Atropisomeric Diaryl Ethers and other Non-Biaryl Atropisomers

A thesis submitted to the University of Manchester
for the degree of Doctor of Philosophy
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Abstract

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Atropisomerism is a property exhibited by molecules where rotation about one or more bonds is restricted. Along with biaryls, which are widely utilised in asymmetric catalysis, several other classes of compounds display atropisomerism. These molecules have applications in enantioselective synthesis, asymmetric catalysis and have been used to relay stereochemical information. There are, however, a number of challenges associated with their asymmetric synthesis (Chapter 1).

This thesis describes research carried out on the synthesis and asymmetric synthesis of atropisomeric diaryl ethers. Chapter 2.1 explains how these ethers are synthesised in multi-gram quantities and to allow the incorporation of large *ortho* substituents.

Having a number of diaryl ethers with suitable substitution patterns to achieve atropisomerism, Chapter 2.2 goes on to report two novel and complimentary biocatalytic approaches to the enantioselective synthesis of diaryl ethers by desymmetrisation. This chapter also describes a possible route towards the synthesis of a diaryl ether based ligand.

Chapter 2.3 reports the lateral lithiation of *meso* diaryl ethers to yield diastereomeric atropisomers stereoselectively. Our attempts to use (–)-sparteine in lateral lithiations to desymmetrise a diaryl ether enantioselectively is also described. We go on to determine the configurational integrity of our organolithiums and the reaction pathway that exists in lithium substitution.

Finally, the diastereoselective synthesis of both a diaryl ether (via a stereoselective reduction of a *pro*-chiral ketone) and a diaryl sulfide (via an addition reaction) is described in chapter 2.4. This chapter also reports the conformational behaviour of a diaryl amide in solution.

Declaration

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Abbreviations

°C	degrees Celsius
Å	Angstrom
ABTS	2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid
Ac	acetyl
aq.	aqueous
Ar	aryl
BINOL	Bi-2-naphthol
br	broad
Bu	butyl
BuLi	butyllithium
CAL-B	*Candida antarctica* lipase-B
$CDCl_3$	deuterated chloroform
CI	chemical ionisation
δ	chemical shift (parts per million)
d_6-DMSO	deuterated dimethylsulfoxide
d	doublet / day (s)
dd	doublet of doublets
ddd	doublet of doublet of doublets
DIBAL-H	di*iso*butylaluminiumhydride
DME	1,2-dimethoxy ethane
DMF	*N*,*N*-dimethylformamide
DMG	directed metalation groups
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
E	electrophile
ee	enantiomeric excess
EI	electron impact
ephedrine	(1*R*,2*S*)-(–)-ephedrine
equiv.	equivalent(s)
e.r.	enantiomeric ratio
ES	electrospray (positive ionisation)
Et	ethyl
Ether / Et_2O	diethyl ether

EtOAc	ethyl acetate
EtOH	ethanol
g	gram(s)
GOase	Galactose Oxidase
h	hour(s)
^{1}H	proton (NMR)
HPLC	high performance liquid chromatography
Hz	Hertz
i-Pr	*iso*propyl
IPA	propan-2-ol
IR	infrared
k	rate constant
KRED	ketoreductase
LDA	lithium diisopropylamide
lit.	literature value
m	multiplet
M	molar / unspecified metal / molecular mass (mass spectrometry)
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MEM	Methoxyethoxymethyl ether
min	minute(s)
mmol	millimole
mol	mole
MOM	Methoxymethyl acetate
m.p.	melting point
MS	mass spectrometry
n	normal
NMR	nuclear magnetic resonance
o	ortho
p	para
PCL	*Pseudomonas cepacia lipase*
petrol	petroleum ether (bp 40-60 ˚C)
PFL	*Pseudomonas fluorescens* lipase
PMB	*para*-methoxy benzyl
Pr	Propyl

Ph	phenyl
ppm	parts per million
q	quartet
R	unspecified substituent
R_f	retention factor
R_t	retention time
RT	room temperature
s	second (s) / singlet
s	secondary
sec	secondary
sept	septet
SiO_2	silica gel
S_NAr	nucleophilic aromatic substitution
t	tertiary
tert	tertiary
TES	triethylsilyl ether
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSCl	trimethylsilyl chloride
Tol	Tolyl
UV	ultraviolet
ν_{max}	absorption maximum
VT	variable temperatures
wk	week (s)

1. Introduction

During the last few decades almost no other aspect of organic synthesis has received as much attention as the preparation of enantiomerically pure compounds. From Pasteur's 1848 separation of tartaric acid into its enantiomerically pure components[1], novel strategies and methodologies have been sought in order to synthesise compounds asymmetrically.

To this end, atropisomerism – the phenomenon of chirality due to restricted rotation about a single bond – has been a widely applicable area of stereochemistry. Since the first chiral atropisomeric biaryl[2] was resolved in 1922, these complexes have seen development as chiral ligands for catalysis and have also been discovered in a range of biologically active compounds.

