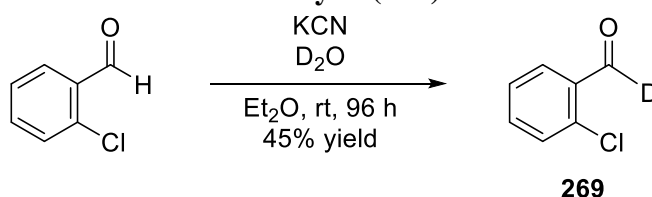
$R_f = 0.55$ (silica gel, dichloromethane 100%); $^1\text{H-NMR}$ spectroscopic evidence indicated 97% deuterium incorporation; FT-IR (thin film) 3076, 1684 (C=O), 1597, 1506, 1412, 1236, 1150, 1095, 882, 813, 597, 505 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.95 – 7.87 (m, 2H, H_{Ar}), 7.24 – 7.18 (m, 2H, H_{Ar}) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz) δ 190.2 (t, $J = 26.3$ Hz, C=O), 166.6 (d, $J = 255.0$ Hz), 132.9 (d, $J = 3.8$ Hz), 132.2 (d, $J = 10.0$ Hz), 116.4 (d, $J = 21.0$ Hz) ppm; MS (EI) m/z 125.0 [M]; HRMS (APCI) Calculated for $\text{C}_7\text{H}_5\text{DFO}$ [M+H] 126.0460, found 126.0457.

General procedure for deuterium incorporation at the aldehyde group of aryl aldehydes **269**, **270**³



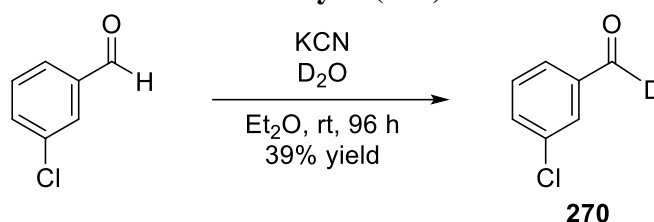
A 1.4 M solution of aryl aldehyde (1 equivalent) in anhydrous diethyl ether was stirred in a 25 mL round-bottom flask at room temperature under a nitrogen atmosphere. A solution of potassium cyanide (2 equivalents) in deuterium oxide (38 equivalents) was added *via* syringe and the reaction mixture stirred vigorously at room temperature under a nitrogen atmosphere for 48 hours. The reaction mixture was transferred to a separating funnel and the organic components extracted with diethyl ether (2×10 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Anhydrous diethyl ether was added and the 1.4 M solution stirred at room temperature under a nitrogen atmosphere. A solution of potassium cyanide (2 equivalents) in deuterium oxide (38 equivalents) was added *via* syringe and the reaction mixture stirred vigorously at room temperature under a nitrogen atmosphere for 48 hours. The reaction mixture was transferred to a separating funnel and the organic components extracted with diethyl ether (2×10 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel afforded the corresponding deuterated aryl aldehydes **269**, **270**.

Synthesis of α -deutero-2-chlorobenzaldehyde (**269**)³



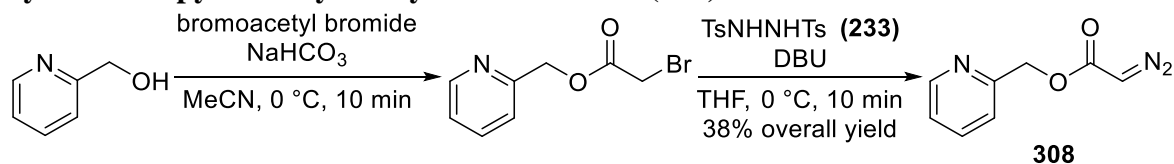
269 (0.27 g, 1.90 mmol, 45% yield) yellow liquid. Purification by flash column chromatography on silica gel (diethyl ether / petroleum ether 1 : 9). $R_f = 0.49$ (silica gel, diethyl ether / *n*-hexane 1 : 9); $^1\text{H-NMR}$ spectroscopic evidence indicated 98% deuterium incorporation; FT-IR (thin film) 3070, 1674 (C=O), 1593, 1441, 1265, 1213, 1075, 795, 754, 710 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.93 – 7.90 (m, 1H, H_{Ar}), 7.54 – 7.50 (m, 1H, H_{Ar}), 7.45 – 7.43 (m, 1H, H_{Ar}), 7.40 – 7.35 (m, 1H, H_{Ar}) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ 189.4 (t, $J = 27.0$ Hz, C=O), 137.9, 135.1, 132.4 (t, $J = 4.0$ Hz), 130.6, 129.4, 127.3 ppm; MS (EI) m/z 164.1 [$\text{M}+\text{Na}$]; HRMS (APCI) Calculated for $\text{C}_7\text{H}_5\text{DClO}$ [$\text{M}+\text{H}$] 142.0164, found 142.0162.

Synthesis of α -deutero-3-chlorobenzaldehyde (**270**)³



270 (0.23 g, 1.60 mmol, 39% yield) yellow liquid. Purification by flash column chromatography on silica gel (diethyl ether / petroleum ether 1 : 9). $R_f = 0.33$ (silica gel, diethyl ether / petroleum ether 1 : 9); $^1\text{H-NMR}$ spectroscopic evidence indicated 97% deuterium incorporation; FT-IR (thin film) 3066, 1684 (C=O), 1575, 1467, 1429, 1278, 1216, 1072, 903, 780, 684, 643 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.85 – 7.84 (m, 1H, H_{Ar}), 7.77 – 7.75 (m, 1H, H_{Ar}), 7.61 – 7.58 (m, 1H, H_{Ar}), 7.50 – 7.46 (m, 1H, H_{Ar}) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ 190.5 (t, $J = 27.0$ Hz, C=O), 137.7 (t, $J = 3.0$ Hz), 135.5, 134.4, 130.4, 129.3, 128.0 ppm; MS (EI) m/z 164.1 [$\text{M}+\text{Na}$]; HRMS (APCI) Calculated for $\text{C}_7\text{H}_5\text{DClO}$ [$\text{M}+\text{H}$] 142.0164, found 142.0163.

Synthesis of pyridin-2-ylmethyl α -diazoacetate (**308**)⁴

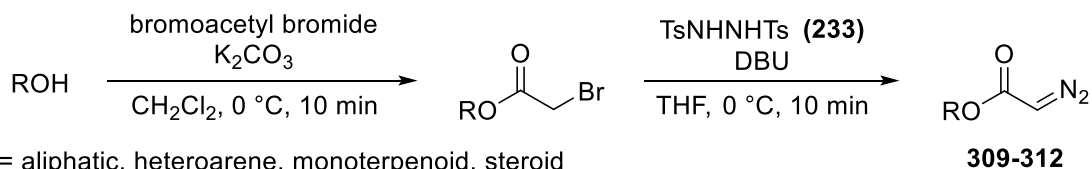


A mixture of pyridin-2-ylmethanol (1.0 g, 9.20 mmol) and sodium bicarbonate (2.31 g, 28.0 mmol) in anhydrous acetonitrile (30 mL) was stirred in a 100 mL round-bottom flask at 0 °C under a nitrogen atmosphere. Bromoacetyl bromide (1.2 mL, 2.77 g, 14.0 mmol) was added dropwise *via* syringe and the reaction mixture stirred at 0 °C under a nitrogen atmosphere for 10 minutes. Water (30 mL) was added, the mixture transferred to a separating funnel and the organic components extracted with dichloromethane

(3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. 4-Methyl-*N'*-tosylbenzenesulfonohydrazide (**233**) (6.24 g, 18.3 mmol) and anhydrous tetrahydrofuran (40 mL) were added and the reaction mixture stirred at 0 °C under a nitrogen atmosphere. 1,8-Diazabicyclo[5.4.0]undec-7-ene (6.85 mL, 6.98 g, 45.8 mmol) was added dropwise *via* syringe and the reaction mixture stirred at 0 °C under a nitrogen atmosphere for 10 minutes. Saturated aqueous sodium bicarbonate solution (30 mL) was added, the mixture transferred to a separating funnel and the organic components extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (ethyl acetate / petroleum ether 3 : 7) afforded **308** as an orange liquid (0.61 g, 3.40 mmol, 38% yield) with the following physicochemical characteristics.

$R_f = 0.21$ (silica gel, ethyl acetate / *n*-hexane 3 : 7); FT-IR (thin film) 3096, 2106 (C=N₂), 1681 (C=O), 1592, 1385, 1348, 1230, 1170, 995, 737 cm⁻¹; ¹H-NMR (CDCl₃, 300 MHz) δ 8.59 (d, $J = 4.8$ Hz, 1H, H_{Ar}), 7.70 (td, $J = 7.7, 1.8$ Hz, 1H, H_{Ar}), 7.34 (d, $J = 7.8$ Hz, 1H, H_{Ar}), 7.25 – 7.19 (m, 1H, H_{Ar}), 5.30 (s, 2H, CH₂), 4.87 (s, 1H, CH=N₂) ppm; ¹³C-NMR (CDCl₃, 100 MHz) δ 173.5 (C=O), 155.9, 149.7, 137.0, 123.1, 121.9, 67.7 (CH₂), 46.7 (CH=N₂) ppm; MALDI-TOF-MS m/z 200.3 [M+Na]; HRMS (NSI) Calculated for C₈H₇O₂N₃Na [M+Na] 200.0430, found 200.0425.

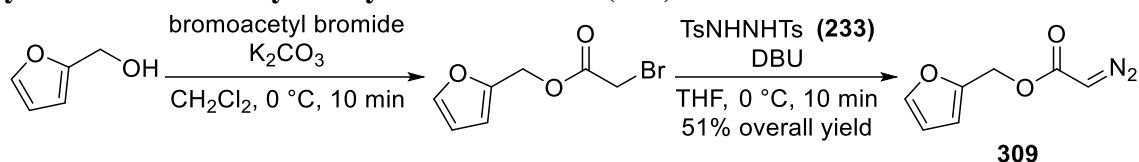
General procedure for the conversion of alcohols into the corresponding α -diazoacetic acid esters **309 – **312** using potassium carbonate as a base⁴**



A mixture of an alcohol (1 equivalent) and potassium carbonate (5 equivalents) in anhydrous dichloromethane (40 mL) was stirred in a 100 mL round-bottom flask at 0 °C under a nitrogen atmosphere. Bromoacetyl bromide (3 equivalents) was added dropwise *via* syringe and the reaction mixture stirred at 0 °C under a nitrogen atmosphere for 10 minutes. Water (30 mL) was added, the mixture transferred to a separating funnel and the organic components extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL),

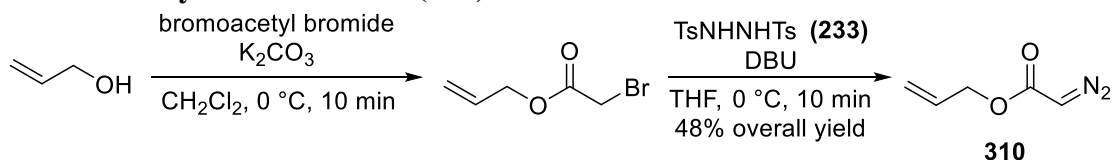
dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. 4-Methyl-*N'*-tosylbenzenesulfonohydrazide (**233**) (2 equivalents) and anhydrous tetrahydrofuran (40 mL) were added and the reaction mixture stirred at 0 °C under a nitrogen atmosphere. 1,8-Diazabicyclo[5.4.0]undec-7-ene (5 equivalents) was added dropwise *via* syringe and the reaction mixture stirred at 0 °C under a nitrogen atmosphere for 10 minutes. Saturated aqueous sodium bicarbonate solution (30 mL) was added, the mixture transferred to a separating funnel and the organic components extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel afforded the corresponding α -diazoacetic acid esters **309** – **312**.

Synthesis of furan-2-ylmethyl α -diazoacetate (**309**)⁴



309 (0.86 g, 5.20 mmol, 51% yield) yellow liquid. Purification by flash column chromatography on silica gel (diethyl ether / petroleum ether 2 : 8). R_f = 0.33 (silica gel, diethyl ether / *n*-hexane 2 : 8); FT-IR (thin film) 3119, 2107 (C=N₂), 1681 (C=O), 1378, 1344, 1231, 1150, 999, 918, 736 cm⁻¹; ¹H-NMR (CD₃CN, 300 MHz) δ 7.51 (dd, J = 1.9, 0.9 Hz, 1H, H_{Ar}), 6.48 – 6.45 (m, 1H, H_{Ar}), 6.43 – 6.40 (m, 1H, H_{Ar}), 5.11 (s, 2H, CH₂), 5.00 (s, 1H, CH=N₂) ppm; ¹³C-NMR (CDCl₃, 100 MHz) δ 149.6, 143.5, 111.0 (C_{Ar}), 110.8 (C_{Ar}), 58.4 (CH₂), 46.5 (CH=N₂) ppm, C=O signal not observed; MALDI-TOF-MS m/z 166.9 [M+H]; HRMS (EI) Calculated for C₇H₆O₃N₂ [M] 166.0373, found 166.0372.

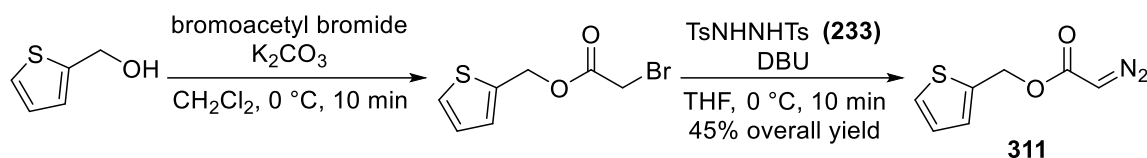
Synthesis of allyl α -diazoacetate (**310**)⁴



310 (1.04 g, 8.20 mmol, 48% yield) yellow liquid. Purification by flash column chromatography on silica gel (diethyl ether / petroleum ether 2 : 8). R_f = 0.36 (silica gel, diethyl ether / *n*-hexane 2 : 8); FT-IR (thin film) 3119, 2107 (C=N₂), 1682 (C=O), 1381, 1338, 1234, 1176, 990, 921, 738 cm⁻¹; ¹H-NMR (CDCl₃, 300 MHz) δ 5.98 – 5.95 (m, 1H, CH₂=CH), 5.35 – 5.21 (m, 2H, CH₂=CH), 4.77 (s, 1H, CH=N₂), 4.66 – 4.64 (m, 2H, CHCH₂O) ppm; ¹³C-NMR (CDCl₃, 100 MHz) δ 132.3 (CH₂=CH), 118.5 (CH₂=CH), 65.6

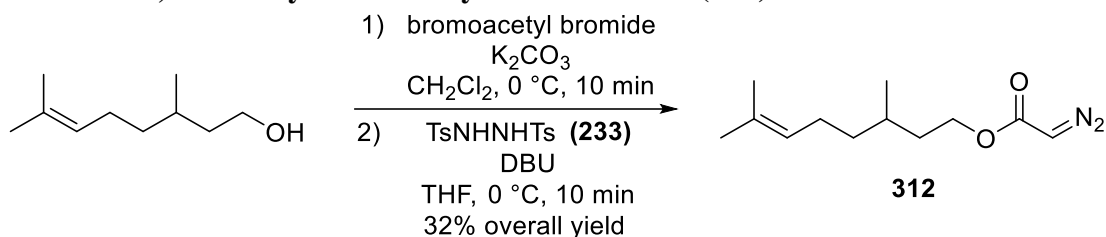
(CHCH₂O), 46.4 (CH=N₂) ppm, C=O signal not observed; MALDI-TOF-MS *m/z* 126.0 [M]; HRMS (EI) Calculated for C₅H₆O₂N₂ [M] 126.0424, found 126.0423.

Synthesis of thiophen-2-ylmethyl α -diazooacetate (**311**)⁴

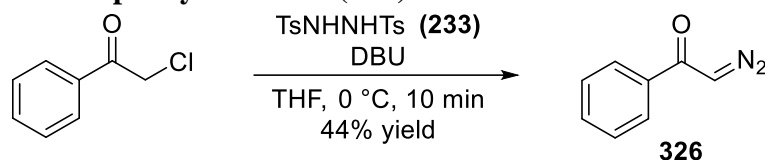


311 (0.71 g, 3.90 mmol, 45% yield) yellow liquid. Purification by flash column chromatography on silica gel (diethyl ether / petroleum ether 2 : 8). *R_f* = 0.37 (silica gel, diethyl ether / *n*-hexane 2 : 8); FT-IR (thin film) 3108, 2106 (C=N₂), 1681 (C=O), 1385, 1339, 1230, 1156, 1001, 834, 738 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 7.33 (dd, *J* = 5.1, 1.2 Hz, 1H, *H_{Ar}*), 7.16 – 7.05 (m, 1H, *H_{Ar}*), 7.05 – 6.93 (m, 1H, *H_{Ar}*), 5.34 (s, 2H, CH₂), 4.78 (s, 1H, CH=N₂) ppm; ¹³C-NMR (CDCl₃, 75 MHz) δ 166.7 (C=O), 137.9, 128.5, 127.1, 126.7, 60.6 (CH₂), 46.6 (CH=N₂) ppm; MALDI-TOF-MS *m/z* 204.9 [M+Na]; HRMS (EI) Calculated for C₇H₆O₂N₂S [M] 182.0144, found 182.0142.

Synthesis of 3,7-dimethyloct-6-en-1-yl α -diazooacetate (**312**)⁴

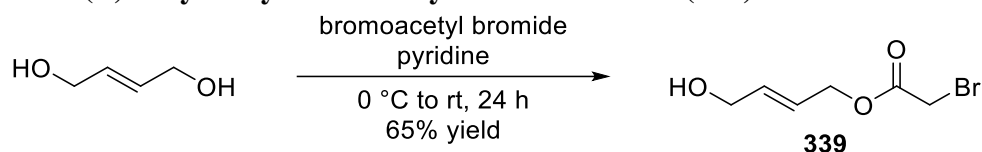


312 (0.45 g, 2.0 mmol, 32% yield) yellow liquid. Purification by flash column chromatography on silica gel (diethyl ether / petroleum ether 2 : 98 → 10 : 90). *R_f* = 0.53 (silica gel, diethyl ether / petroleum ether 2 : 8); FT-IR (thin film) 2914, 2106 (C=N₂), 1690 (C=O), 1397, 1358, 1237, 1180, 1055, 740 cm⁻¹; ¹H-NMR (CDCl₃, 300 MHz) δ 5.15 – 5.00 (m, 1H, (CH₃)₂C=CH), 4.73 (s, 1H, CH=N₂), 4.26 – 4.12 (m, 2H, CH₂CH₂O), 2.06 – 1.86 (m, 2H, (CH₃)₂C=CHCH₂), 1.72 – 1.12 (m, 11H, (CH₃)₂C=CH, CH₂CHCH₂), 0.91 (d, *J* = 6.4 Hz, 3H, CH₃) ppm; ¹³C-NMR (CDCl₃, 100 MHz) δ C=O signal not observed, 131.5 ((CH₃)₂C=CH), 124.7 ((CH₃)₂C=CH), 63.6 (CH₂CH₂O), 46.3 (CH=N₂), 37.1 (CH₂CHCH₂), 35.8 (CH₂CHCH₂), 29.6 (CH₂CHCH₂), 25.9 ((CH₃)₂C=CH), 25.5 ((CH₃)₂C=CHCH₂), 19.6 (CH₃CH), 17.8 ((CH₃)₂C=CH) ppm; MALDI-TOF-MS *m/z* 242.2 [M+NH₄]; HRMS (CI) Calculated for C₁₂H₂₄O₂N₃ [M+NH₄] 242.1863, found 242.1862.