This thesis is focused on research into the development of new synthetic methodologies for the stereoselective syntheses and reactivities of non-biaryl atropisomers. The introduction will therefore discuss the importance and need for asymmetric synthesis, before considering the chemical and biological significance of atropisomers – in particular the non-biaryls – and the challenges associated with their stereoselective synthesis.

1.1 Chirality and the Need for Asymmetric Synthesis

The word chiral comes from the Greek *chaire* (meaning hand) and is often equated to "handedness" with the left and right forms referred to as enantiomers. Through an increased understanding of biological processes chemists have acknowledged the fact that enantiopurity is related to biological properties.[3] Our bodies, for example, are a chiral environment (the protein molecules that make up the majority of our receptors are made exclusively of L-amino acids) and one in which left- or right-handedness matters. Opposite enantiomers interact differently with these chiral receptors and can display various activities; these may range from distinguishable smells (*S*-limonene smells like lemons, *R*-limonene like oranges) and flavours, to different clinical effects.[4]

In the case of the non-steroidal anti-inflammatory drug Naproxen, only the *(S)*-enantiomer **1** has anti-inflammatory activity (Figure 1). Marketing the drug as a racemic mixture would have required patients to take twice as much so its manufactures, Syntex, found a route to synthesise the compound in its purely active form.

More seriously, as in the case of DOPA used in the treatment of Parkinson's disease, one of the forms can have dangerous effects. The active drug is the achiral compound dopamine formed enzymatically from L-DOPA **2**, the isomer of which (D-DOPA), is known to be toxic. It is therefore essential to administer DOPA as enantiomerically pure L-DOPA in order to prevent the build up of D-DOPA in the body, which cannot be metabolised by the enzymes.

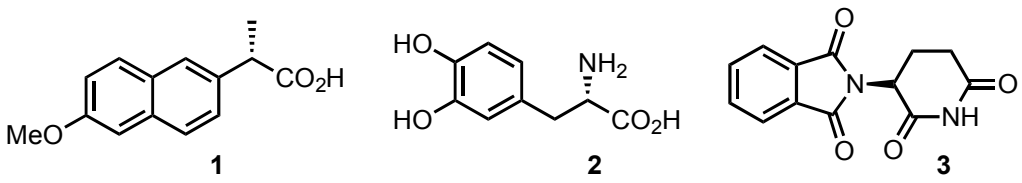

Figure 1: Chiral structures of Naproxen **1**, DOPA **2** and Thalidomide **3**

Perhaps the most infamous example of the enantiomeric effects in chiral drugs is that of Thalidomide. Between 1958 and 1962, the worldwide use of this racemic drug by pregnant women resulted in severe birth defects in approximately 10,000 children. Both enantiomers elicited the desired sedative effect, however the lesser sedating enantiomer **3** also gave teratogenic side effects. In hindsight however, even the pure

(+)-enantiomer would have caused problems since the two interconvert under physiological conditions (Figure 1).

Drug regulation legislation now include highly restrictive guidelines for the marketing of synthetic chiral drugs, requiring as much of the drug as possible to consist of the correct form, or enantiomer. In 2000 40% of all drugs on the market were single enantiomers with an estimated 80% of all new drugs entering the market now being enantiomerically pure. But separating isomers is difficult; they have the same melting point, the same boiling point and are soluble in the same solvents.

There are therefore three general approaches to an optically active compound; (1) use of the chiral pool (R-amino acids, R-hydroxyacids, etc.), (2) separation of racemates (classical resolution, direct crystallization, kinetic resolution using an enzyme), and (3) asymmetric synthesis (noncatalytic, catalytic, enzyme mediated).

The large list of examples of manufacturing using chiral pool technology include the top-selling ACE inhibitors enalapril, captopril, and lisinopril, which are all derived from L-proline.[5] However, this methodology is limited by the naturally occurring isomer and also by the cost; large quantities of enantiomerically pure starting materials can be expensive. There is an even longer list of manufacturing processes incorporating a resolution, including the aforementioned NSAID *(S)*-Naproxen. The main problem with these classical resolution methods is that they are highly wasteful; the maximum yield can only be 50% and large quantities of high quality waste must be disposed of.

The least precedented manufacturing processes to obtain optically active targets employ asymmetric synthetic methods. Examples include catalytic asymmetric hydrogenation; a key step in the manufacture of the antiparkinsonian drug L-DOPA, the antibiotic stabilizer cilistatin, and the sweetener aspartame. Such a small but compelling list of examples is indicative of the huge need to develop new methodologies for the asymmetric synthesis of single enantiomers.