Synthesis of α -diazo-1-phenylethanone (326**)⁴**

A mixture of 2-chloro-1-phenylethanone (2.5 g, 16.0 mmol) and 4-methyl-*N*'-tosyl benzenesulfonohydrazide (**233**) (11.0 g, 32.0 mmol) in anhydrous tetrahydrofuran (60 mL) was stirred in a 250 mL round-bottom flask at 0 °C under a nitrogen atmosphere. Diazabicyclo[5.4.0]undec-7-ene (12.0 mL, 12.3 g, 80.9 mmol) was added dropwise *via* syringe and the reaction mixture stirred at 0 °C under a nitrogen atmosphere for 10 minutes. Saturated aqueous sodium bicarbonate solution (50 mL) was added, the mixture transferred to a separating funnel and the organic components extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (150 mL), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (diethyl ether / petroleum ether 3 : 7) afforded **326** as a yellow solid (1.04 g, 7.10 mmol, 44% yield) with the following physicochemical characteristics.

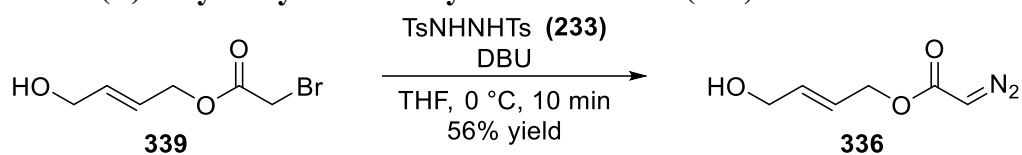
R_f = 0.48 (silica gel, diethyl ether / *n*-hexane 3 : 7); ¹H-NMR (CDCl₃, 300 MHz) δ 7.80 – 7.72 (m, 2H, H_{Ar}), 7.58 – 7.51 (m, 1H, H_{Ar}), 7.48 – 7.42 (m, 2H, H_{Ar}), 5.90 (s, 1H, CH=N₂) ppm; ¹³C-NMR (CDCl₃, 100 MHz) δ 186.4 (C=O), 136.8, 132.8, 128.8, 126.8, 54.3 (CH=N₂) ppm. The physicochemical analysis data corresponded closely to those reported in the literature by Toma *et al.*⁴

Synthesis of (*E*)-4-hydroxybut-2-en-1-yl 2-bromoacetate (339**)⁵**

A solution of (*E*)-but-2-ene-1,4-diol (4.66 mL, 5.0 g, 57.0 mmol) and pyridine (0.64 mL, 0.60 g, 7.90 mmol) was stirred in a 25 mL round-bottom flask at 0 °C under a nitrogen atmosphere. Bromoacetyl bromide (0.69 mL, 1.59 g, 7.90 mmol) was added dropwise *via* syringe, the reaction mixture allowed to warm to room temperature and stirred for 24 hours. The reaction mixture was filtered through a plug of silica gel eluting with ethyl acetate and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (ethyl acetate / petroleum ether 1 : 1) afforded **339** as a pale yellow liquid (1.08 g, 5.20 mmol, 65% yield) with the following physicochemical characteristics.

$R_f = 0.39$ (silica gel, ethyl acetate / *n*-hexane 1 : 1); FT-IR (thin film) 3370 (OH), 2968, 1730 (C=O), 1407, 1278, 1160, 1109, 960 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 5.93 – 5.83 (m, 1H, CH=CH), 5.67 – 5.58 (m, 1H, CH=CH), 4.79 – 4.74 (m, 2H, CH=CHCH₂), 4.28 – 4.23 (m, 2H, HOCH₂), 3.83 (s, 2H, CH₂Br), 2.13 (s, 1H, OH) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 167.4 (C=O), 134.4 (CH=CH), 124.5 (CH=CH), 61.7 (CH=CHCH₂), 58.4 (HOCH₂), 25.6 (CH₂Br) ppm; MALDI-TOF-MS m/z 232.8 [M+Na]; HRMS (NSI) Calculated for C₆H₉O₃BrNa [M+Na] 232.9607, found 232.9607.

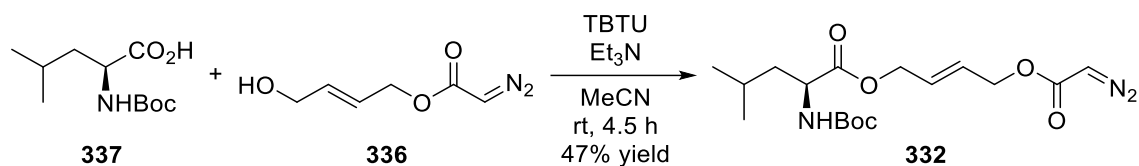
Synthesis of (*E*)-4-hydroxybut-2-en-1-yl α -diazoacetate (**336**)⁴



A mixture of (*E*)-4-hydroxybut-2-en-1-yl 2-bromoacetate (**339**) (0.20 g, 1.0 mmol) and 4-methyl-*N'*-tosylbenzenesulfonylhydrazide (**233**) (0.65 g, 1.90 mmol) in anhydrous tetrahydrofuran (5 mL) was stirred in a 25 mL round-bottom flask at 0 °C under a nitrogen atmosphere. Diazabicyclo[5.4.0]undec-7-ene (0.72 mL, 0.73 g, 4.80 mmol) was added dropwise *via* syringe and the reaction mixture stirred at 0 °C under a nitrogen atmosphere for 10 minutes. Saturated aqueous sodium bicarbonate solution (5 mL) was added, the mixture transferred to a separating funnel and the organic components extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (diethyl ether 100%) afforded **336** as a yellow liquid (0.08 g, 0.50 mmol, 56% yield) with the following physicochemical characteristics.

$R_f = 0.37$ (silica gel, ethyl acetate / *n*-hexane 1 : 1); FT-IR (thin film) 3374 (OH), 2967, 2107 (C=N₂), 1671 (C=O), 1377, 1236, 1176, 1016, 739 cm^{-1} ; $^1\text{H-NMR}$ (CD_3CN , 300 MHz) δ 5.82 – 5.68 (m, 1H, CH=CH), 5.64 – 5.47 (m, 1H, CH=CH), 4.98 (s, 1H, CH=N₂), 4.72 – 4.69 (m, 2H, CH=CHCH₂), 4.16 – 4.08 (m, 2H, HOCH₂), 2.86 (t, $J = 5.6$ Hz, 1H, OH) ppm; $^{13}\text{C-NMR}$ (CD_3CN , 100 MHz) δ 135.5 (CH=CH), 125.8 (CH=CH), 61.6 (CH=CHCH₂), 58.8 (HOCH₂), 47.3 (CH=N₂) ppm, C=O signal not observed; MALDI-TOF-MS m/z 156.1 [M]; HRMS (CI) Calculated for C₆H₉N₂O₃ [M+H] 157.0608, found 157.0609.

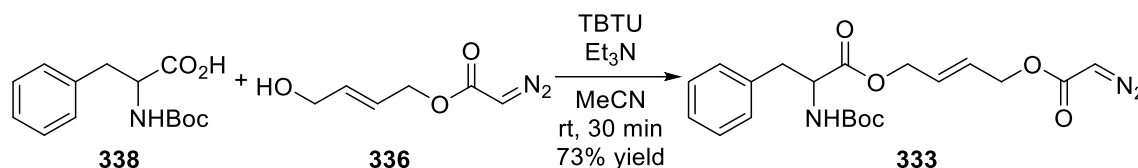
Synthesis of (*S,E*)-4-(α -diazoacetoxy)but-2-en-1-yl 2-((*t*-butoxycarbonyl)amino)-4-methyl pentanoate (**332**)⁶



(*S*)-2-((*t*-Butoxycarbonyl)amino)-4-methylpentanoic acid (**337**) (0.04 g, 0.20 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (0.06 g, 0.20 mmol) were combined and stirred in anhydrous acetonitrile (3 mL) in a 10 mL round-bottom flask at room temperature under a nitrogen atmosphere. Triethylamine (0.05 mL, 0.04 g, 0.40 mmol) was added *via* syringe and the reaction mixture stirred at room temperature under a nitrogen atmosphere for 5 minutes. A solution of (*E*)-4-hydroxybut-2-en-1-yl α -diazoacetate (**336**) (0.03 g, 0.20 mmol) in anhydrous acetonitrile (1 mL) was added *via* syringe and the reaction mixture stirred for a further 4.5 hours. Water (4 mL) was added, the mixture transferred to a separating funnel and the organic components extracted with ethyl acetate (3 \times 5 mL). The combined organic layers were washed with water (20 mL), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (ethyl acetate / petroleum ether 2 : 8) afforded **332** as a pale yellow oil (0.03 g, 0.10 mmol, 47% yield) with the following physicochemical characteristics.

$R_f = 0.38$ (silica gel, ethyl acetate / *n*-hexane 3 : 7); $[\alpha]_D^{21} -11.9$ (*c* 1.0, CHCl_3); FT-IR (thin film) 2959, 2111 ($\text{C}=\text{N}_2$), 1694 ($\text{C}=\text{O}$), 1511, 1385, 1366, 1240, 1161, 1023, 977, 741 cm^{-1} ; $^1\text{H-NMR}$ (CD_3CN , 300 MHz) δ 5.82 – 5.66 (m, 2H, $\text{CH}=\text{CH}$), 5.56 (d, $J = 6.8$ Hz, 1H, *NH*), 4.99 (s, 1H, $\text{CH}=\text{N}_2$), 4.79 – 4.65 (m, 4H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 4.12 (dd, $J = 15.5, 7.8$ Hz, 1H, αCH), 1.73 – 1.60 (m, 1H, γCH), 1.51 (t, $J = 7.2$ Hz, 2H, βCH_2), 1.40 (s, 9H, $(\text{CH}_3)_3\text{C}$), 0.91 (t, $J = 6.6$ Hz, 6H, $(\text{CH}_3)_2\text{CH}$) ppm; $^{13}\text{C-NMR}$ (CD_3CN , 100 MHz) δ 174.3 ($\text{CH}_2\text{CHC}=\text{O}$), 163.1 ($\text{C}=\text{OCH}=\text{N}_2$), 157.0 ($\text{NHC}=\text{O}$), 129.7 ($\text{CH}=\text{CH}$), 129.1 ($\text{CH}=\text{CH}$), 80.2 ($(\text{CH}_3)_3\text{C}$), 61.6 ($\text{CH}_2\text{CH}=\text{CH}$), 61.4 ($\text{CH}=\text{CHCH}_2$), 53.5 (αCH), 47.4 ($\text{CH}=\text{N}_2$), 41.5 (βCH_2), 28.9 ($(\text{CH}_3)_3\text{C}$), 25.9 (γCH), 23.5 (CH_3), 22.0 (CH_3) ppm; MALDI-TOF-MS m/z 409.0 [$\text{M}+\text{K}$]; HRMS (NSI) Calculated for $\text{C}_{17}\text{H}_{31}\text{N}_4\text{O}_6$ [$\text{M}+\text{NH}_4$] 387.2238, found 387.2241.

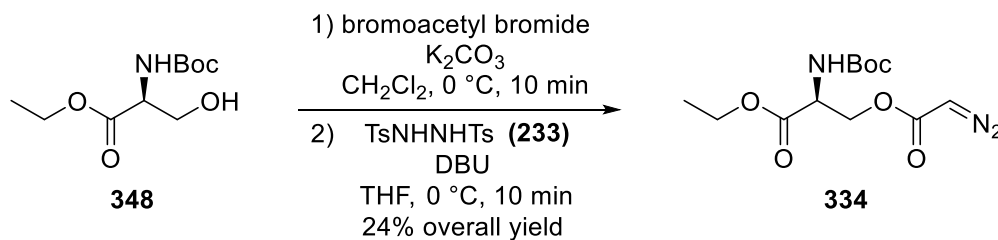
Synthesis of (*E*)-4-(α -diazoacetoxy)but-2-en-1-yl 2-((*t*-butoxycarbonyl)amino)-3-phenyl propanoate (**333**)⁶



2-((*t*-Butoxycarbonyl)amino)-3-phenylpropanoic acid (**338**) (0.04 g, 0.20 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (0.05 g, 0.20 mmol) were combined and stirred in anhydrous acetonitrile (2 mL) in a 10 mL round-bottom flask at room temperature under a nitrogen atmosphere. Triethylamine (0.04 mL, 0.03 g, 0.30 mmol) was added *via* syringe and the reaction mixture stirred at room temperature under a nitrogen atmosphere for 5 minutes. A solution of (*E*)-4-hydroxybut-2-en-1-yl α -diazoacetate (**336**) (0.03 g, 0.17 mmol) in anhydrous acetonitrile (1 mL) was added *via* syringe and the reaction mixture stirred for a further 30 minutes. Water (3 mL) was added, the mixture transferred to a separating funnel and the organic components extracted with ethyl acetate (3 \times 5 mL). The combined organic layers were washed with water (20 mL), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (ethyl acetate / petroleum ether 3 : 7) afforded **333** as a pale yellow oil (0.04 g, 0.10 mmol, 73% yield) with the following physicochemical characteristics.

R_f = 0.62 (silica gel, ethyl acetate / *n*-hexane 1 : 1); FT-IR (thin film) 2977, 2109 (C=N₂), 1687 (C=O), 1497, 1365, 1240, 1158, 1021, 739 cm⁻¹; ¹H-NMR (CD₃CN, 300 MHz) δ 7.35 – 7.18 (m, 5H, *H*_{Ar}), 5.85 – 5.61 (m, 2H, CH=CH), 5.55 (d, *J* = 7.3 Hz, 1H, NH), 5.00 (s, 1H, CH=N₂), 4.74 – 4.67 (m, 4H, CH₂CH=CHCH₂), 4.39 – 4.32 (m, 1H, α CH), 3.10 (dd, *J* = 14.0, 5.5 Hz, 1H, β CHH), 2.91 (dd, *J* = 13.7, 8.7 Hz, 1H, β CHH), 1.35 (s, 9H, (CH₃)₃C) ppm; ¹³C-NMR (CD₃CN, 75 MHz) δ 173.2 (CH₂CHC=O), 163.0 (C=OCH=N₂), 156.8 (NHC=O), 138.5, 130.7, 129.9 (two overlapping signals: *C*_{Ar}, CH=CH), 129.0 (CH=CH), 128.2, 80.4 ((CH₃)₃C), 61.7 (CH₂CH=CH), 61.3 (CH=CHCH₂), 56.4 (α CH), 47.2 (C=N₂), 38.4 (β CH₂), 28.7 ((CH₃)₃C) ppm; MALDI-TOF-MS *m/z* 442.1 [M+K]; HRMS (NSI) Calculated for C₂₀H₂₅N₃O₆Na [M+Na] 426.1636, found 426.1639.

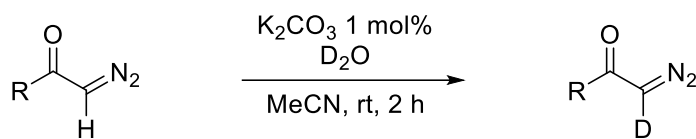
Synthesis of (S)-ethyl 2-((t-butoxycarbonyl)amino)-3-(α -diazoacetoxy)propanoate (**334**)⁴



A mixture of (S)-ethyl 2-((t-butoxycarbonyl)amino)-3-hydroxypropanoate (**348**) (0.30 g, 1.30 mmol) and potassium carbonate (0.89 g, 6.40 mmol) in anhydrous dichloromethane (7 mL) was stirred in a 25 mL round-bottom flask at 0 °C under a nitrogen atmosphere. Bromoacetyl bromide (0.34 mL, 0.78 g, 3.90 mmol) was added dropwise *via* syringe and the reaction mixture stirred at 0 °C under a nitrogen atmosphere for 10 minutes. Water (5 mL) was added, the mixture transferred to a separating funnel and the organic components extracted with dichloromethane (3 \times 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. 4-Methyl-*N'*-tosylbenzenesulfonylhydrazide (**233**) (0.88 g, 2.60 mmol) and anhydrous tetrahydrofuran (7 mL) were added and the reaction mixture stirred at 0 °C under a nitrogen atmosphere. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.96 mL, 0.98 g, 6.40 mmol) was added dropwise *via* syringe and the reaction mixture stirred at 0 °C under a nitrogen atmosphere for 10 minutes. Saturated aqueous sodium bicarbonate solution (5 mL) was added, the mixture transferred to a separating funnel and the organic components extracted with diethyl ether (3 \times 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (diethyl ether / petroleum ether 1 : 9) afforded **334** as a yellow oil (0.09 g, 0.30 mmol, 24% yield) with the following physicochemical characteristics.

R_f = 0.28 (silica gel, diethyl ether / petroleum ether 1 : 1); $[\alpha]_D^{21} +42.50$ (c 1.0, $CHCl_3$); FT-IR (thin film) 2979, 2113 (C=N₂), 1694 (C=O), 1502, 1391, 1348, 1159, 1058, 1026 cm^{-1} ; ¹H-NMR ($CDCl_3$, 300 MHz) δ 5.30 (d, J = 7.8 Hz, 1H, NH), 4.76 (s, 1H, CH=N₂), 4.59 – 4.36 (m, 3H, α CH, β CH₂), 4.21 (q, J = 7.2 Hz, 2H, CH₃CH₂), 1.43 (s, 9H, (CH₃)₃), 1.26 (t, J = 7.1 Hz, 3H, CH₃CH₂) ppm; ¹³C-NMR ($CDCl_3$, 75 MHz) δ 169.9 (CH₃CH₂OC=O), 155.4 (NHC=O), 80.4 ((CH₃)₃C), 64.7 (β CH₂), 62.0 (CH₃CH₂), 53.3 (α CH), 46.4 (CH=N₂), 28.3 ((CH₃)₃C), 14.1 (CH₃CH₂) ppm, C=OCH=N₂ signal not observed; MALDI-TOF-MS m/z 340.0 [M+K]; HRMS (NSI) Calculated for C₁₂H₁₉N₃O₆Na [M+Na] 324.1166, found 324.1163.

General procedure for the hydrogen / deuterium exchange reaction at the α -carbon atom of α -diazocarbonyl compounds 271, 274 – 276, 278, 325, 349 – 358⁷

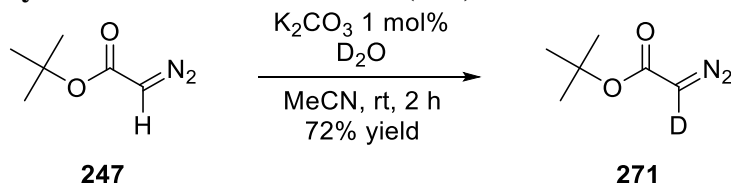


R = aliphatic, aryl, heteroarene, monoterpene, alcohol, amino acid, natural product

271, 274-276, 278, 325, 349-358

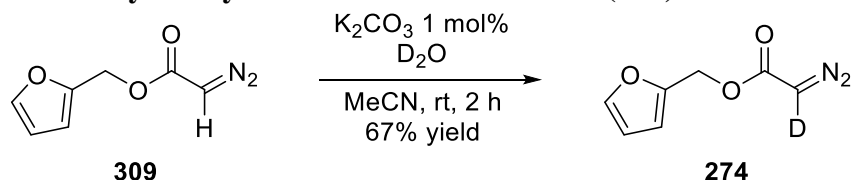
A mixture of α -diazocarbonyl compound (1 equivalent) and potassium carbonate (1 mol%) was stirred in acetonitrile (41 equivalents) in a 5 mL round-bottom flask at room temperature under a nitrogen atmosphere. Deuterium oxide (100 equivalents) was added *via* syringe and the reaction mixture stirred vigorously at room temperature under a nitrogen atmosphere for 2 hours. The mixture was transferred to a separating funnel and the organic components extracted with dichloromethane (3×5 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo* affording the corresponding α -deutero- α -diazocarbonyl compounds **271, 274 – 276, 278, 325, 349 – 358** without any further purification.

Synthesis of *t*-butyl α -deutero- α -diazoacetate (271)⁷



271 (0.04 g, 0.30 mmol, 72% yield) yellow liquid. ¹H-NMR spectroscopic evidence indicated $\geq 99\%$ deuterium incorporation; FT-IR (thin film) 2979, 2105 (C=N₂), 1685 (C=O), 1316, 1148, 992, 844, 741 cm⁻¹; ¹H-NMR (CD₃CN, 300 MHz) δ 1.45 (s, 9H, (CH₃)₃) ppm; ¹³C-NMR (CD₃CN, 100 MHz) δ 163.1 (C=O), 82.2 ((CH₃)₃C), 28.8 ((CH₃)₃C) ppm, C-D signal not observed.

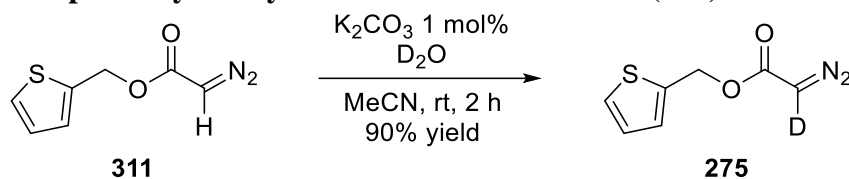
Synthesis of furan-2-ylmethyl α -deutero- α -diazoacetate (274)⁷



274 (0.04 g, 0.20 mmol, 67% yield) yellow liquid. ¹H-NMR spectroscopic evidence indicated $\geq 98\%$ deuterium incorporation; FT-IR (thin film) 2106 (C=N₂), 1681 (C=O), 1371, 1301, 1161, 999, 918, 736 cm⁻¹; ¹H-NMR (CD₃CN, 300 MHz) δ 7.52 – 7.49 (m, 1H, H_{Ar}), 6.48 – 6.45 (m, 1H, H_{Ar}), 6.43 – 6.40 (m, 1H, H_{Ar}), 5.12 (s, 2H, CH₂) ppm; ¹³C-NMR (CD₃CN, 100 MHz) δ 163.0 (C=O), 151.1, 144.9, 112 (two overlapping signals:

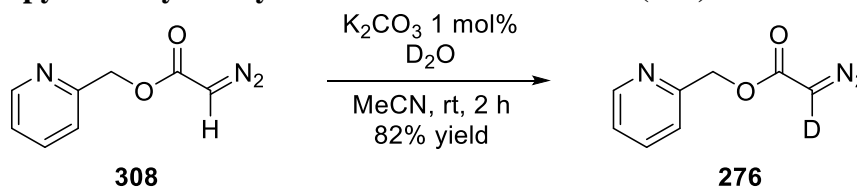
2 x C_{Ar}), 59.1 (CH_2) ppm, C-D signal not observed; MALDI-TOF-MS m/z 190.0 [$M+Na$]; HRMS (CI) Calculated for $C_7H_9DN_3O_3$ [$M+NH_4$] 185.0779, found 185.0780.

Synthesis of thiophen-2-ylmethyl α -deutero- α -diazoacetate (**275**)⁷



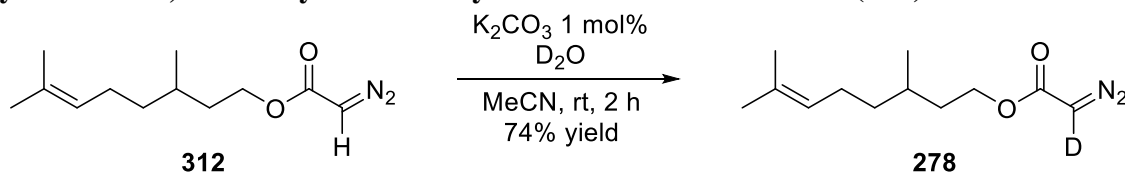
275 (0.05 g, 0.30 mmol, 90% yield) yellow liquid. 1H -NMR spectroscopic evidence indicated $\geq 97\%$ deuterium incorporation; FT-IR (thin film) 2108 ($C=N_2$), 1679 ($C=O$), 1378, 1304, 1158, 1001, 835, 737 cm^{-1} ; 1H -NMR (CD_3CN , 300 MHz) δ 7.42 (dd, $J = 5.1$, 1.2 Hz, 1H, H_{Ar}), 7.16 – 7.10 (m, 1H, H_{Ar}), 7.02 – 6.99 (m, 1H, H_{Ar}), 5.32 (s, 2H, CH_2) ppm; ^{13}C -NMR (CD_3CN , 100 MHz) δ 138.7, 128.7, 127.5, 127.2, 60.6 (CH_2) ppm, $C=O$ and C-D signals not observed; MALDI-TOF-MS m/z 206.1 [$M+Na$].

Synthesis of pyridin-2-ylmethyl α -deutero- α -diazoacetate (**276**)⁷



276 (0.04 g, 0.20 mmol, 82% yield) yellow liquid. 1H -NMR spectroscopic evidence indicated $\geq 98\%$ deuterium incorporation; FT-IR (thin film) 2105 ($C=N_2$), 1680 ($C=O$), 1593, 1302, 1167, 995, 736 cm^{-1} ; 1H -NMR (CD_3CN , 300 MHz) δ 8.55 (d, $J = 4.7$ Hz, 1H, H_{Ar}), 7.77 (td, $J = 7.7$, 1.8 Hz, 1H, H_{Ar}), 7.37 (d, $J = 7.8$ Hz, 1H, H_{Ar}), 7.32 – 7.21 (m, 1H, H_{Ar}), 5.23 (s, 2H, CH_2) ppm; ^{13}C -NMR (CD_3CN , 100 MHz) δ 156.4, 149.6, 137.1, 123.2, 121.7, 66.8 (CH_2) ppm, $C=O$ and C-D signals not observed; MALDI-TOF-MS m/z 201.0 [$M+Na$]; HRMS (NSI) Calculated for $C_8H_6DN_3O_2Na$ [$M+Na$] 201.0493, found 201.0492.

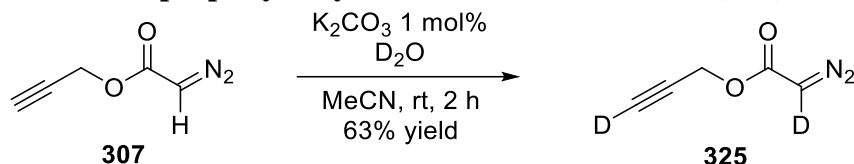
Synthesis of 3,7-dimethyloct-6-en-1-yl α -deutero- α -diazoacetate (**278**)⁷



278 (0.02 g, 0.10 mmol, 74% yield) yellow liquid. 1H -NMR spectroscopic evidence indicated $\geq 99\%$ deuterium incorporation; FT-IR (thin film) 2913, 2106 ($C=N_2$), 1687 ($C=O$), 1456, 1308, 1177, 995, 738 cm^{-1} ; 1H -NMR (CD_3CN , 300 MHz) δ 5.14 – 5.07 (m, 1H, $(CH_3)_2C=CH$), 4.19 – 4.12 (m, 2H, CH_2CH_2O), 2.05 – 1.95 (m, 2H, $(CH_3)_2C=CHCH_2$), 1.67 (s, 3H, $(CH_3CH_3)C=CH$), 1.60 (s, 3H, $(CH_3CH_3)C=CH$),

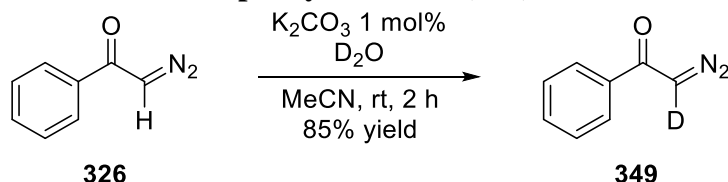
1.54 – 1.10 (m, 5H, CH_2CHCH_2), 0.90 (d, $J = 6.5$ Hz, 3H, CH_3) ppm; ^{13}C -NMR (CD_3CN , 100 MHz) δ 163.1 ($\text{C}=\text{O}$), 132.4 ($(\text{CH}_3)_2\text{C}=\text{CH}$), 125.9 ($(\text{CH}_3)_2\text{C}=\text{CH}$), 64.2 ($\text{CH}_2\text{CH}_2\text{O}$), 38.0 (CH_2CHCH_2), 36.7 (CH_2CHCH_2), 30.5 (CH_2CHCH_2), 26.4 ($(\text{CH}_3\text{CH}_3)\text{C}=\text{CH}$), 26.2 ($(\text{CH}_3)_2\text{C}=\text{CHCH}_2$), 20.1 (CH_3CH), 18.1 ($(\text{CH}_3\text{CH}_3)\text{C}=\text{CH}$) ppm, C-D signal not observed; MALDI-TOF-MS m/z 243.3 [$\text{M}+\text{NH}_4$].

Synthesis of 1-deutero-prop-2-yn-1-yl α -deutero- α -diazoacetate (**325**)⁷



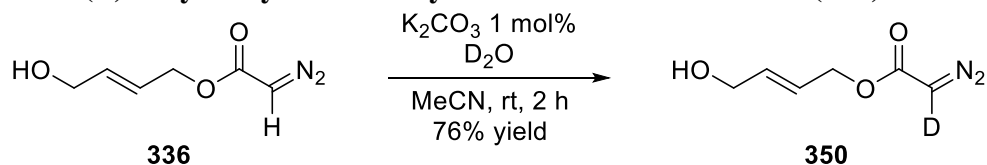
325 (0.03 g, 0.20 mmol, 63% yield) yellow liquid. ^1H -NMR spectroscopic evidence indicated $\geq 99\%$ deuterium incorporation; FT-IR (thin film) 2108 ($\text{C}=\text{N}_2$), 1680 ($\text{C}=\text{O}$), 1374, 1300, 1161, 1026, 992, 736 cm^{-1} ; ^1H -NMR (CD_3CN , 300 MHz) δ 4.73 (s, 2H, CH_2) ppm; ^{13}C -NMR (CD_3CN , 100 MHz) δ 163.1 ($\text{C}=\text{O}$), 78.9 (t, $J = 7.0$ Hz, $\text{C}\equiv\text{CD}$), 76.3 (t, $J = 39.0$ Hz, $\text{C}\equiv\text{CD}$), 53.1 (CH_2) ppm, C-D signal not observed; MALDI-TOF-MS m/z 149.0 [$\text{M}+\text{Na}$]; HRMS (CI) Calculated for $\text{C}_5\text{H}_6\text{D}_2\text{N}_3\text{O}_2$ [$\text{M}+\text{NH}_4$] 144.0737, found 144.0737.

Synthesis of α -deutero- α -diazo-1-phenylethanone (**349**)⁷



349 (0.04 g, 0.30 mmol, 85% yield) yellow solid. ^1H -NMR spectroscopic evidence indicated $\geq 99\%$ deuterium incorporation; mp 38 – 40 $^\circ\text{C}$; FT-IR (thin film) 3056, 2109 ($\text{C}=\text{N}_2$), 1599 ($\text{C}=\text{O}$), 1571, 1447, 1323, 1303, 1072, 921, 826 cm^{-1} ; ^1H -NMR (CD_3CN , 300 MHz) δ 7.81 – 7.77 (m, 2H, H_{Ar}), 7.63 – 7.56 (m, 1H, H_{Ar}), 7.53 – 7.45 (m, 2H, H_{Ar}) ppm; ^{13}C -NMR (CD_3CN , 100 MHz) δ 187.4 ($\text{C}=\text{O}$), 137.9, 134.0, 130.0, 127.9 ppm, C-D signal not observed; MALDI-TOF-MS m/z 186.2 [$\text{M}+\text{K}$]; HRMS (CI) Calculated for $\text{C}_8\text{H}_6\text{DN}_2\text{O}$ [$\text{M}+\text{H}$] 148.0616, found 148.0614.

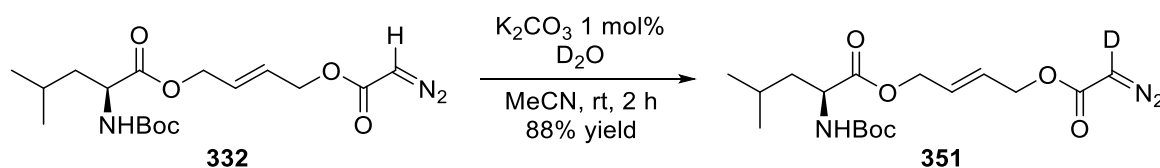
Synthesis of (*E*)-4-hydroxybut-2-en-1-yl α -deutero- α -diazoacetate (**350**)⁷



350 (0.04 g, 0.30 mmol, 76% yield) yellow liquid. ^1H -NMR spectroscopic evidence indicated $\geq 97\%$ deuterium incorporation; FT-IR (thin film) 3380 (OH), 2106 ($\text{C}=\text{N}_2$), 1670

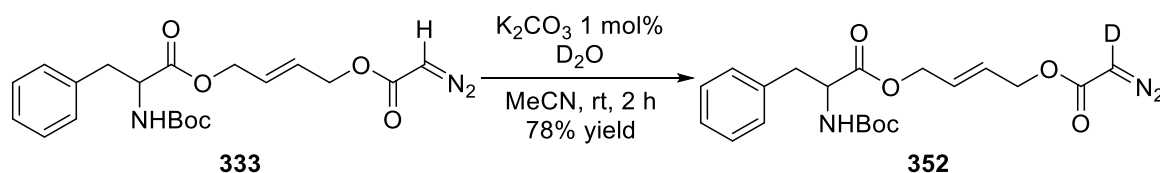
(C=O), 1300, 1172, 1016, 737 cm^{-1} ; $^1\text{H-NMR}$ (CD_3CN , 300 MHz) δ 5.80 – 5.71 (m, 1H, CH=CH), 5.61 – 5.51 (m, 1H, CH=CH), 4.72 – 4.69 (m, 2H, CH=CHCH₂), 4.15 – 4.11 (m, 2H, HOCH₂), 2.87 (t, J = 5.6 Hz, 1H, OH) ppm; $^{13}\text{C-NMR}$ (CD_3CN , 100 MHz) δ 163.0 (C=O), 135.5 (CH=CH), 125.8 (CH=CH), 61.6 (CH=CHCH₂), 58.8 (HOCH₂) ppm, C-D signal not observed; MALDI-TOF-MS m/z 180.0 [M+Na]; HRMS (NSI) Calculated for C₆H₇DN₂O₃Na [M+Na] 180.0490, found 180.0485.

Synthesis of (*S,E*)-4-(α -deutero- α -diazoacetoxy)but-2-en-1-yl 2-((*t*-butoxycarbonyl)amino)-4-methylpentanoate (**351**)⁷



351 (0.02 g, 0.10 mmol, 88% yield) yellow oil. $^1\text{H-NMR}$ spectroscopic evidence indicated $\geq 98\%$ deuterium incorporation; $[\alpha]_{\text{D}}^{21}$ -5.6 (c 1.0, CHCl_3); FT-IR (thin film) 2959, 2109 (C=N₂), 1686 (C=O), 1366, 1305, 1159, 1021, 739 cm^{-1} ; $^1\text{H-NMR}$ (CD_3CN , 300 MHz) δ 5.83 – 5.64 (m, 2H, CH=CH), 5.57 (d, J = 7.6 Hz, 1H, NH), 4.75 – 4.66 (m, 4H, CH₂CH=CHCH₂), 4.13 (dd, J = 13.2, 7.4 Hz, 1H, αCH), 1.72 – 1.60 (m, 1H, γCH), 1.51 (t, J = 7.2 Hz, 2H, βCH_2), 1.40 (s, 9H, (CH₃)₃C), 0.91 (t, J = 6.6 Hz, 6H, (CH₃)₂CH) ppm; $^{13}\text{C-NMR}$ (CD_3CN , 100 MHz) δ 174.4 (CH₂CHC=O), 163.1 (C=OCH=N₂), 157.0 (NHC=O), 129.7 (CH=CH), 129.1 (CH=CH), 80.2 ((CH₃)₃C), 61.6 (CH₂CH=CH), 61.4 (CH=CHCH₂), 53.6 (αCH), 41.5 (βCH_2), 28.9 ((CH₃)₃C), 25.9 (γCH), 23.5 (CH₃), 22.0 (CH₃) ppm, C-D signal not observed; MALDI-TOF-MS m/z 393.2 [M+Na]; HRMS (NSI) Calculated for C₁₇H₂₆DN₃O₆Na [M+Na] 393.1855, found 393.1844.