1.2 Atropisomers: Discovery and Use

The name atropisomer (from the Greek *a* which means not and *tropos* meaning turn) was coined by Kuhn[6] in 1933 to describe molecules with a chiral axis maintained by hindered rotation about a single bond. This restricted rotation sees the origin of chirality come not from a centre or a plane, but an axis,[7] and such compounds - in which the enantiomers can interconvert without breaking any covalent bonds - are said to exhibit conformational chirality, or atropisomerism, where the enantiomers are called atropisomers.[8]

Predating Kuhn's name for them, atropisomerism was first detected in 6,6'-dinitro-2,2'-diphenic acid **4**, the enantiomers of which were successfully resolved by Christie and Kenner[2] in 1922 (Figure 2). Before this, it was commonly assumed that a single bond could have complete free rotation at ambient temperature. In the 1980's, Oki further delineated the boundary between atropisomers and conformers (and therefore between configuration and conformation) with his arbitrary definition that atropisomers are conformers, which (at a given temperature), interconvert with a half-life $t_{1/2}$ of at least 1000s (16.7 min).[9] By this definition, BINAP **5** is atropisomeric up to at least 200 °C, 1,1'-binaphthyl **6** ceases to be atropisomeric just below 50 °C,[10] and butane **7** becomes atropisomeric at temperatures below about –220 °C[1] (Figure 3).

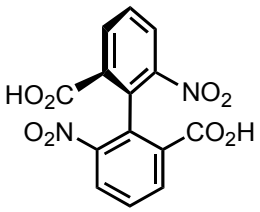

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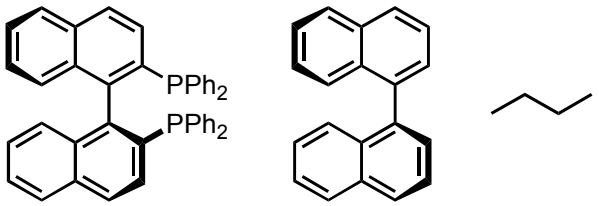
Figure 2: 6,6'-dinitro-2,2'-diphenic acid

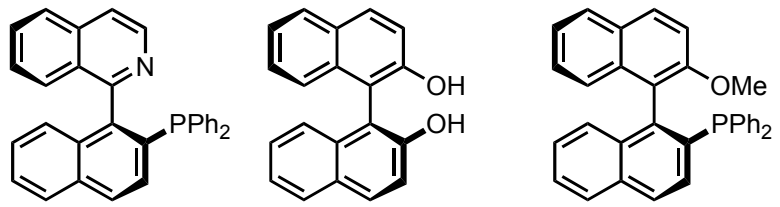


5 **6** **7**

Figure 3: Barriers to atropisomerism

The steric requirements for biphenyls to exist as separable atropisomers were investigated by Adams[11] who concluded that the ease of racemisation largely depended on the size of the *ortho* groups. He also demonstrated that restricted bond rotation was present in other non-biaryls including terphenyl compounds and binuclear compounds such as *N*-phenylpyrroles.

Bringman further affirmed the preconditions for axial chirality in his review[7] of 2005, adding that three major factors govern the minimum free energy barrier to rotation; (1) the combined steric demands of substituents close to the axis; (2) the length and rigidity of bridges (if present); and (3) the mechanisms involved in isomerisation. The past 15 years have since seen specific requirements for chirality based on the C- CO bond of amides,[42,54,69] the C-N bond of anilides[12] and urea derivatives,[13] the C-O bond of ethers[25,26] and the C-S bond of sulfones[14,15] be determined.



8 **9** **10**

Figure 4: Atropisomeric ligands

A high point in the history of atropisomerism, and the cause of much interest in these compounds, was the development of the atropisomeric diphosphine ligand BINAP **5**. This axially chiral biaryl is used in Ru–catalysed asymmetric hydrogenations of C=O and C=C bonds[16] and earned Noyori a share of the Nobel Prize for chemistry in 2001. Indeed, atropisomers have seen outstanding success as chiral ligands for metals; they lend themselves to use in a range of asymmetric reactions because of their ability to modify "bite angle" to suit metal and manner of coordination. Other examples include QUINAP **8**, an axially chiral heteroaromatic used in (among others) Pd catalysed asymmetric allylic alkylations and Rh catalysed hydroborations,[17] BINOL **9** and MeOMOP **10** (Figure 4).

A number of important biological molecules also exhibit atropisomerism (Figure 5). These include the glycopeptide antibiotic vancomycin **12**[18,19] which has become the last line of defence against methicillin-resistant *S. aureus* (MRSA) bacterial strains, the michellamine / korupensamine family of anti-HIV compounds, the anti-malarial

dioncophylline A, the biosynthetically remarkable longithorones **13**, and the marine bastadins, which have a range of biological activities.[20] Some limited degree of conformational flexibility is thought to favour binding in biological systems via the "induced fit"[21] model and in fact a number of recently reported pharmalogically active compounds are atropisomeric.[22] For example, compound **14** was identified as a NK1 and NK2 antagonist and advanced as a treatment for depression.[23]