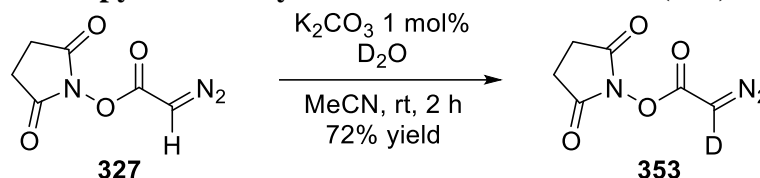
Synthesis of (*E*)-4-(α -deutero- α -diazoacetoxy)but-2-en-1-yl 2-((*t*-butoxycarbonyl)amino)-3-phenylpropanoate (**352**)⁷



352 (0.02 g, 0.10 mmol, 78% yield) yellow oil. $^1\text{H-NMR}$ spectroscopic evidence indicated $\geq 99\%$ deuterium incorporation; FT-IR (thin film) 2977, 2109 (C=N₂), 1692 (C=O), 1498, 1364, 1307, 1166, 1023, 740 cm^{-1} ; $^1\text{H-NMR}$ (CD_3CN , 300 MHz) δ 7.34 – 7.20 (m, 5H, H_{Ar}), 5.86 – 5.61 (m, 2H, CH=CH), 5.55 (d, J = 7.7 Hz, 1H, NH), 4.74 – 4.66 (m, 4H, CH₂CH=CHCH₂), 4.38 – 4.32 (m, 1H, αCH), 3.09 (dd, J = 14.0, 5.6 Hz, 1H, βCHH), 2.91 (dd, J = 13.8, 8.9 Hz, 1H, βCHH), 1.35 (s, 9H, (CH₃)₃C) ppm; $^{13}\text{C-NMR}$ (CD_3CN ,

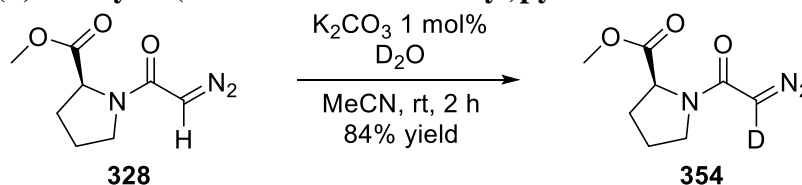
100 MHz) δ 173.1 (CH₂CHC=O), 163.1 (C=OCH=N₂), 138.4, 130.6, 129.8 (two overlapping signals: C_{Ar}, CH=CH), 128.9 (CH=CH), 128.1, 80.4 ((CH₃)₃C), 61.8 (CH₂CH=CH), 61.4 (CH=CHCH₂), 56.4 (α CH), 38.5 (β CH₂), 28.8 ((CH₃)₃C) ppm, NHC=O and C-D signals not observed; MALDI-TOF-MS m/z 443.0 [M+K]; HRMS (NSI) Calculated for C₂₀H₂₄DN₃O₆Na [M+Na] 427.1698, found 427.1697.

Synthesis of 2,5-dioxopyrrolidin-1-yl α -deutero- α -diazoacetate (**353**)⁷



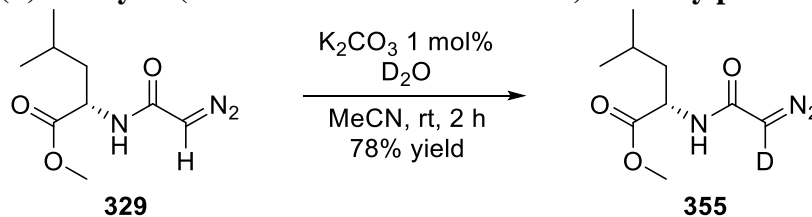
353 (0.03 g, 0.20 mmol, 72% yield) pale yellow solid. ¹H-NMR spectroscopic evidence indicated $\geq 99\%$ deuterium incorporation; mp 92 – 94 °C; FT-IR (thin film) 2122 (C=N₂), 1720 (C=O), 1367, 1304, 1198, 1098, 1069, 941, 813, 711 cm⁻¹; ¹H-NMR (CD₃CN, 300 MHz) δ 2.77 (s, 4H, CH₂) ppm; ¹³C-NMR (CD₃CN, 100 MHz) δ 171.7 (C=OCH₂), 163.0 (C=OCD=N₂), 26.6 (CH₂) ppm, C-D signal not observed.

Synthesis of (S)-methyl 1-(α -deutero- α -diazoacetyl)pyrrolidine-2-carboxylate (**354**)⁷



354 (0.02 g, 0.10 mmol, 84% yield) yellow oil. ¹H-NMR spectroscopic evidence indicated $\geq 99\%$ deuterium incorporation; $[\alpha]_D^{21}$ –124.70 (*c* 1.0, CHCl₃); FT-IR (thin film) 2106 (C=N₂), 1737 (C=O), 1699, 1406, 1175, 1027, 728 cm⁻¹; ¹H-NMR (CD₃CN, 300 MHz) δ 4.43 – 4.29 (m, 1H, α CH), 3.66 (s, 3H, CH₃), 3.37 – 3.24 (m, 2H, CH₂N), 2.22 – 2.12 (m, 1H, β CHH), 1.99 – 1.89 (m, 3H, β CHH, γ CH₂) ppm; ¹³C-NMR (CD₃CN, 100 MHz) δ 174.3 (CH₃OC=O), 160.4 (NC=O), 60.2 (α CH), 52.9 (CH₃O), 47.6 (CH₂N), 30.4 (β CH₂), 25.6 (γ CH₂) ppm, C-D signal not observed; MALDI-TOF-MS m/z 221.1 [M+Na]; HRMS (NSI) Calculated for C₈H₁₀DN₃O₃Na [M+Na] 221.0755, found 221.0753.

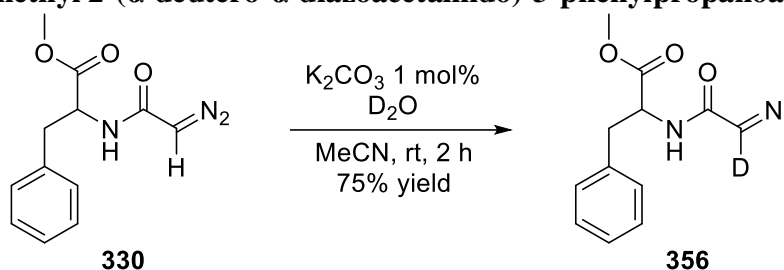
Synthesis of (S)-methyl 2-(α -deutero- α -diazoacetamido)-4-methylpentanoate (**355**)⁷



355 (0.03 g, 0.10 mmol, 78% yield) yellow oil. ¹H-NMR spectroscopic evidence indicated $\geq 99\%$ deuterium incorporation; $[\alpha]_D^{21}$ –6.00 (*c* 1.0, CHCl₃); FT-IR (thin film) 3283, 2957,

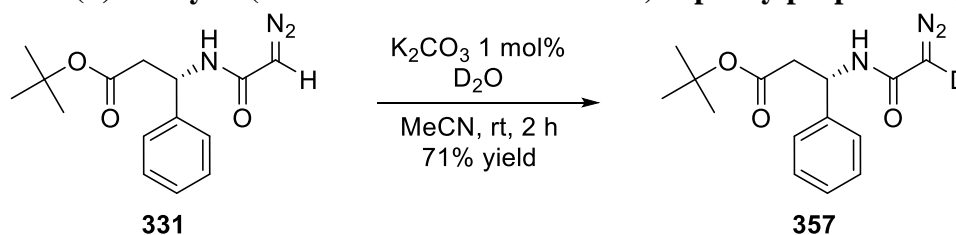
2100 (C=N₂), 1740 (C=O), 1612, 1536, 1434, 1338, 1203, 1150, 1010, 735 cm⁻¹; ¹H-NMR (CD₃CN, 300 MHz) δ 6.35 (s, 1H, NH), 4.49 – 4.35 (m, 1H, αCH), 3.66 (s, 3H, OCH₃), 1.71 – 1.50 (m, 3H, γCH, βCH₂), 0.92 (d, *J* = 6.6 Hz, 3H, (CH₃)₂CH), 0.90 (d, *J* = 6.6 Hz, 3H, (CH₃)₂CH) ppm; ¹³C-NMR (CD₃CN, 100 MHz) δ 174.7 (CH₃OC=O), 166.9 (NHC=O), 53.0 (αCH), 52.4 (CH₃O), 41.7 (βCH₂), 25.9 (γCH), 23.4 (CH₃), 22.1 (CH₃) ppm, C-D signal not observed; MALDI-TOF-MS *m/z* 253.1 [M+K]; HRMS (NSI) Calculated for C₉H₁₄DN₃O₃Na [M+Na] 237.1068, found 237.1068.

Synthesis of methyl 2-(α-deutero-α-diazoacetamido)-3-phenylpropanoate (**356**)⁷



356 (0.03 g, 0.10 mmol, 75% yield) yellow solid. ¹H-NMR spectroscopic evidence indicated ≥99% deuterium incorporation; mp 80 – 82 °C; FT-IR (thin film) 3279, 2960, 2099 (C=N₂), 1736 (C=O), 1610, 1530, 1432, 1332, 1207, 1002, 733 cm⁻¹; ¹H-NMR (CD₃CN, 300 MHz) δ 7.34 – 7.17 (m, 5H, H_{Ar}), 6.35 (d, *J* = 6.3 Hz, 1H, NH), 4.73 – 4.66 (m, 1H, αCH), 3.66 (s, 3H, OCH₃), 3.11 (dd, *J* = 13.9, 5.6 Hz, 1H, βCHH), 2.94 (dd, *J* = 13.9, 8.1 Hz, 1H, βCHH) ppm; ¹³C-NMR (CD₃CN, 100 MHz) δ 173.4 (CH₃OC=O), 166.7 (NHC=O), 138.2, 130.6, 129.7, 128.1, 55.3 (αCH), 53.1 (CH₃O), 38.7 (βCH₂) ppm, C-D signal not observed; MALDI-TOF-MS *m/z* 271.1 [M+Na].

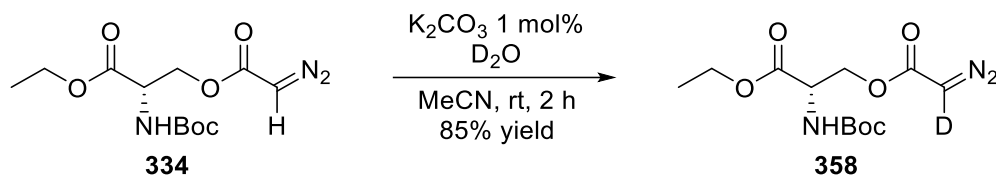
Synthesis of (*S*)-*t*-butyl 3-(α-deutero-α-diazoacetamido)-3-phenylpropanoate (**357**)⁷



357 (0.02 g, 0.10 mmol, 71% yield) yellow oil. ¹H-NMR spectroscopic evidence indicated ≥96% deuterium incorporation; [α]_D²¹ –35.4 (*c* 1.0, CHCl₃); FT-IR (thin film) 3282, 2979, 2106 (C=N₂), 1691 (C=O), 1691, 1612, 1540, 1315, 1149, 844, 759 cm⁻¹; ¹H-NMR (CD₃CN, 300 MHz) δ 7.41 – 7.23 (m, 5H, H_{Ar}), 6.60 (d, *J* = 6.8 Hz, H, NH), 5.37 – 5.17 (m, 1H, βCH), 2.75 – 2.60 (m, 2H, αCH₂), 1.34 (s, 9H, (CH₃)₃) ppm; ¹³C-NMR (CD₃CN, 100 MHz) δ 171.0 (CH₂C=O), 163.1 (NHC=O), 143.3, 129.8, 128.7, 127.8, 81.8 ((CH₃)₃C), 51.9 (βCH), 43.3 (αCH₂), 28.5 ((CH₃)₃) ppm, C-D signal not observed;

MALDI-TOF-MS m/z 313.1 [M+Na]; HRMS (NSI) Calculated for $C_{15}H_{18}DN_3O_3Na$ [M+Na] 313.1381, found 313.1381.

Synthesis of (S)-ethyl 2-((t-butoxycarbonyl)amino)-3-(α -deutero- α -diazoacetoxy) propanoate (358)⁷



358 (0.03 g, 0.10 mmol, 85% yield) yellow oil. 1H -NMR spectroscopic evidence indicated $\geq 99\%$ deuterium incorporation; $[\alpha]_D^{22} +40.20$ (c 1.0, $CHCl_3$); FT-IR (thin film) 2980, 2110 ($C=N_2$), 1686 ($C=O$), 1505, 1368, 1310, 1158, 1014, 856, 737 cm^{-1} ; 1H -NMR (CD_3CN , 300 MHz) δ 5.78 (d, $J = 6.2$ Hz, 1H, NH), 4.44 – 4.32 (m, 3H, αCH , βCH_2), 4.16 (q, $J = 7.2$ Hz, 2H, CH_3CH_2), 1.41 (s, 9H, $(CH_3)_3$), 1.23 (t, $J = 7.1$ Hz, 3H, CH_3CH_2) ppm; ^{13}C -NMR (CD_3CN , 100 MHz) δ 171.1 ($CH_3CH_2OC=O$), 163.1 ($C=OCH=N_2$), 156.7 ($NHC=O$), 80.6 ($(CH_3)_3C$), 65.1 (βCH_2), 62.8 (CH_3CH_2), 54.5 (αCH), 28.8 ($(CH_3)_3C$), 14.8 (CH_3CH_2) ppm, C-D signal not observed; MALDI-TOF-MS m/z 341.2 [M+K]; HRMS (NSI) Calculated for $C_{12}H_{18}DN_3O_6Na$ [M+Na] 325.1229, found 325.1231.

6.4. References

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Chapter 7

(S)-N-Triflyl VANOL phosphoramidate ((S)-359)

7.1. Synthesis of (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-359) as a catalyst for asymmetric aziridine reactions

Catalysts for asymmetric catalytic reactions are often based on axially chiral, non-racemic, biaryl compounds, which are among the most versatile and efficient ligands that have been found.¹ Much effort has been put by various research groups around the world into the development of such compounds as chiral, non-racemic ligands.² Their employment in catalytic aziridine synthesis has also been intensively explored. For example, two classes of the axially chiral biaryl compounds have found application in asymmetric aziridination reactions; linear (*S*)- and (*R*)-BINOL,^{3,4} (*S*)-360 and (*R*)-360 respectively, and vaulted (*S*)- and (*R*)-VANOL,^{5,6} (*S*)-361 and (*R*)-361, and (*S*)- and (*R*)-VAPOL,^{5,6} (*S*)-362 and (*R*)-362 respectively (Figure 7.1).

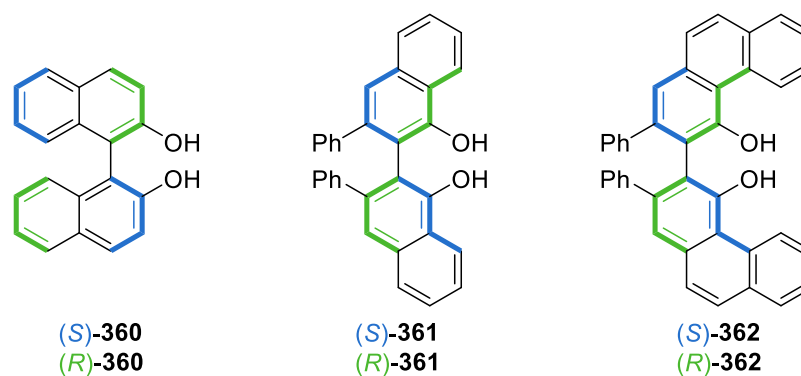
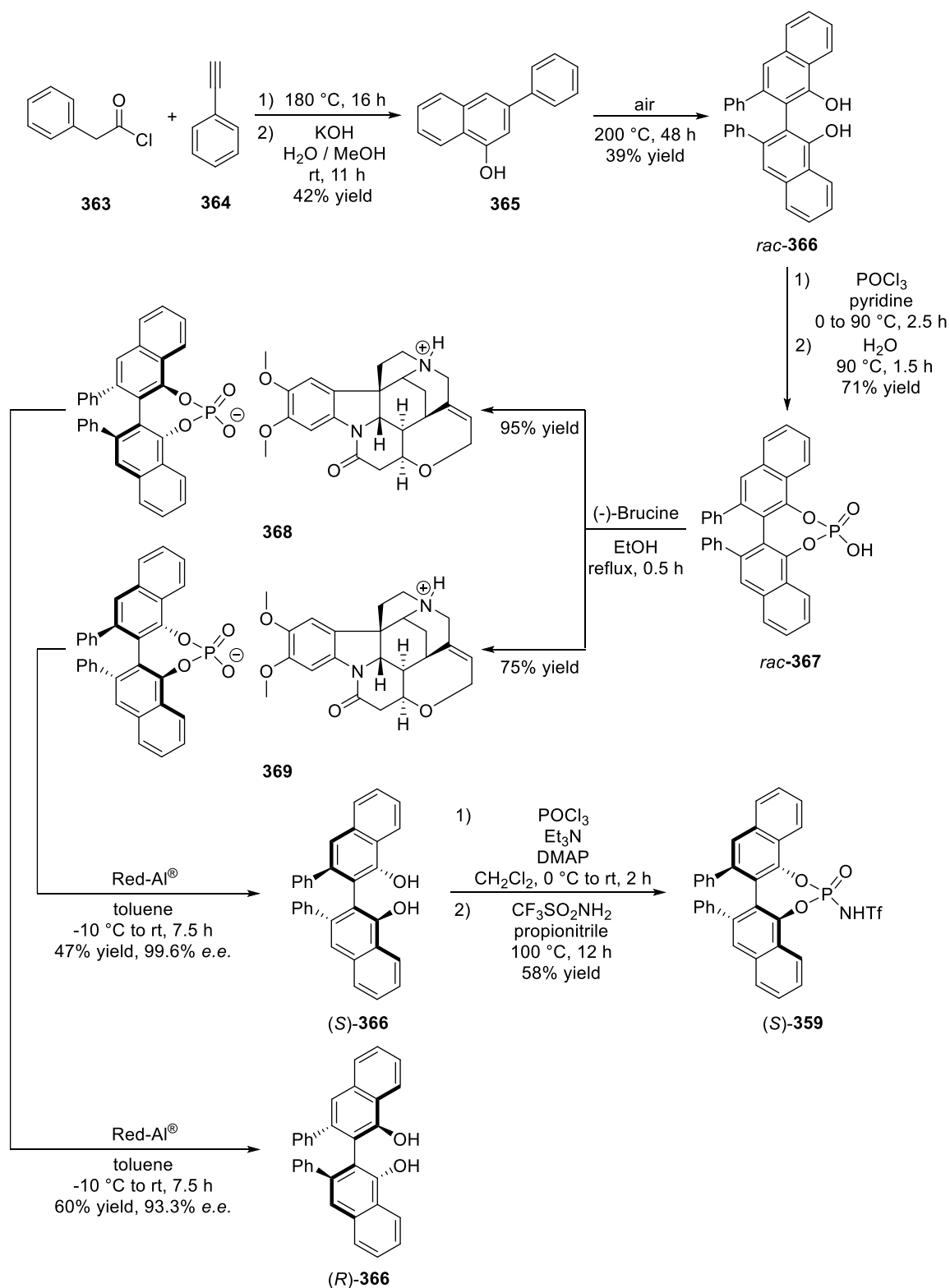


Figure 7.1 Biaryl ligands for the catalytic asymmetric aziridination reaction.

It was previously noted in this PhD thesis (Chapter 4 Introduction; section 4.4.) that one of the ongoing research projects in the Bew research group focuses on the catalytic enantioselective aziridination reaction. Extensive studies have been carried out that have led to the development of an efficient catalytic asymmetric aziridination system with the use of (*S*)-*N*-triflyl BINOL-derived phosphoramidate ((*S*)-248) as the reaction catalyst. *N*-Aryl-*cis*-aziridine-2-carboxylates were obtained with high enantiomeric excess values (67% to 97%) and in excellent yields (87% to 98%).⁷

In view of the fact that the vaulted VANOL and VAPOL ligands have been used successfully as catalysts for the asymmetric aziridination reaction,⁸ it was of interest to the Bew research group to synthesise (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-359) and investigate its effectiveness in the aziridination reactions conducted in the research laboratory.