In the case of vancomycin - a useful template for the design of future antibacterial agents – the ability to recognise and specifically bind to the D-alainine-D-alanine terminus of bacterial cell-wall peptides is an important characteristic.[24] The mechanism of complexation has been extensively studied and is known to be due to the formation of hydrogen bonds between vancomycin and bacterial dipeptide sequences; their formation in such an efficient manner is favoured by the rigid three-dimensional architecture of the molecule, brought about by the cross-linking of the constituent amino acids by these atropisomeric linkages.[24]

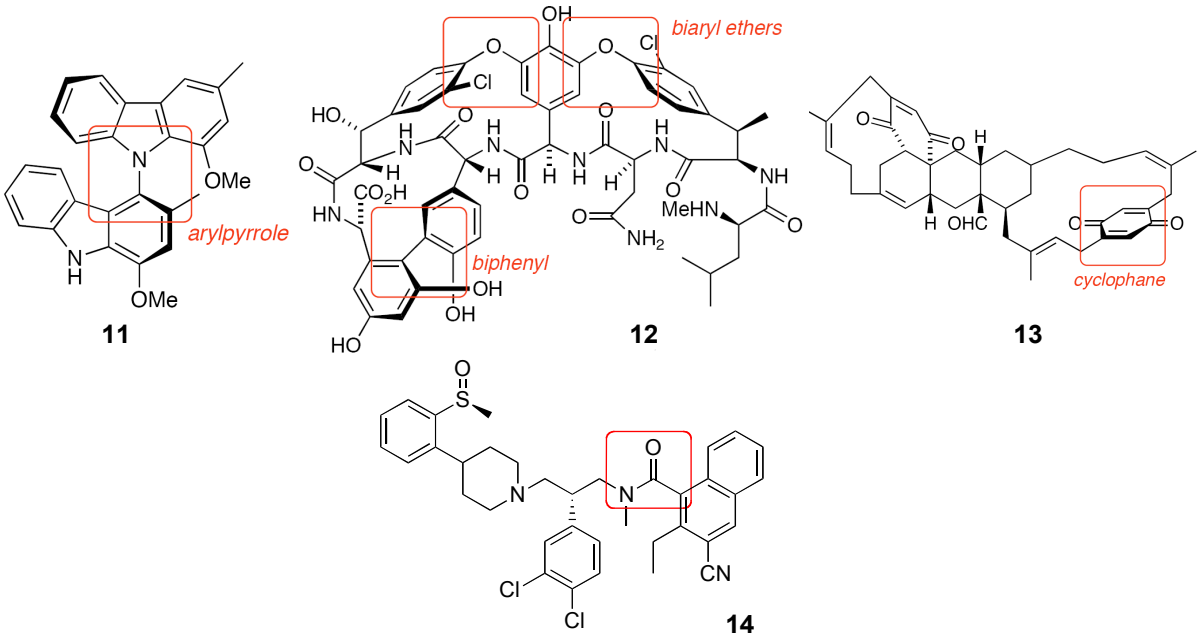
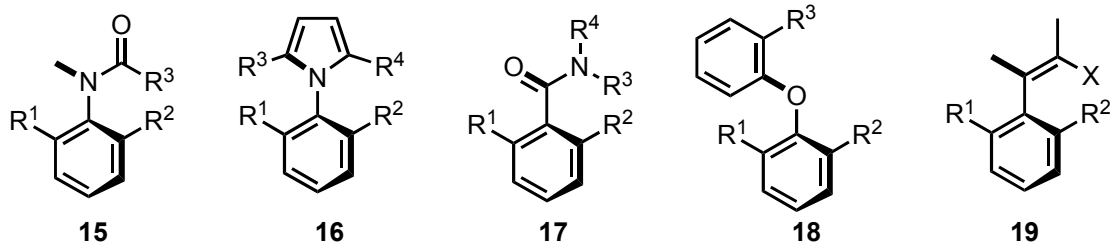


Figure 5: Atropisomeric features in some natural products and pharmaceuticals

These two respective functions – chemical and biological - can be seen as a result of the "adaptability" or "responsiveness" ("softness") of the stereochemistry of atropisomers. And while the vast majority of atropisomers that have been studied have been carbocyclic biaryls, these form only one of dozens of conceivable families of atropisomers. A number of these non-biaryl atropisomers - diaryl ethers, **18**[25,26] diaryl

ureas,[27] anilides,**15** [28,29] benzamides **17** and thioamides,[30] styrenes **19** and aryl ketones,[31] *N*-aryl carbamates, aryl sulfides and sulfones,[14,32] *N*-arylpyrroles **16**, indoles and carbazoles[33] among many more – may offer at least as many benefits in the fields of biology or catalysis as the biaryls themselves (Figure 6).