The synthetic approach to (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-359) is outlined in **Scheme 7.1**.



Scheme 7.1 Synthesis of (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-**359**) as a catalyst for asymmetric aziridine reactions.

The synthesis of (*S*)-**359** was initiated by following a protocol reported by Bao *et al.*⁹ for the preparation of 3-phenylnaphthalen-1-ol (**365**). Reaction of phenylacetyl chloride (**363**) with phenylacetylene (**364**) at 180 °C for 16 hours and subsequent treatment with potassium hydroxide in a mixture of water and methanol at room temperature afforded,

after 11 hours, the desired **365** in 42% yield. Adopting a procedure reported by Bao *et al.*,⁹ *rac*-3,3'-diphenyl-2,2'-bi-1-naphthol (*rac*-**366**) was prepared in 39% yield by an oxidative coupling of 3-phenylnaphthalen-1-ol (**365**) carried out at 200 °C for 48 hours. The obtained *rac*-**366** was taken into the next step (according to a protocol reported by Bao *et al.*⁹) and dissolved in pyridine and treated with phosphorus oxychloride at 0 °C. Consecutive heating of the reaction mixture at 90 °C for 2.5 hours and treatment with water and heating at 90 °C for 1.5 hours, and thereafter with 6 M aqueous hydrochloric acid solution and heating at reflux for 1.5 hours afforded after precipitation with *n*-hexane from dichloromethane the desired *rac*-**367** in 71% yield.

With *rac*-3,3'-diphenyl-2,2'-bi-1-naphthylphosphoric acid (*rac*-**367**) in hand, its resolution with (–)-brucine was explored. Employing a protocol reported by Hu *et al.*,¹ refluxing *rac*-**367** with (–)-brucine in ethanol for 30 minutes led to a precipitation of a pale yellow solid **369** that was collected by filtration. To ensure that the precipitate **369** was free of the other diastereoisomer of the brucine salt **368** (present in the mother liquor), the crystallisation from ethanol was then repeated to afford ultimately the desired **369** as a white solid in 75% yield (based on the maximum of 50% per diastereoisomer in a resolution). The mother liquors were combined and after evaporation of the solvent *in vacuo* the other diastereoisomer of the brucine salt **368** was isolated as a pale yellow solid in 95% yield. The cleavage of thus prepared salts **368** and **369** (according to a procedure reported by Hu *et al.*¹) was performed by a treatment with excess sodium bis(2-methoxy ethoxy)aluminium hydride (6 equivalents) in toluene at –10 °C. Further stirring of the reaction mixture at 0 °C for 1.5 hours and at room temperature for 6 hours generated, after acidification of the mixture to pH \approx 2 by addition of 2 M aqueous hydrochloric acid solution, the impure (*S*)-**366** and (*R*)-**366**. Purification by flash column chromatography on silica gel (ethyl acetate / petroleum ether 1: 9) afforded the desired (*S*)-**366** (white solid) in 47% yield and (*R*)-**366** (pale yellow solid) in 60% yield. The enantiomeric excesses of (*S*)-**366** and (*R*)-**366** (99.6% and 93.3% respectively) were determined based on chiral analytical HPLC analysis (Eurocel® 01, 5 μ m 250 \times 4.6 mm ID, *iso*-hexane / isopropyl alcohol 95.5 : 4.5, 0.5 mL / min) of (*S*)-**366** and (*R*)-**366** with the employment of *rac*-**366** as a standard (**Figure 7.2**).

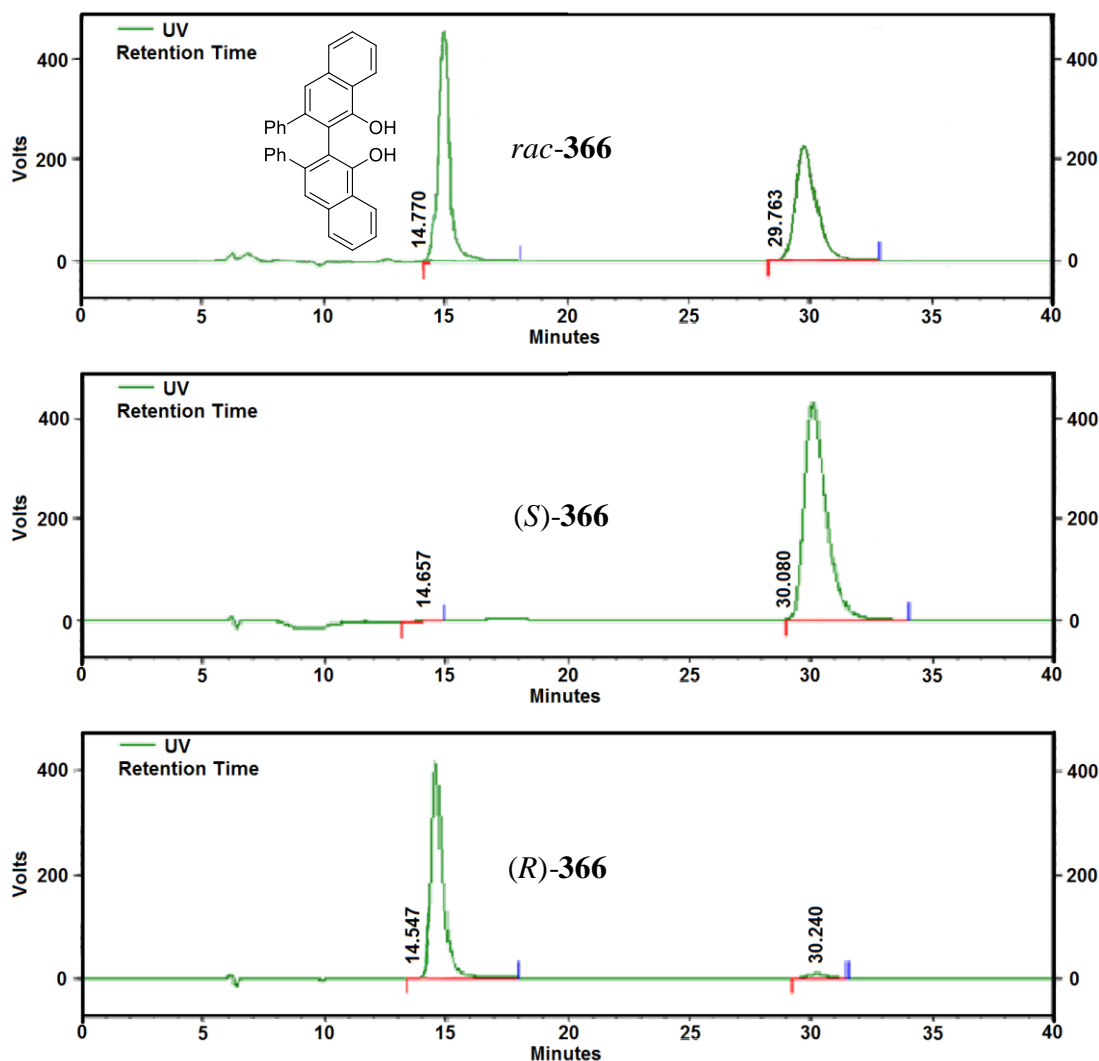


Figure 7.2 The chiral HPLC analysis of *rac*-**366**, (*S*)-**366**, and (*R*)-**366**.

In the last step of the synthetic route to (*S*)-**359** only (*S*)-3,3'-diphenyl-2,2'-bi-1-naphthol ((*S*)-**366**) was utilised due to a higher enantiomeric excess compared to (*R*)-**366**. The desired (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-**359**) was prepared in a one-pot two-step procedure reported by Desai and Wulff² from (*S*)-**366** without the isolation of the intermediate (*S*)-VANOL phosphoric acid. In the first step (*S*)-**366** was treated with excess of triethylamine (7 equivalents) at 0 °C in dichloromethane. Afterwards phosphorus oxychloride and excess of 4-dimethylaminopyridine (2 equivalents) were added and stirred for 2 hours at room temperature. In the second step propionitrile and excess of trifluoromethanesulfonamide (2 equivalents) were added and the reaction mixture heated at 100 °C for 12 hours to afford the anticipated (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-**359**) as a white solid in 58% yield. The purification of (*S*)-**359** proved to be difficult and only after two purifications by flash column chromatography on a mixture of silica gel and Celite® (1st column: ethyl acetate 100%; 2nd column: ethyl acetate / petroleum ether

1 : 1) and subsequent precipitation with *n*-pentane from a minimum amount of dichloromethane the major impurities were separated from (*S*)-**359**.

Although the $^1\text{H-NMR}$ spectral data (**Figure 7.3**) of a small sample of the material dissolved in $\text{DMSO-}d_6$ confirmed the structure of (*S*)-**359** and corresponded closely to those reported in the literature,² a residual peak of solvent could still be observed and therefore (*S*)-**359** was subjected to Genevac's high performance centrifugal solvent evaporator system for an extended period of time.

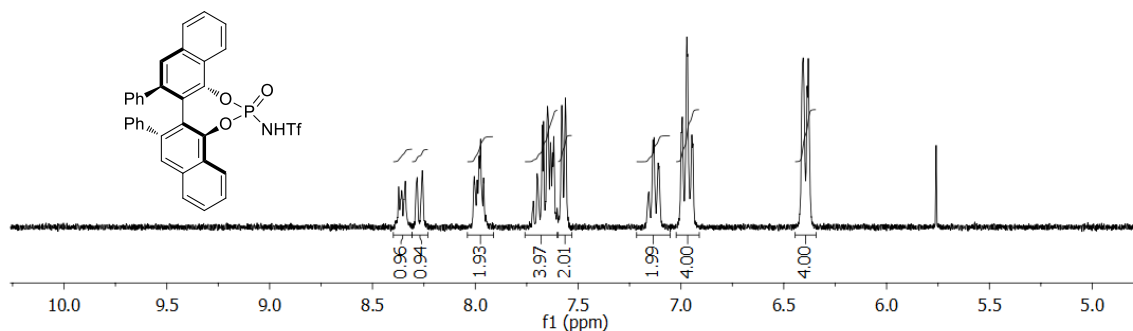


Figure 7.3 The $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) spectrum of (*S*)-**359**.

Due to the limited amount of (*S*)-**359**, subsequent $^1\text{H-NMR}$ analysis was performed in CDCl_3 (**Figure 7.4**) to allow for recovery of the sample after the measurement. It is worth mentioning that supplementary material with the $^1\text{H-}$ and $^{13}\text{C-NMR}$ spectra for this compound is not available in the literature. The specific rotation $[\alpha]_D^{18}$ of (*S*)-**359** was $+157.00$ (*c* 1.0, CH_2Cl_2) (reported by Desai and Wulff;² $[\alpha]_D^{23} +137.30$ (*c* 1.0, CH_2Cl_2)). High-resolution mass spectrometry (NSI) displayed m/z at 649.1166 (calculated for $\text{C}_{33}\text{H}_{25}\text{F}_3\text{N}_2\text{O}_5\text{PS}$ $[\text{M}+\text{NH}_4]$ 649.1168) confirming the identity of (*S*)-**359**.

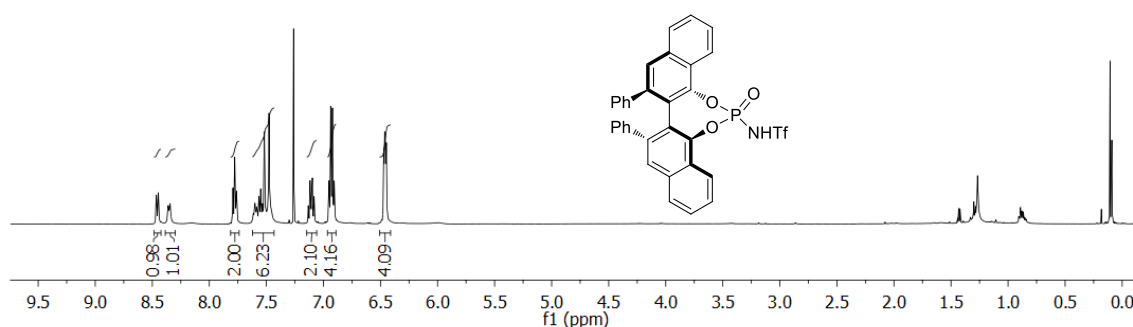
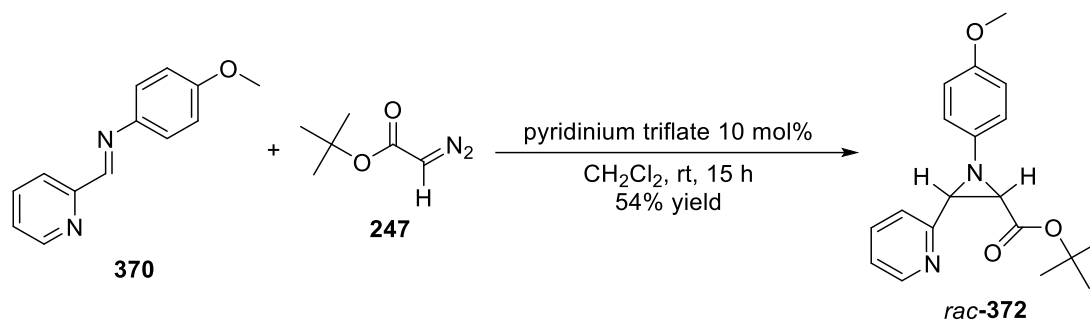


Figure 7.4 The $^1\text{H-NMR}$ (CDCl_3) spectrum of (*S*)-**359**.

Having successfully prepared (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-**359**), its application for the catalytic asymmetric aziridination reactions conducted in the Bew research group was investigated. The starting materials chosen, *N*-aryl imines **370** and **371**, were readily available in the research laboratory and had been prepared by a former PhD student according to a procedure reported by Bew *et al.*¹⁰

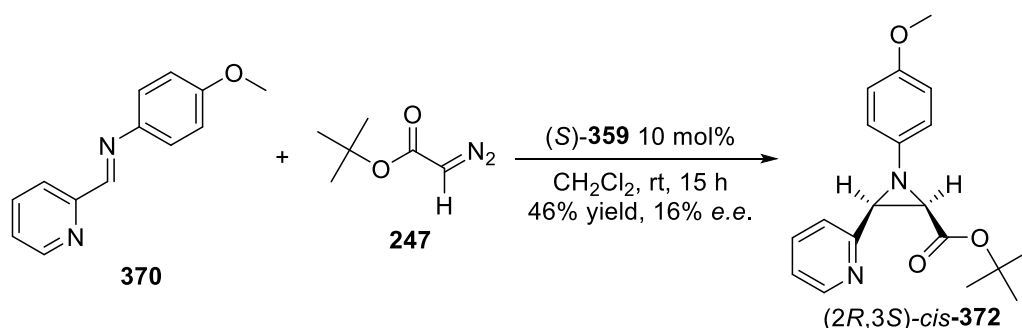
Following a protocol established by P. Pesce,⁷ *rac*-*t*-butyl 1-(4-methoxyphenyl)-3-(pyridin-2-yl)aziridine-2-carboxylate (*rac*-**372**) was first prepared to serve as a standard for the chiral HPLC analysis of the subsequently synthesised (*2R,3S*)-*cis*-**372** (although the (*2R,3S*)-enantiomer of *cis*-**372** is indicated, the absolute configuration is not known at this time). Pyridinium triflate (10 mol%) catalysed the reaction of (*E*)-4-methoxy-*N*-(pyridin-2-ylmethylene)aniline (**370**) with **247** in dichloromethane at room temperature to afford, after 15 hours, the desired *rac*-**372** in 54% yield (**Scheme 7.2**). The *cis*-isomer is formed selectively.



Scheme 7.2 Pyridinium triflate-catalysed synthesis of *rac*-**372**.

The structure of *rac*-**372** was verified by analysis of the physicochemical data that corresponded closely to those previously reported.⁷ The ¹H-NMR spectrum displayed two doublets at δ 3.62 and 3.11 ppm for the protons of the aziridine moiety confirming the formation of *rac*-**372**. Furthermore the ¹³C-NMR spectrum revealed two peaks at δ 48.3 and 46.4 ppm for the carbons of the aziridine moiety.

The synthesis of (*2R,3S*)-*cis*-**372** was simultaneously executed employing (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-**359**) (10 mol%) as the reaction catalyst. (*2R,3S*)-*cis*-*t*-Butyl 1-(4-methoxyphenyl)-3-(pyridin-2-yl)aziridine-2-carboxylate ((*2R,3S*)-*cis*-**372**) was obtained in 46% yield (**Scheme 7.3**).



Scheme 7.3 Synthesis of (*2R,3S*)-*cis*-**372** catalysed by (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-**359**).

The enantiomeric excess of (*2R,3S*)-*cis*-**372** (16%) was determined based on the chiral analytical HPLC analysis (Eurocel[®] 01, 250 \times 4.6 mm ID, *iso*-hexane / isopropyl alcohol

95 : 5, 1 mL / min) of (*2R,3S*)-*cis*-**372** with the employment of *rac*-**372** as a standard (Figure 7.5).

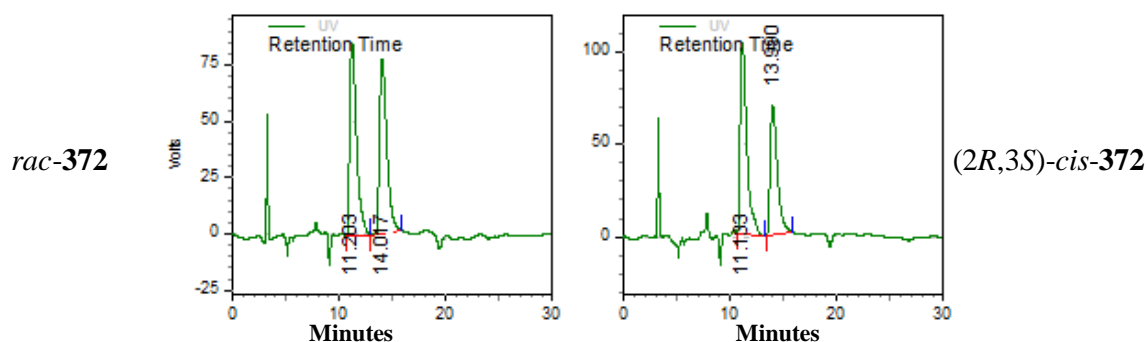
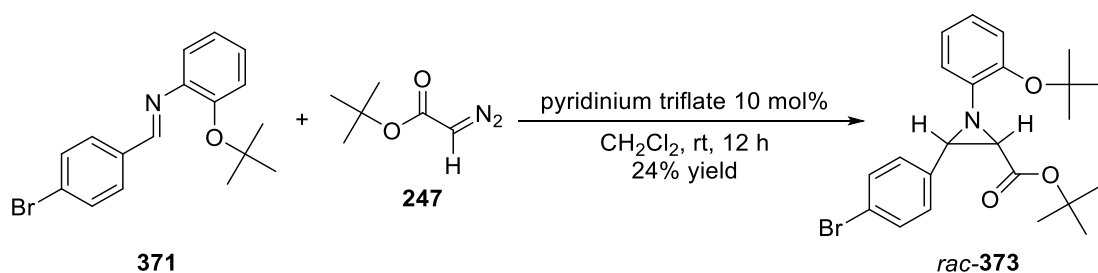


Figure 7.5 The chiral HPLC analysis of *rac*-**372** and (*2R,3S*)-*cis*-**372**.

With the first results for the (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-**359**)-catalysed aziridination reaction in hand, it was decided to prepare (*2R,3R*)-*cis*-*t*-butyl 3-(4-bromophenyl)-1-(2-(*t*-butoxy)phenyl)aziridine-2-carboxylate ((*2R,3R*)-*cis*-**373**) (although (*2R,3R*)-enantiomer of the *cis*-**373** is presented, the absolute configuration is not known at this time). Its synthesis was performed at $-60\text{ }^{\circ}\text{C}$ as it was previously established in the Bew research group that lowering the temperature of the reaction typically enhances the level of enantiomeric excess.

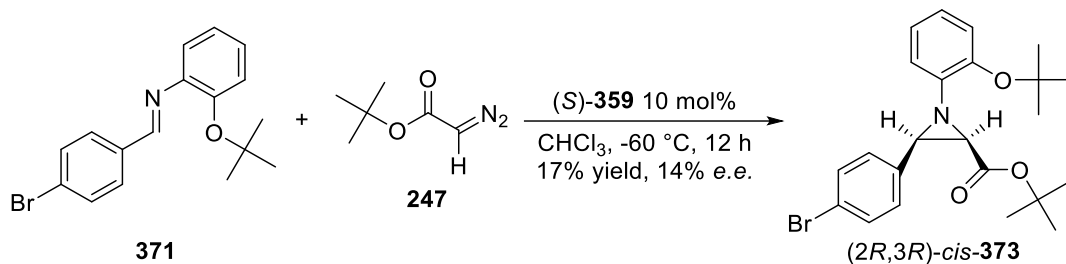
To begin with, *rac*-**373** was synthesised employing a protocol reported by Bew *et al.*,¹¹ to serve as a standard for the chiral HPLC analysis of the consecutively prepared (*2R,3R*)-*cis*-**373**. Reaction of **371** with *t*-butyl α -diazoacetate (**247**) in the presence of pyridinium triflate (10 mol%) as the reaction catalyst afforded, after 12 hours, at room temperature the *rac*-**373** in a low 24% yield (Scheme 7.4). The *cis*-isomer is obtained selectively.



Scheme 7.4 Synthesis of *rac*-**373** utilising pyridinium triflate as the reaction catalyst.

Analysis of the physicochemical data confirmed the structure of *rac*-**373** and corresponded closely to those reported by Bew *et al.*¹¹ Two doublets at δ 3.42 and 3.04 ppm for the protons of the aziridine moiety were observed in the ^1H -NMR spectrum. Additionally the ^{13}C -NMR spectrum revealed two peaks at δ 47.5 and 47.0 ppm for the carbons of aziridine moiety further verifying the identity of *rac*-**373**.

Adopting a protocol reported by P. Pesce,⁷ but using (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-**359**) instead of (*S*)-*N*-triflyl BINOL-derived phosphoramidate ((*S*)-**248**) as the reaction catalyst, (*2R,3R*)-*cis*-*t*-butyl 3-(4-bromophenyl)-1-(2-(*t*-butoxy)phenyl)aziridine-2-carboxylate ((*2R,3R*)-*cis*-**373**) was prepared. The (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-**359**) (10 mol%) catalysed the reaction of (*E*)-*N*-(4-bromobenzylidene)-2-(*t*-butoxy)aniline (**371**) with **247** in chloroform at $-60\text{ }^{\circ}\text{C}$ to afford, after 12 hours, (*2R,3R*)-*cis*-**373** in a poor 17% yield (**Scheme 7.5**).



Scheme 7.5 Synthesis of (*2R,3R*)-*cis*-**373** employing (*S*)-**359** as the reaction catalyst.

The enantiomeric excess of (*2R,3R*)-*cis*-**373** (14%) was determined based on the chiral analytical HPLC analysis (Chiralpak[®] AD, 250 × 4.6 mm ID, *iso*-hexane / isopropyl alcohol 95 : 5, 1 mL / min) of (*2R,3R*)-*cis*-**373** with the employment of *rac*-**373** as a standard (**Figure 7.6**).

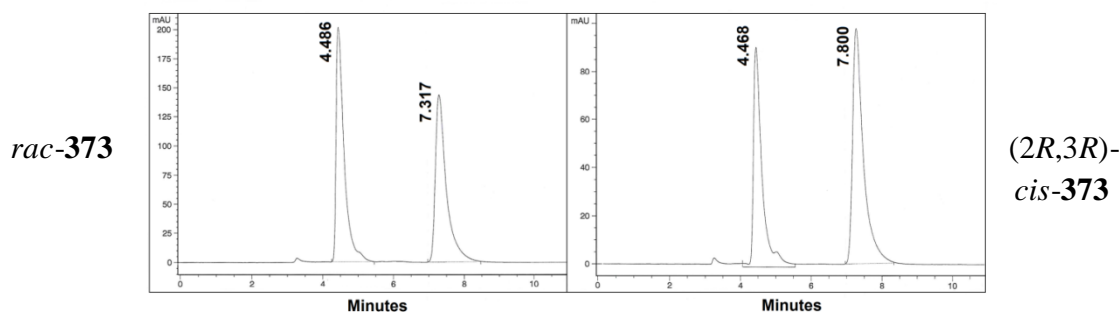


Figure 7.6 The chiral HPLC analysis of *rac*-**373** and (*2R,3R*)-*cis*-**373**.

Interestingly, for both experiments performed with the use of (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-**359**), not only the yields of the reactions but also the enantiomeric excess of the obtained *N*-aryl-*cis*-aziridine-2-carboxylates, (*2R,3S*)-*cis*-**372** and (*2R,3R*)-*cis*-**373**, remained significantly lower in comparison to the values obtained from the previously performed syntheses of (*2R,3S*)-*cis*-**372** and (*2R,3R*)-*cis*-**373** in the Bew research group^{7,12} employing (*S*)-*N*-triflyl BINOL-derived phosphoramidate ((*S*)-**248**) as the reaction catalyst (**Table 7.1**).

	Yield of (<i>2R,3S</i>)- <i>cis</i> - 372 (%)	Enantiomeric excess of (<i>2R,3S</i>)- <i>cis</i> - 372 (%)	Yield of (<i>2R,3R</i>)- <i>cis</i> - 373 (%)	Enantiomeric excess of (<i>2R,3R</i>)- <i>cis</i> - 373 (%)
(<i>S</i>)- 248	87	67	96	93
(<i>S</i>)- 359	46	16	17	14

Table 7.1 Asymmetric aziridination reactions catalysed by (*S*)-*N*-triflyl BINOL-derived phosphoramidate ((*S*)-**248**) and (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-**359**).

Low yields of the aziridination reactions using (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-**359**) may arise due to a possibly lower reactivity of (*S*)-**359** under the reaction conditions previously described because the bulk of the starting materials used was still present in the reaction mixtures (based on the ¹H-NMR spectral data) after the designated reaction time. Furthermore (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-**359**) provided lower asymmetric inductions (16% and 14% *e.e.*) for the addition of *t*-butyl α -diazoacetate (**247**) to *N*-aryl imines **370** and **371** respectively. This could be due to a less well defined chiral pocket of (*S*)-**359** in comparison to (*S*)-**248**, which resulted in a decreased enantioselectivity of *N*-aryl-*cis*-aziridine-2-carboxylates, (*2R,3S*)-*cis*-**372** and (*2R,3R*)-*cis*-**373**.

7.2. Experimental

General methods

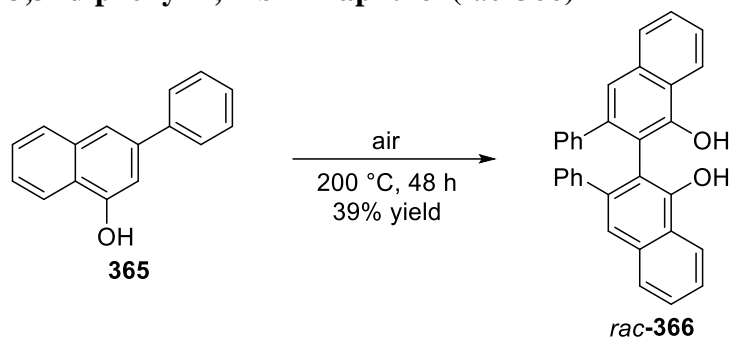
All reactions described as being carried out under a nitrogen atmosphere were always performed in flame-dried glassware, which was allowed to cool under an inert atmosphere. For those reactions not carried out under nitrogen atmosphere ordinary glassware was used without special precautions for drying. All reactions were stirred using a magnetic stirrer plate and a stirrer bar. Reactions carried out at 0 °C were cooled using a water and ice bath and those at -10 °C using an ice and salt bath. Petroleum ether refers to the fraction that boils in the range 40 – 60 °C. Toluene was freshly distilled over sodium under an argon atmosphere. Dichloromethane, ethanol, propionitrile, and triethylamine were freshly distilled over calcium hydride under an argon atmosphere. All other commercially available reagents were used as supplied unless otherwise specified. Column chromatography was carried out on Fluka silica gel (pore size 60 Å, 70 – 230 mesh). TLC was performed on Merck plates (aluminium coated with 0.2 mm silica gel 60 F₂₅₄). NMR solvent (CDCl₃) was dried over type 4 Å molecular sieves and further filtered through basic aluminium oxide prior to use.

Aziridination reactions were performed in a flame-dried Biotage microwave vials, equipped with PTFE coated magnetic stirrer bars, which were allowed to cool under an inert atmosphere employing standard Schlenk-line technique. To ensure an air-free atmosphere of the reaction, the vials were subjected to three purge-and-refill cycles. Each cycle was accomplished by evacuation of the air from the vials under vacuum, followed by an introduction of an inert gas into the vials. To avoid any fluctuations in the temperatures of reactions and to ensure the reactions were performed at a constant temperature of $-60\text{ }^{\circ}\text{C}$, a chiller was employed in the experiments and a cooling bath was prepared. The chiller was a Julabo FT902 Immersion Cooler equipped with a setpoint control, an external Pt100 sensor, an insulated flexible hose and exposed rigid cold-finger probe. The probe was shaped into a spiral leaving the central area empty. It was further placed into a dish-shaped stainless steel and glass Dewar vessel filled with isopropyl alcohol and containing magnetic stirrer bar. A thermometer was situated in the Dewar vessel in order to establish a correlation between the temperature of the cooling bath and the temperature set on the chiller. If any differences occurred the required temperature of the cooling bath was established by adjustment of the temperature on the chiller. Thus prepared cooling bath was placed on a magnetic stirrer plate and used in aziridination reactions.

Characterisation

^1H - and ^{13}C -NMR spectra were recorded on Varian Gemini 300 MHz and 400 MHz, Bruker UltraShield 400 MHz and Bruker Ascend 500 MHz spectrometers at the field strength indicated and deuterated solvents were used as specified. Chemical shifts (δ) are reported in parts per million (ppm) and referenced to the residual solvent signal for ^1H -NMR ($\text{CDCl}_3 = 7.26\text{ ppm}$, $\text{DMSO} = 2.50\text{ ppm}$) and ^{13}C -NMR ($\text{CDCl}_3 = 77.16\text{ ppm}$, $\text{DMSO} = 39.52\text{ ppm}$). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (reported in Hertz), and integration. FT-IR spectra were recorded on a Perkin-Elmer Spectrum 100 spectrometer. Ion mass/charge (m/z) ratios are reported as values in atomic mass units and were determined on Shimadzu LCMS and Axima-CFR MALDI-TOF instruments. HRMS was carried out by EPSRC National Mass Spectrometry Service Centre at the Swansea University, Wales. Optical rotation values were measured on a Perkin-Elmer 241 polarimeter. HPLC analyses were performed on PerkinElmer Series 200, Hewlett-Packard 1100 Series and VWR-Hitachi LaChrom Elite[®] systems.

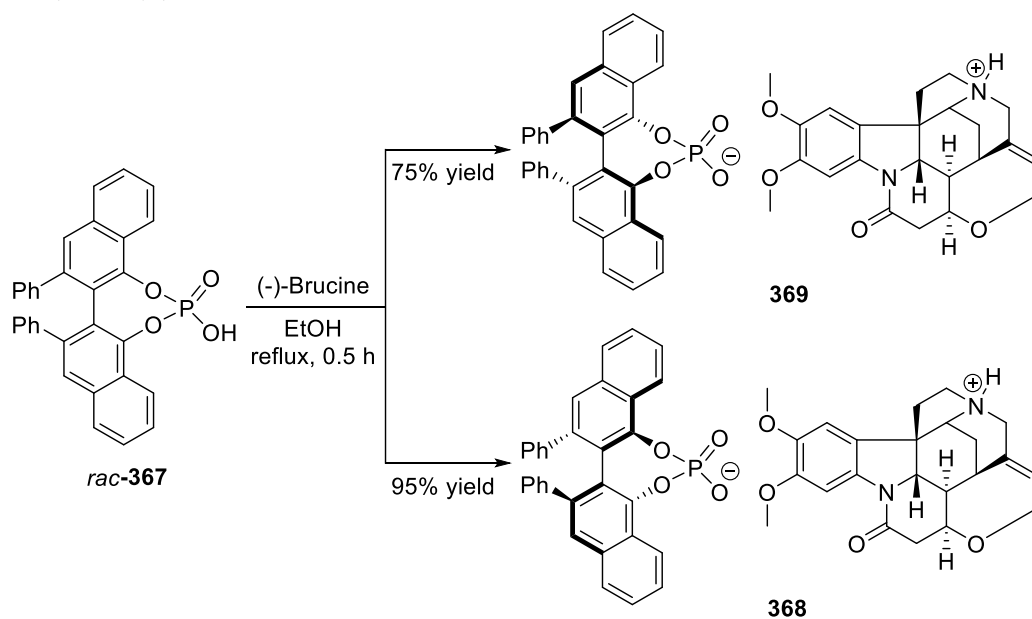
Synthesis of *rac*-3,3'-diphenyl-2,2'-bi-1-naphthol (*rac*-366)⁹



3-Phenylnaphthalen-1-ol (**365**) (1.0 g, 4.50 mmol) was stirred in Carousel 150 mm × 24 mm Ø glass reaction tube at 200 °C under an air atmosphere for 48 hours. The reaction mixture was purified by flash column chromatography on silica gel (diethyl ether / petroleum ether 1 : 9) affording *rac*-**366** as a pale yellow solid (0.39 g, 1.0 mmol, 39% yield). A sample was submitted for chiral analytical HPLC analysis (Eurocel[®] 01, 5µm 250 × 46 mm ID, *iso*-hexane / isopropyl alcohol 95.5 : 4.5, 0.5 mL / min, 14.77 (1st peak), 29.76 (2nd peak)).

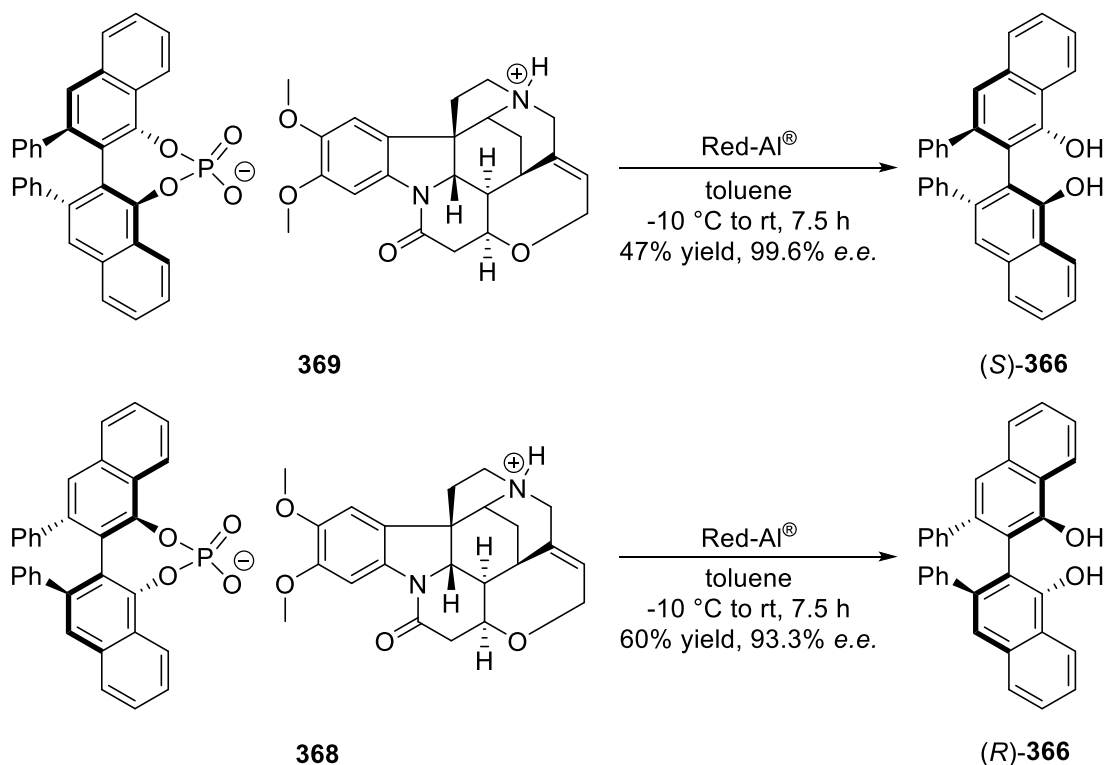
R_f = 0.33 (diethyl ether / *n*-hexane 2 : 8); ¹H-NMR (CDCl₃, 300 MHz) δ 8.44 – 8.30 (m, 2H, H_{Ar}), 7.84 – 7.76 (m, 2H, H_{Ar}), 7.63 – 7.51 (m, 4H, H_{Ar}), 7.34 (s, 2H, H_{Ar}), 7.09 (t, J = 7.4 Hz, 2H, H_{Ar}), 6.98 (t, J = 7.4 Hz, 4H, H_{Ar}), 6.65 (d, J = 7.1 Hz, 4H, H_{Ar}), 5.86 (s, 2H, OH) ppm; ¹³C-NMR (CDCl₃, 100 MHz) δ 150.5, 140.8, 140.3, 134.7, 129.0, 127.8, 127.7, 127.6, 126.7, 125.8, 123.0, 122.9, 122.2, 112.8 ppm. The physicochemical analysis data corresponded closely to those reported in the literature by Bao *et al.*⁹

Synthesis of salts **368**, **369** from *rac*-3,3'-diphenyl-2,2'-bi-1-naphthylphosphoric acid (*rac*-367) and (-)-brucine⁹



A solution of (\pm)-3,3'-diphenyl-2,2'-bi-1-naphthylphosphoric acid (*rac*-**367**) (0.4 g, 0.80 mmol) in anhydrous ethanol (15 mL) was stirred in a 25 mL round-bottom flask equipped with a condenser at room temperature under a nitrogen atmosphere. (–)-Brucine (0.34 g, 0.80 mmol) was added and the reaction mixture heated at reflux for 30 minutes under a nitrogen atmosphere. After cooling to room temperature, the precipitate was collected by filtration, redissolved in ethanol (7.5 mL) and heated at reflux for a further 5 minutes. After cooling to room temperature, the precipitate was collected by filtration affording **369** as a white solid (0.26 g, 0.30 mmol, 75% yield; calculated on the maximum of 50% per diastereoisomer in a resolution). The filtrates (mother liquors) were combined and the ethanol evaporated *in vacuo* affording **368** as a pale yellow solid (0.34 g, 0.40 mmol, 95% yield; calculated on the maximum of 50% per diastereoisomer in a resolution). Thus prepared salts were used in the next step.