15 **16** **17** **18** **19**

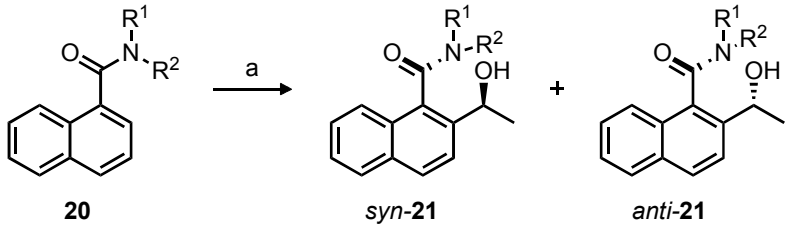
Figure 6: Non-Biaryl Atropisomers

1.3 Non-Biaryl Atropisomers: Tools for Stereoselective Synthesis?

Biaryls are easily the most common atropisomer and only during the last 15 years has the chemistry of non-biaryl atropisomers moved beyond simple structural observations. Some of the interesting and valuable biological properties[34] of non-biaryl atropisomers have already been mentioned, yet the properties of abnormally large barriers to rotation and labile axes are also introducing a number of new concepts and strategies that are proving to be a useful tool in the area of stereoselective synthesis. In the quest for stable atropisomeric systems usable as chiral ligands, chemists have tended to ignore compounds close to Oki's boundary[9], presumably reasoning that they would be too easily racemised for general use in asymmetric reactions. However, in recent years molecules close to this boundary (ie atropisomers which can be induced to isomerise by thermal bond rotation) have begun to facilitate insights into mechanisms,[35,36,37] structures,[38,39] stereochemistry[40] and synthesis.[14,41,42,43]

1.3.1 Amide axis controlled formation of new chial centres

A central aim of the Clayden group's research is to understand how to exert rational and predictable control over the conformation of acyclic molecules, especially those with chiral axes. In 1998 Clayden outlined in a review[44] the remarkable ability of rotationally restricted amides to control stereochemistry. Here it was demonstrated that steric (bulky NR_2) and electronic (electron rich O) contrast about a stereogenic axis provided a powerful stereocontrolling influence over the formation of new chiral centres. For example, the addition of benzaldehyde to *ortho*-lithiated benzamide **20** created a new chiral centre and produced two separable diastereoisomers *syn*-**21** and *anti*-**21** with regard to the OH and the carbonyl oxygen (Scheme 1).



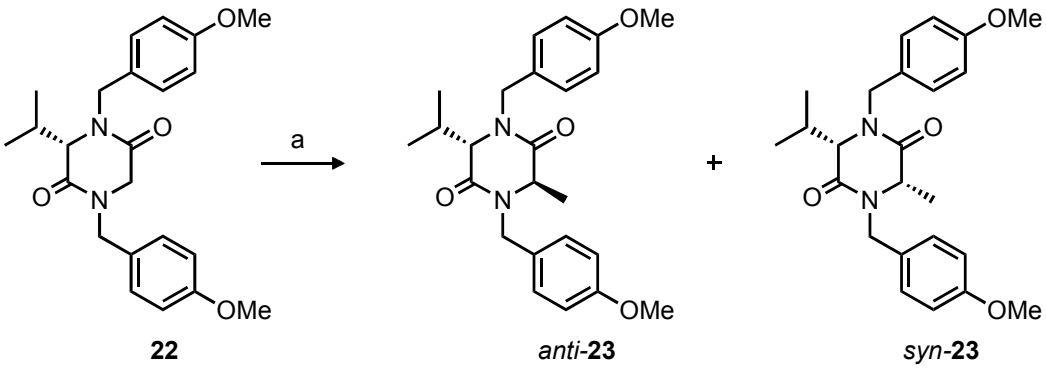
Scheme 1: Products from the addition of aldehydes to lithiated **20**
(a) i. *sec*BuLi, THF -78 °C; (b) R^2CHO, –78 °C

A variety of aldehyde quenches were explored with most exhibiting reasonable levels of diastereoselectivity in favour of the *syn*-conformation.

The significant feature of this chemistry was that the stereochemistry of the non-biaryl atropisomer was able to govern the formation of a new stereogenic centre, and a few research groups around the world have also demonstrated similar atroposelective reactions.[45]

1.3.2 Utilising conformational interplay to control stereoselectivity

The term "chiral relay" was coined by Davies[46] in reference to chiral auxiliary controlled reactions that employ a stereogenic centre to both relay and amplify the stereochemical information of an existing stereocentre. Their approach towards the asymmetric synthesis of α-amino acids utilised the conformationally flexible *N*-benzyl groups of **22** inserted between a stereogenic centre and a prochiral reacting site. Deprotonation and quenching with iodomethane yielded *anti*-**23** in 93 % ee (Scheme 2).



Scheme 2: Alkylation of amino acid derived diazines via a chiral relay
(a) i. LHMDS, THF, –78 °C; ii. MeI

During their own chiral-relay work, Clayden utilised the fact that when

condensed with aromatic aldehydes, (−)-ephedrine imposes a preferred orientation on the adjacent amide axis, which adjusts its conformation to ensure that the oxygen atoms of the oxazolidine and carbonyl group (and likewise their bulky substituted nitrogen atoms) lay on opposing faces of the ring[69a] (Figure 7). This control over conformation can then be exploited either by trapping the favoured conformer as an atropisomer (as in their enantioselective syntheses of atropisomers – see section x) or by using it to relay information about the stereochemistry of the controlling centre in order to exert control over the formation of a new chiral centre.

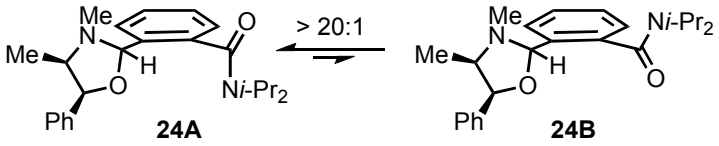
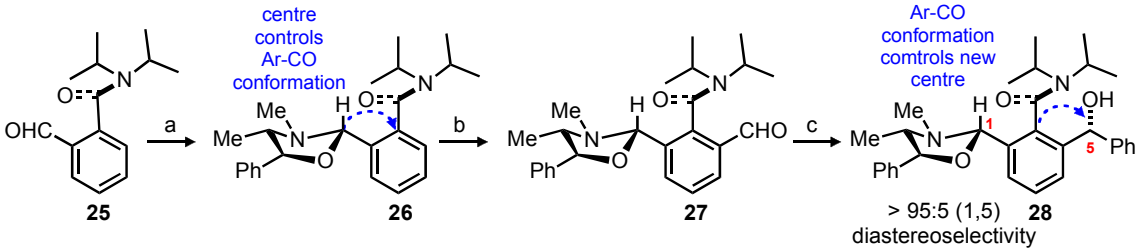


Figure 7: Predferred conformation of (–)-ephedrine adjacent to an amide axis

Condensation of **25** with (–)-ephedrine gave **26** as a single diastereomer both at the new chiral centre and at the amide axis, which preferentially adopted the conformation shown in scheme 3. This amide was able to retain its conformation through both the formylation and addition reactions, eventually leading to **28**. The stereoselectivity of Grignard additions is governed by amide conformation and the reaction of **27** with PhMgBr was fully diastereoselective (Scheme 3).



Scheme 3: 1,5-stereocontrol by stereochemical relay from an oxazolidine
(a) (–)-ephedrine, toluene, heat
(b) i. *s*-Buli ii. DMF
(c) PhMgBr

The operation of this stereochemical relay (also termed "chiral relay") effect has also been deduced in other contexts, for example in asymmetric Diels Alder reactions.[47]

1.3.3 Non-Biaryl Atropisomers as Molecular Machines?

Biological systems commonly transmit information on a molecular scale through conformational changes. For instance, ligand-linked conformational changes in the allosteric protein haemoglobin affect the molecule's binding affinity to further ligands thus regulating gaseous exchange and oxygen delivery in the body. In analogous chemical systems, stereocontrol is the mode of communicating chemical information through space, where the shape or configuration of a molecule governs the reactivity and selectivity of reactions occurring elsewhere on the molecule. Remote stereocontrol is of interest to chemists as it provides us with a model to mimic biology and enables us to develop a chemical method to transmit information.

The Clayden group, who have done much work on the conformational interplay of aromatic amides, observed that the adjacent amides in aromatic dicarboxamides **29** adopted a preferential conformation (lieing *anti* with respect to one another), suggesting that they were in communication despite their remoteness.

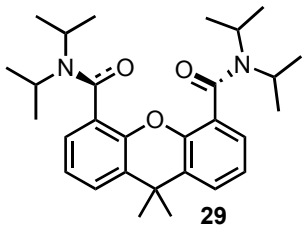


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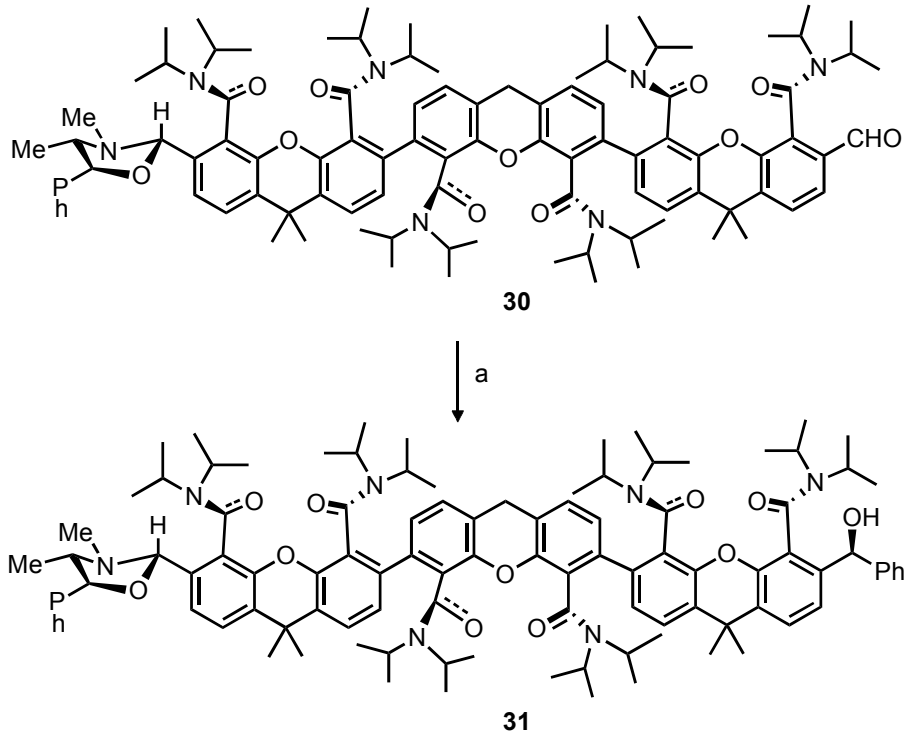
Figure 8: Conformational preference of Xanthene