Synthesis of (S)- and (R)-3,3'-diphenyl-2,2'-bi-1-naphthol ((S)-366, (R)-366) from the (–)-brucine salts 369, 368 by cleavage with Red-Al[®]



A suspension of salt (**369**) (0.26 g, 0.30 mmol) in anhydrous toluene (4 mL) was stirred in a 10 mL round-bottom flask at -10 °C under a nitrogen atmosphere. Sodium bis(2-methoxyethoxy)aluminium hydride (0.5 mL, 0.35 g, 1.70 mmol, 3.5 M solution in toluene) was added dropwise *via* syringe, the reaction mixture stirred at 0 °C under a nitrogen atmosphere for 1.5 hours and allowed to warm to room temperature and stirred for a further 6 hours. The reaction mixture was acidified to pH \approx 2 by addition of 2 M

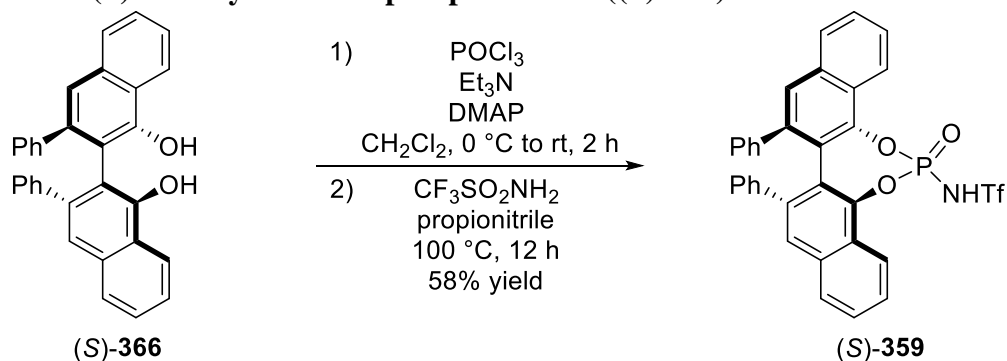
aqueous hydrochloric acid solution and transferred to a separating funnel. The organic components were extracted with ethyl acetate (3×10 mL) and the combined organic layers washed with saturated aqueous sodium chloride solution (2×30 mL), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. Purification by flash column chromatography on silica gel (ethyl acetate / petroleum ether 1: 9) afforded (S)-**366** as a white solid (0.06 g, 0.10 mmol, 47% yield). A sample was submitted for chiral analytical HPLC analysis (Eurocel[®] 01, 5 μ m 250 \times 4.6 mm ID, *iso*-hexane / isopropyl alcohol 95.5 : 4.5, 0.5 mL / min, 14.66 (1st peak), 30.08 (2nd peak), 99.6% *e.e.*).

$R_f = 0.36$ (silica gel, ethyl acetate / *n*-hexane 1 : 9); ¹H-NMR (CDCl₃, 400 MHz) δ 8.39 – 8.34 (m, 2H, H_{Ar}), 7.82 – 7.78 (m, 2H, H_{Ar}), 7.60 – 7.55 (m, 4H, H_{Ar}), 7.33 (s, 2H, H_{Ar}), 7.11 – 7.05 (m, 2H, H_{Ar}), 7.00 – 6.95 (m, 4H, H_{Ar}), 6.66 – 6.62 (m, 4H, H_{Ar}), 5.85 (s, 2H, OH) ppm. The physicochemical analysis data corresponded closely to those reported in the literature by Bao *et al.*⁹

Salt (**368**) (0.34 g, 0.40 mmol) was treated with sodium bis(2-methoxyethoxy)aluminium hydride (0.65 mL, 0.46 g, 2.30 mmol, 3.5 M solution in toluene) according to the procedure described above affording (R)-**366** as a pale yellow solid (0.1 g, 0.20 mmol, 60% yield) with the following physicochemical characteristics. A sample was submitted for chiral analytical HPLC analysis (Eurocel[®] 01, 5 μ m 250 \times 4.6 mm ID, *iso*-hexane / isopropyl alcohol 95.5 : 4.5, 0.5 mL / min, 14.55 (1st peak), 30.24 (2nd peak), 93.3% *e.e.*).

$R_f = 0.36$ (silica gel, ethyl acetate / *n*-hexane 1 : 9); ¹H-NMR (CDCl₃, 400 MHz) δ 8.40 – 8.33 (m, 2H, H_{Ar}), 7.81 – 7.78 (m, 2H, H_{Ar}), 7.61 – 7.55 (m, 4H, H_{Ar}), 7.33 (s, 2H, H_{Ar}), 7.11 – 7.04 (m, 2H, H_{Ar}), 7.00 – 6.93 (m, 4H, H_{Ar}), 6.66 – 6.62 (m, 4H, H_{Ar}), 5.85 (s, 2H, OH) ppm. The physicochemical analysis data corresponded closely to those reported in the literature by Bao *et al.*⁹

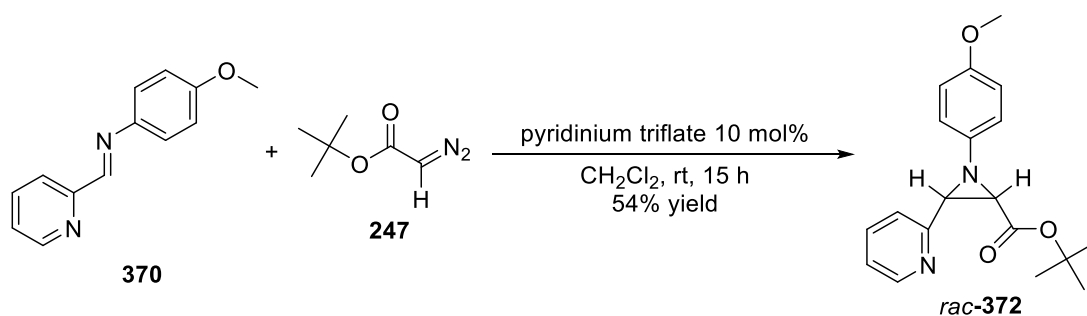
Synthesis of (S)-N-triflyl VANOL phosphoramidate ((S)-**359**)²



A solution of (S)-3,3'-diphenyl-2,2'-bi-1-naphthol ((S)-**366**) (0.06 g, 0.10 mmol) in anhydrous dichloromethane (1 mL) was stirred in a 10 mL round-bottom flask equipped with a condenser at 0 °C under a nitrogen atmosphere. Triethylamine (0.14 mL, 0.1 g, 1.0 mmol), phosphorus oxychloride (0.016 mL, 0.03 g, 0.20 mmol) and a solution of 4-dimethylaminopyridine (0.03 g, 0.30 mmol) in anhydrous dichloromethane (0.5 mL) were successively added dropwise *via* syringe, the reaction mixture allowed to warm to room temperature and stirred for 2 hours under a nitrogen atmosphere. Anhydrous propionitrile (1.5 mL) and trifluoromethanesulfonamide (0.04 g, 0.30 mmol) were added and the reaction mixture heated at 100 °C for 12 hours under a nitrogen atmosphere. After cooling to room temperature, water (4 mL) was added, the mixture transferred to a separating funnel and the organic components extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (12 mL) and 4 M aqueous hydrochloric acid solution (2 × 12 mL), dried over magnesium sulfate, filtered through a plug of Celite[®] and the solvent evaporated *in vacuo*. Purification by flash column chromatography on a mixture of silica gel and Celite[®] 1 : 1 (1st column: ethyl acetate 100%; 2nd column: ethyl acetate / petroleum ether 1 : 1) and precipitation with *n*-pentane from a minimum amount of dichloromethane afforded (S)-**359** as a white solid (0.05 g, 0.10 mmol, 58% yield) with the following physicochemical characteristics.

$R_f = 0.29$ (ethyl acetate / *n*-hexane 1 : 1); $[\alpha]_D^{18} +157.00$ (*c* 1.0, CH₂Cl₂); ¹H-NMR (DMSO-*d*₆, 300 MHz) δ 8.40 – 8.31 (m, 1H, *H*_{Ar}), 8.27 (d, *J* = 7.5 Hz, 1H, *H*_{Ar}), 8.01 – 7.96 (m, 2H, *H*_{Ar}), 7.76 – 7.60 (m, 4H, *H*_{Ar}), 7.57 (d, *J* = 5.2 Hz, 2H, *H*_{Ar}), 7.13 (t, *J* = 6.8 Hz, 2H, *H*_{Ar}), 6.97 (t, *J* = 7.0 Hz, 4H, *H*_{Ar}), 6.44 – 6.34 (m, 4H, *H*_{Ar}) ppm; HRMS (NSI) Calculated for C₃₃H₂₅F₃N₂O₅PS [M+NH₄] 649,1168, found 649.1166. The physicochemical analysis data corresponded closely to those reported in the literature by Desai and Wulff.²

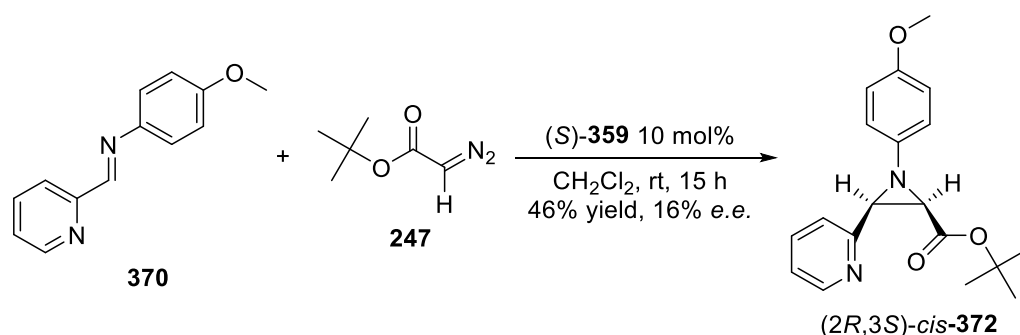
Synthesis of *rac*-*t*-butyl 1-(4-methoxyphenyl)-3-(pyridin-2-yl)aziridine-2-carboxylate (*rac*-**372**)¹¹



A solution of (*E*)-4-methoxy-*N*-(pyridin-2-ylmethylene)aniline (**370**) (0.06 g, 0.30 mmol) and pyridinium triflate (0.01 g, 0.03 mmol) was stirred in anhydrous dichloromethane (1 mL) in a Biotage 2 mL microwave vial sealed with a PTFE crimp cap at room temperature under a nitrogen atmosphere. *t*-Butyl α -diazoacetate (**247**) (0.04 mL, 0.04 g, 0.30 mmol) was added *via* syringe and the reaction mixture stirred at room temperature under a nitrogen atmosphere for 15 hours. The solvent was evaporated *in vacuo*. Purification by flash column chromatography on silica gel (diethyl ether 100%) afforded *rac*-**372** as a yellow oil (0.05g, 0.20 mmol, 54% yield). A sample was submitted for chiral analytical HPLC analysis (Eurocel[®] 01, 250 \times 4.6 mm ID, *iso*-hexane / isopropyl alcohol 95 : 5, 1 mL / min, 11.20 (1st peak), 14.02 (2nd peak)).

R_f = 0.61 (silica gel, diethyl ether 100%); FT-IR (thin film) 2979, 2934, 1742 (C=O), 1591, 1508, 1367, 1242, 1153, 1037, 831 cm^{-1} ; ¹H-NMR (CDCl₃, 500 MHz) δ 8.55 – 8.54 (m, 1H, H_{Ar}), 7.70 – 7.64 (m, 2H, H_{Ar}), 7.21 – 7.18 (m, 1H, H_{Ar}), 6.99 (d, J = 9.0 Hz, 2H, H_{Ar}), 6.81 (d, J = 8.9 Hz, 2H, H_{Ar}), 3.76 (s, 3H, CH₃O), 3.62 (d, J = 6.9 Hz, 1H, CH-CH), 3.11 (d, J = 6.9 Hz, 1H, CH-CH), 1.23 (s, 9H, (CH₃)₃C) ppm; ¹³C-NMR (CDCl₃, 125 MHz) δ 166.7 (C=O), 156.0, 155.5, 149.0, 145.6, 136.2, 122.8, 122.7, 121.0, 114.5, 81.8 ((CH₃)₃C), 55.7 (CH₃O), 48.3 (HC-CH), 46.4 (HC-CH), 27.9 ((CH₃)₃C) ppm; MALDI-TOF-MS m/z 326.2 [M]; HRMS (NSI) Calculated for C₁₉H₂₃N₂O₃ [M+H] 327.1703, found 327.1708.

Synthesis of (2*R*,3*S*)-*cis*-*t*-butyl 1-(4-methoxyphenyl)-3-(pyridin-2-yl)aziridine-2-carboxylate ((2*R*,3*S*)-*cis*-**372**)⁷

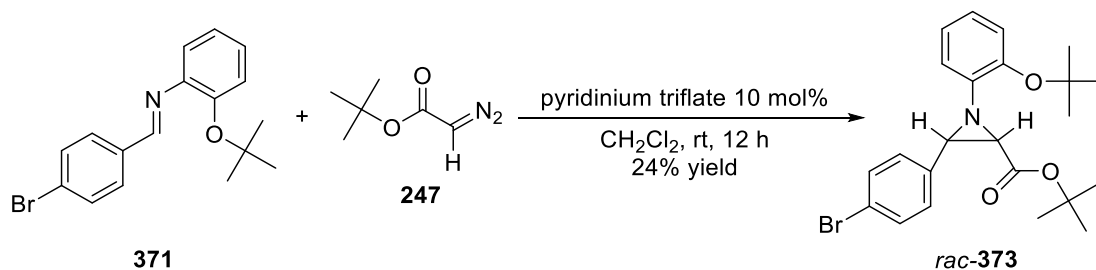


(*E*)-4-Methoxy-*N*-(pyridin-2-ylmethylene)aniline (**370**) (0.03 g, 0.10 mmol) and (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-**359**) (0.01 g, 0.01 mmol) were combined and stirred in anhydrous dichloromethane (0.5 mL) in a Biotage 2 mL microwave vial sealed with a PTFE crimp cap at room temperature under a nitrogen atmosphere. *t*-Butyl α -diazoacetate (**247**) (0.02 mL, 0.02 g, 0.20 mmol) was added *via* syringe and the reaction mixture stirred at room temperature under a nitrogen atmosphere for 15 hours. The solvent

was evaporated *in vacuo*. Purification by flash column chromatography on silica gel (diethyl ether 100%) afforded (2*R*,3*S*)-*cis*-**372** as a yellow oil (0.02g, 0.10 mmol, 46% yield). A sample was submitted for chiral analytical HPLC analysis (Eurocel[®] 01, 250 × 4.6 mm ID, *iso*-hexane / isopropyl alcohol 95 : 5, 1 mL / min, 11.13 (1st peak), 13.99 (2nd peak), 16% *e.e.*).

$R_f = 0.61$ (silica gel, diethyl ether 100%); $[\alpha]_D^{19} +5.40$ (c 1.0, CHCl_3); FT-IR (thin film) 2979, 2934, 1742 (C=O), 1591, 1509, 1368, 1242, 1154, 1037, 831 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 8.56 – 8.54 (m, 1H, H_{Ar}), 7.71 – 7.65 (m, 2H, H_{Ar}), 7.22 – 7.19 (m, 1H, H_{Ar}), 7.00 (d, $J = 8.9$ Hz, 2H, H_{Ar}), 6.81 (d, $J = 8.9$ Hz, 2H, H_{Ar}), 3.77 (s, 3H, CH_3O), 3.63 (d, $J = 6.9$ Hz, 1H, CH-CH), 3.12 (d, $J = 6.9$ Hz, 1H, CH-CH), 1.23 (s, 9H, $(\text{CH}_3)_3\text{C}$) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ 166.7 (C=O), 156.0, 155.4, 148.9, 145.6, 136.3, 122.8, 122.7, 121.0, 114.5, 81.8 ($(\text{CH}_3)_3\text{C}$), 55.7 (CH_3O), 48.3 (HC-CH), 46.4 (HC-CH), 27.9 ($(\text{CH}_3)_3\text{C}$) ppm; MALDI-TOF-MS m/z 349.0 [$\text{M}+\text{Na}$]; HRMS (NSI) Calculated for $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] 327.1703, found 327.1709.

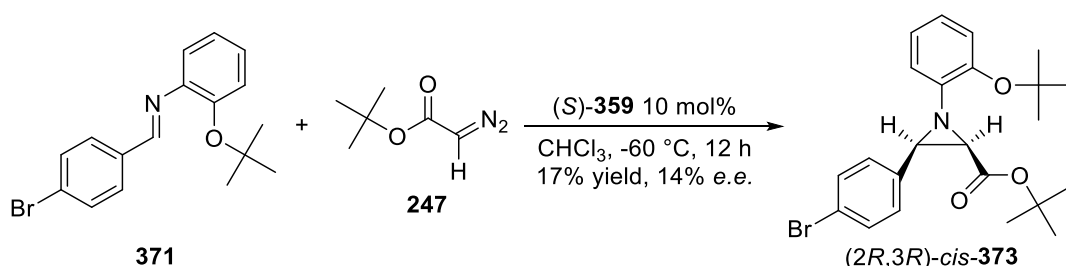
Synthesis of *rac-t*-butyl 3-(4-bromophenyl)-1-(2-(*t*-butoxy)phenyl)aziridine-2-carboxylate (*rac*-**373**)¹¹



A solution of (*E*)-*N*-(4-bromobenzylidene)-2-(*t*-butoxy)aniline (**371**) (0.07 g, 0.20 mmol) and pyridinium triflate (0.005 g, 0.02 mmol) was stirred in anhydrous dichloromethane (0.85 mL) in a Biotage 2 mL microwave vial sealed with a PTFE crimp cap at room temperature under a nitrogen atmosphere. *t*-Butyl α -diazoacetate (**247**) (0.04 mL, 0.03 g, 0.20 mmol) was added *via* syringe and the reaction mixture stirred at room temperature under a nitrogen atmosphere for 12 hours. The solvent was evaporated *in vacuo*. Purification by flash column chromatography on silica gel (diethyl ether / petroleum ether 1.5 : 8.5) afforded *rac*-**373** as a pale yellow oil (0.02 g, 0.10 mmol, 24% yield). A sample was submitted for chiral analytical HPLC analysis (Chiralpak[®] AD, 250 × 4.6 mm ID, *iso*-hexane / isopropyl alcohol 95 : 5, 1 mL / min, 4.49 (1st peak), 7.32 (2nd peak)).