Given that Clayden could also control the conformation of an amide using the oxazolidine, this gave the group the ideal opportunity to combine both respective features of the conformational preferences of amides and perform an ultra-remote 1,23 stereocontrol. Trisxanthene **30** was therefore synthesised by employing a sequence of ortholithiation and palladium-catalysed coupling reactions followed by the addition of an oxazolidine (scheme 4).



Scheme 4: 1,23 remote stereocontrol in trisxanthene
(a) PhMgBr, THF, –78 °C

As expected, the conformational preference imposed by the oxazolidine was propagated through the chain of amide groups and the terminal amide was then able to control the attack of a nucleophile at the aldehyde to afford **31** as a single diastereomer. Here the oxazolidine ring is shown to be transmitting conformational control by a series of amide-amide interactions through 23 bond lengths, a record at the time.[40] So far the "output" of the conformational change has been a stereoselective reaction, detectable chromatographically or spectroscopically. Other inputs and outputs can be envisaged, though: for example, the possibility that the synthetic methodology of remote stereocontrol might be applied to a challenge in nanotechnology – signal transduction and processing – is intriguing, and it is clear that the future in this area is very bright.[48] There are huge opportunities for the combination of various types of conformational control elements to lead not just to systems capable of relaying information but of processing and storing that information as well.

1.3.4 Non-biaryl atropisomers in catalysis and synthesis

Atropisomeric biaryls are well established as one of the most important classes of ligands for asymmetric catalysis by metals,[49] some of which have been mentioned in the previous section. The angled aromatic rings serve as a useful scaffold for the attachment of metal-coordinating heteroatoms, and biaryl-complexed transition metals provide modern chemistry with some of its most powerful asymmetric catalysts.[50]

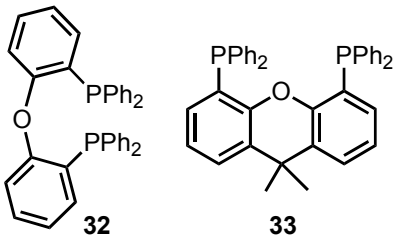
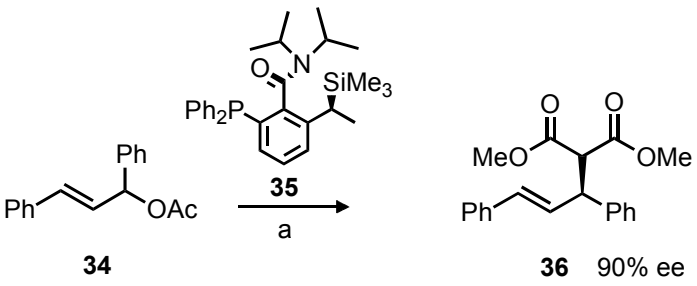


Figure 9: Diarylether based ligands

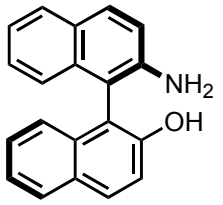
The use of non-biaryl atropisomers in catalytic applications has to date been limited.[51] Diarylether bisphosphines (Figure 9) such as DPEPhos **32**, Xantphos **33**, and their analogues[52] are wide bite angle ligands which have been used to promote metal-catalysed hydroformylation[52a] and more recently also for C-H insertions,[52b] carboetherificaions[52c] and aminations.[52e] With few exceptions,[53] chiral analogues of these ligands are unknown and only within last decade have some useful chiral metal ligands based on non-biaryl atropisomers been reported by the Clayden group[54] and others.[55] In the first ever instance of a non-biaryl atropisomeric chiral ligand, Clayden[54] reported that atropisomeric amide **35** was effectively used for the asymmetric allylic substitution of **34** to yield **36** in 90% enantiomeric excess, ee (Scheme 5).