$R_f = 0.51$ (silica gel, diethyl ether / petroleum ether 1.5 : 8.5); $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 7.47 – 7.44 (m, 2H, H_{Ar}), 7.42 – 7.39 (m, 2H, H_{Ar}), 7.04 – 6.99 (m, 1H, H_{Ar}), 6.97 – 6.93 (m, 3H, H_{Ar}), 3.42 (d, $J = 6.7$ Hz, 1H, CH-CH), 3.04 (d, $J = 6.7$ Hz, 1H, CH-CH), 1.36 (s, 9H, $(\text{CH}_3)_3\text{CO}$), 1.23 (s, 9H, $(\text{CH}_3)_3\text{COC=O}$) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz) δ 166.9 (C=O), 148.1, 146.3, 134.6, 131.0, 129.9, 123.3, 123.22, 123.20, 121.5, 121.0, 81.6 ($(\text{CH}_3)_3\text{CO}$), 80.5 ($(\text{CH}_3)_3\text{COC=O}$), 47.5 (HC-CH), 47.0 (HC-CH), 28.8 ($(\text{CH}_3)_3\text{COC=O}$), 28.0 ($(\text{CH}_3)_3\text{CO}$) ppm. The physicochemical analysis data corresponded closely to those reported in the literature by Bew *et al.*¹¹

Synthesis of (2R,3R)-cis-t-butyl 3-(4-bromophenyl)-1-(2-(t-butoxy)phenyl)aziridine-2-carboxylate ((2R,3R)-cis-373)⁷



(*E*)-*N*-(4-Bromobenzylidene)-2-(*t*-butoxy)aniline (**371**) (0.09 g, 0.30 mmol) and (*S*)-*N*-triflyl VANOL phosphoramidate ((*S*)-**359**) (0.002 g, 0.003 mmol) were combined and stirred in anhydrous chloroform (1 mL) in a Biotage 2 mL microwave vial sealed with a PTFE crimp cap at -60°C under a nitrogen atmosphere. *t*-Butyl α -diazoacetate (**247**) (0.04 mL, 0.40 g, 0.30 mmol) was added *via* syringe and the reaction mixture stirred at -60°C under a nitrogen atmosphere for 12 hours. After warming to room temperature, the solvent was evaporated *in vacuo*. Purification by flash column chromatography on silica gel (diethyl ether / petroleum ether 1.5 : 8.5) afforded (2*R*,3*R*)-*cis*-**373** as a pale yellow oil (0.02 g, 0.10 mmol, 17% yield). A sample was submitted for chiral analytical HPLC analysis (Chiralpak[®] AD, 250 \times 4.6 mm ID, *iso*-hexane / isopropyl alcohol 95 : 5, 1 mL / min, 4.47 (1st peak), 7.30 (2nd peak), 14% *e.e.*).

$R_f = 0.51$ (silica gel, diethyl ether / petroleum ether 1.5 : 8.5); $[\alpha]_D^{19} +6.50$ (c 1.0, CHCl_3); FT-IR (thin film) 2978, 2933, 1746 (C=O), 1594, 1489, 1367, 1262, 1163, 1012, 843, 752 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 7.47 – 7.44 (m, 2H, H_{Ar}), 7.43 – 7.39 (m, 2H, H_{Ar}), 7.04 – 7.00 (m, 1H, H_{Ar}), 6.97 – 6.92 (m, 3H, H_{Ar}), 3.42 (d, $J = 6.7$ Hz, 1H, CH-CH), 3.04 (d, $J = 6.7$ Hz, 1H, CH-CH), 1.36 (s, 9H, $(\text{CH}_3)_3\text{CO}$), 1.23 (s, 9H, $(\text{CH}_3)_3\text{COC=O}$) ppm; $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz) δ 166.9 (C=O), 148.1, 146.3, 134.6, 131.0, 129.9, 123.3, 123.22, 123.20, 121.5, 121.0, 81.6 ($(\text{CH}_3)_3\text{CO}$), 80.5 ($(\text{CH}_3)_3\text{COC=O}$), 47.5

(HC-CH), 47.0 (HC-CH), 28.8 ((CH₃)₃COC=O), 28.0 ((CH₃)₃CO) ppm; MALDI-TOF-MS *m/z* 483.9 [M+K]; HRMS (NSI) Calculated for C₂₃H₂₉BrNO₃ [M+H] 446.1325, found 446.1326.

7.3. References

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Appendix

Crystal structure data for compound 161

Table 1. Crystal data and structure refinement details.

Identification code	2012ncs0654 (DB 599)	
Empirical formula	C ₂₄ H ₂₀ N ₆ O ₄	
Formula weight	456.46	
Temperature	100(2) K	
Wavelength	0.71075 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	$a = 14.262(8)$ Å	$\alpha = 90^\circ$
	$b = 10.345(5)$ Å	$\beta = 115.13(4)^\circ$
	$c = 16.499(7)$ Å	$\gamma = 90^\circ$
Volume	2203.8(19) Å ³	
Z	4	
Density (calculated)	1.376 Mg / m ³	
Absorption coefficient	0.097 mm ⁻¹	
$F(000)$	952	
Crystal	Fragment; yellow	
Crystal size	0.26 × 0.14 × 0.04 mm ³	
θ range for data collection	2.73 – 27.51°	
Index ranges	-17 ≤ h ≤ 18, -12 ≤ k ≤ 13, -21 ≤ l ≤ 21	
Reflections collected	7385	
Independent reflections	4175 [$R_{int} = 0.0155$]	
Completeness to $\theta = 27.51^\circ$	98.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9961 and 0.9751	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4175 / 1 / 309	
Goodness-of-fit on F^2	1.030	
Final R indices [$F^2 > 2\sigma(F^2)$]	$RI = 0.0324$, $wR2 = 0.0797$	
R indices (all data)	$RI = 0.0338$, $wR2 = 0.0806$	
Largest diff. peak and hole	0.197 and -0.168 e Å ⁻³	

Diffractometer: Rigaku AFC12 goniometer equipped with an enhanced sensitivity (HG) Saturn724+ detector mounted at the window of an FR-E+ SuperBright molybdenum rotating anode generator with VHF Varimax optics (70µm focus). **Cell determination and data collection:** CrystalClear-SM Expert 2.0 r11 (Rigaku, 2011). **Data reduction, cell refinement and absorption correction:** CrystalClear-SM Expert 2.0 r13 (Rigaku, 2011). **Structure solution:** SHELXS97 (Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122). **Structure refinement:** SHELXL97 (Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122).

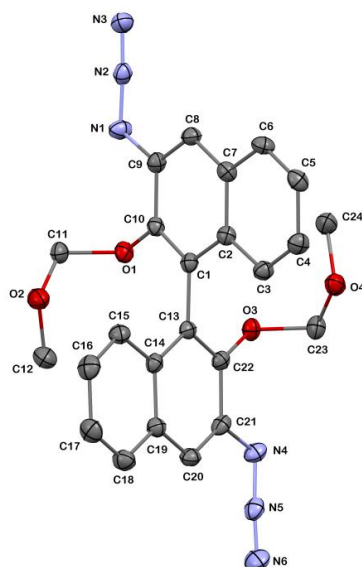


Figure 1. Crystal structures of **161**; hydrogen atoms have been omitted for clarity.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$\text{\AA}^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalised U^{ij} tensor.

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}	<i>S.o.f.</i>
C1	591(1)	-142(1)	2344(1)	17(1)	1
C2	-361(1)	-819(1)	2129(1)	18(1)	1
C3	-1134(1)	-346(2)	2381(1)	21(1)	1
C4	-2035(1)	-1009(2)	2174(1)	23(1)	1
C5	-2213(1)	-2193(2)	1706(1)	23(1)	1
C6	-1487(1)	-2672(2)	1447(1)	22(1)	1
C7	-552(1)	-2001(2)	1645(1)	19(1)	1
C8	201(1)	-2470(1)	1373(1)	20(1)	1
C9	1104(1)	-1804(2)	1568(1)	20(1)	1
C10	1299(1)	-626(1)	2060(1)	17(1)	1
C11	3143(1)	-408(2)	2842(1)	23(1)	1
C12	3518(1)	1214(2)	3941(1)	30(1)	1
C13	786(1)	1065(1)	2886(1)	17(1)	1
C14	1061(1)	962(2)	3828(1)	18(1)	1
C15	1221(1)	-252(2)	4271(1)	22(1)	1
C16	1466(1)	-314(2)	5170(1)	27(1)	1
C17	1573(1)	819(2)	5670(1)	28(1)	1
C18	1431(1)	2002(2)	5268(1)	26(1)	1
C19	1172(1)	2102(2)	4340(1)	20(1)	1
C20	1025(1)	3318(2)	3915(1)	21(1)	1
C21	780(1)	3411(1)	3019(1)	20(1)	1
C22	642(1)	2269(1)	2494(1)	18(1)	1
C23	-632(1)	2749(2)	1017(1)	24(1)	1
C24	-1168(1)	781(2)	228(1)	29(1)	1
N1	1892(1)	-2206(1)	1302(1)	24(1)	1

N2	1685(1)	-3241(1)	870(1)	21(1)	1
N3	1562(1)	-4168(1)	475(1)	27(1)	1
N4	645(1)	4612(1)	2552(1)	24(1)	1
N5	769(1)	5578(1)	3042(1)	24(1)	1
N6	853(1)	6515(1)	3424(1)	34(1)	1
O1	2177(1)	82(1)	2195(1)	20(1)	1
O2	3311(1)	-123(1)	3716(1)	27(1)	1
O3	417(1)	2393(1)	1594(1)	21(1)	1
O4	-1310(1)	1709(1)	809(1)	25(1)	1

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

C1-C10	1.375(2)
C1-C2	1.432(2)
C1-C13	1.491(2)
C2-C3	1.420(2)
C2-C7	1.422(2)
C3-C4	1.366(2)
C3-H3	0.9500
C4-C5	1.413(2)
C4-H4	0.9500
C5-C6	1.371(2)
C5-H5	0.9500
C6-C7	1.413(2)
C6-H6	0.9500
C7-C8	1.416(2)
C8-C9	1.373(2)
C8-H8	0.9500
C9-C10	1.425(2)
C9-N1	1.430(2)
C10-O1	1.3852(19)
C11-O2	1.3903(18)
C11-O1	1.4300(19)
C11-H11A	0.9900
C11-H11B	0.9900
C12-O2	1.430(2)
C12-H12A	0.9800
C12-H12B	0.9800
C12-H12C	0.9800
C13-C22	1.378(2)
C13-C14	1.435(2)
C14-C19	1.420(2)
C14-C15	1.423(2)
C15-C16	1.373(2)

C15–H15	0.9500
C16–C17	1.404(2)
C16–H16	0.9500
C17–C18	1.365(2)
C17–H17	0.9500
C18–C19	1.419(2)
C18–H18	0.9500
C19–C20	1.412(2)
C20–C21	1.370(2)
C20–H20	0.9500
C21–C22	1.429(2)
C21–N4	1.4308(19)
C22–O3	1.3845(17)
C23–O4	1.389(2)
C23–O3	1.4398(19)
C23–H23A	0.9900
C23–H23B	0.9900
C24–O4	1.431(2)
C24–H24A	0.9800
C24–H24B	0.9800
C24–H24C	0.9800
N1–N2	1.2500(19)
N2–N3	1.1304(19)
N4–N5	1.2499(19)
N5–N6	1.1346(19)
C10–C1–C2	119.55(13)
C10–C1–C13	122.16(13)
C2–C1–C13	118.29(12)
C3–C2–C7	118.24(13)
C3–C2–C1	122.05(14)
C7–C2–C1	119.71(13)
C4–C3–C2	121.23(15)
C4–C3–H3	119.4
C2–C3–H3	119.4
C3–C4–C5	120.28(14)
C3–C4–H4	119.9
C5–C4–H4	119.9
C6–C5–C4	119.97(14)
C6–C5–H5	120.0
C4–C5–H5	120.0
C5–C6–C7	120.93(14)
C5–C6–H6	119.5
C7–C6–H6	119.5

C6-C7-C8	121.79(14)
C6-C7-C2	119.33(13)
C8-C7-C2	118.87(13)
C9-C8-C7	121.06(14)
C9-C8-H8	119.5
C7-C8-H8	119.5
C8-C9-C10	119.98(13)
C8-C9-N1	124.20(14)
C10-C9-N1	115.82(13)
C1-C10-O1	119.82(13)
C1-C10-C9	120.81(13)
O1-C10-C9	119.20(13)
O2-C11-O1	112.67(12)
O2-C11-H11A	109.1
O1-C11-H11A	109.1
O2-C11-H11B	109.1
O1-C11-H11B	109.1
H11A-C11-H11B	107.8
O2-C12-H12A	109.5
O2-C12-H12B	109.5
H12A-C12-H12B	109.5
O2-C12-H12C	109.5
H12A-C12-H12C	109.5
H12B-C12-H12C	109.5
C22-C13-C14	119.56(13)
C22-C13-C1	121.41(12)
C14-C13-C1	118.90(12)
C19-C14-C15	118.34(12)
C19-C14-C13	119.52(13)
C15-C14-C13	122.14(13)
C16-C15-C14	120.53(14)
C16-C15-H15	119.7
C14-C15-H15	119.7
C15-C16-C17	120.70(15)
C15-C16-H16	119.7
C17-C16-H16	119.7
C18-C17-C16	120.41(13)
C18-C17-H17	119.8
C16-C17-H17	119.8
C17-C18-C19	120.44(15)
C17-C18-H18	119.8
C19-C18-H18	119.8
C20-C19-C18	121.16(14)

C20–C19–C14	119.26(12)
C18–C19–C14	119.58(14)
C21–C20–C19	120.97(13)
C21–C20–H20	119.5
C19–C20–H20	119.5
C20–C21–C22	120.17(13)
C20–C21–N4	123.77(13)
C22–C21–N4	116.06(13)
C13–C22–O3	120.54(12)
C13–C22–C21	120.49(12)
O3–C22–C21	118.87(13)
O4–C23–O3	112.57(13)
O4–C23–H23A	109.1
O3–C23–H23A	109.1
O4–C23–H23B	109.1
O3–C23–H23B	109.1
H23A–C23–H23B	107.8
O4–C24–H24A	109.5
O4–C24–H24B	109.5
H24A–C24–H24B	109.5
O4–C24–H24C	109.5
H24A–C24–H24C	109.5
H24B–C24–H24C	109.5
N2–N1–C9	113.52(13)
N3–N2–N1	175.26(15)
N5–N4–C21	113.38(12)
N6–N5–N4	174.39(15)
C10–O1–C11	116.84(12)
C11–O2–C12	113.57(13)
C22–O3–C23	115.81(12)
C23–O4–C24	113.80(13)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$\text{\AA}^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	17(1)	16(1)	17(1)	3(1)	7(1)	0(1)
C2	17(1)	17(1)	19(1)	1(1)	8(1)	-1(1)
C3	21(1)	20(1)	23(1)	-1(1)	11(1)	0(1)
C4	21(1)	26(1)	25(1)	-2(1)	14(1)	-1(1)
C5	19(1)	26(1)	24(1)	-2(1)	9(1)	-7(1)
C6	24(1)	20(1)	22(1)	-5(1)	11(1)	-6(1)

C7	18(1)	21(1)	17(1)	0(1)	8(1)	-2(1)
C8	21(1)	17(1)	22(1)	-3(1)	10(1)	-1(1)
C9	18(1)	22(1)	19(1)	1(1)	9(1)	1(1)
C10	14(1)	17(1)	20(1)	1(1)	6(1)	-1(1)
C11	16(1)	24(1)	27(1)	-2(1)	7(1)	1(1)
C12	27(1)	28(1)	31(1)	-6(1)	7(1)	-3(1)
C13	13(1)	17(1)	22(1)	-2(1)	8(1)	-2(1)
C14	15(1)	18(1)	21(1)	1(1)	8(1)	0(1)
C15	23(1)	19(1)	24(1)	-1(1)	9(1)	-2(1)
C16	30(1)	23(1)	28(1)	7(1)	12(1)	1(1)
C17	32(1)	32(1)	20(1)	3(1)	11(1)	1(1)
C18	30(1)	26(1)	21(1)	-2(1)	11(1)	-1(1)
C19	18(1)	20(1)	22(1)	-1(1)	9(1)	-2(1)
C20	21(1)	18(1)	25(1)	-4(1)	10(1)	-3(1)
C21	18(1)	14(1)	29(1)	3(1)	12(1)	0(1)
C22	16(1)	18(1)	20(1)	0(1)	9(1)	0(1)
C23	20(1)	24(1)	25(1)	5(1)	8(1)	3(1)
C24	27(1)	33(1)	23(1)	-3(1)	8(1)	6(1)
N1	22(1)	24(1)	30(1)	-7(1)	15(1)	-3(1)
N2	17(1)	26(1)	22(1)	1(1)	9(1)	3(1)
N3	25(1)	28(1)	27(1)	-6(1)	11(1)	2(1)
N4	28(1)	16(1)	29(1)	1(1)	14(1)	0(1)
N5	22(1)	18(1)	30(1)	5(1)	10(1)	2(1)
N6	41(1)	18(1)	37(1)	1(1)	11(1)	2(1)
O1	15(1)	21(1)	25(1)	1(1)	9(1)	-3(1)
O2	29(1)	22(1)	25(1)	0(1)	7(1)	0(1)
O3	18(1)	25(1)	20(1)	3(1)	9(1)	2(1)
O4	20(1)	29(1)	25(1)	-3(1)	10(1)	-1(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$\text{\AA}^2 \times 10^3$].

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U_{eq}</i>	<i>S.o.f.</i>
H3	-1022	447	2699	25	1
H4	-2543	-672	2346	27	1
H5	-2836	-2658	1572	27	1
H6	-1614	-3466	1128	26	1
H8	80	-3259	1049	24	1
H11A	3157	-1358	2773	27	1
H11B	3713	-36	2724	27	1
H12A	4129	1481	3856	45	1
H12B	3646	1346	4567	45	1
H12C	2920	1732	3553	45	1
H15	1159	-1027	3943	27	1
H16	1563	-1132	5456	33	1

H17	1745	762	6292	33	1
H18	1506	2763	5613	31	1
H20	1098	4083	4255	25	1
H23A	-865	3428	1313	28	1
H23B	-652	3118	456	28	1
H24A	-1217	1213	-317	43	1
H24B	-1706	115	69	43	1
H24C	-485	378	533	43	1