Scheme 5: First non-biaryl atropisomeric chiral ligand
(a) dimethyl propanedioate, $[PdCl(C_3H_5)]_2$, $MeC(OSiMe_3)=NSiMe_3$, CH_2Cl_2

However work with these types of ligands has so far been limited, perhaps due to the difficulty of their enantioselective synthesis and the trial and error procedure of matching their suitability to a reaction type.

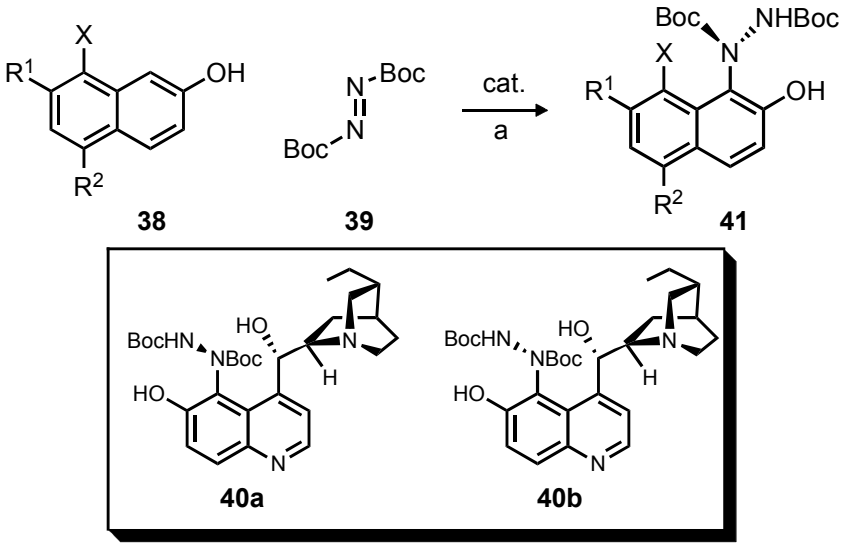
The field of organocatalysis is a rapidly growing area of research and currently a focus of several groups.[56] To date most of these organoctalysts are biomolecules such as proline and cinchona alkaloids or derivatives of these, such as Macmillan's imidazolidinones. Other organocatalysts are related to thioureas. Atropisomeric biaryl examples in this area of catalysis include NOBIN **37**, a derivative of BINOL.



37

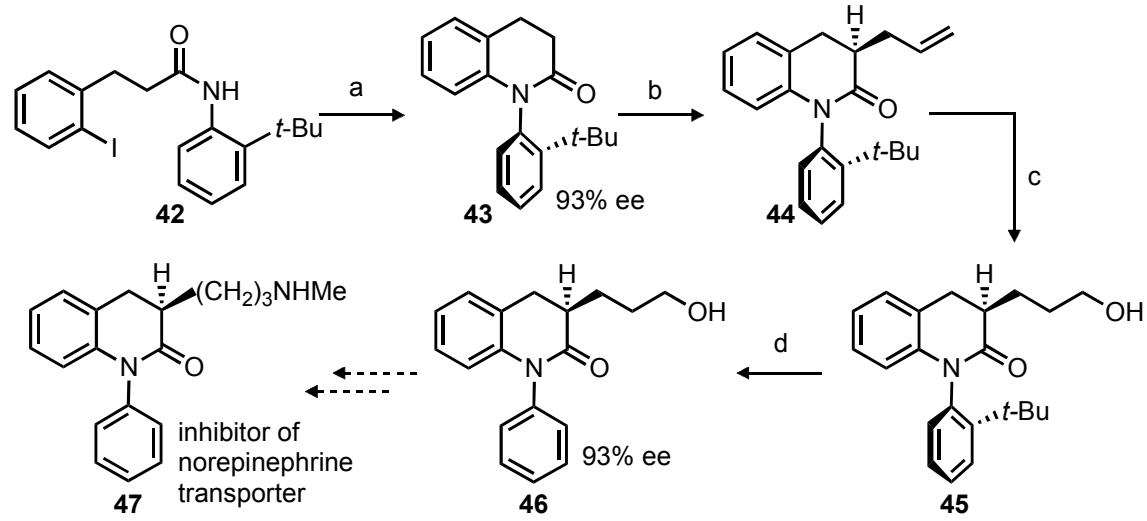
Figure 10: Atropisomeric organocatalyst NOBIN

Recently, Jørgensen[51a] reported the use of non-biaryl atropisomers as organocatalysts. The catalysts, which are 6'-hydroxy cinchona alkaloids **40**, feature atropisomeric functionalisation at position 5' of the quinoline core. These molecules are organocatalysts for the Michael addition of **β**-keto esters to acrolein and methyl vinyl ketone as well as for the asymmetric Friedel-Crafts amination of a range of 2-naphthols (Scheme 6).



Scheme 6: Non-biaryl atropisomeric organocatalysis
(a) -20 °C, DCE

Enantioselective synthesis using non-biaryls, especially anilides and their derivatives, has been the research interest of numerous groups. The group of Taguchi has generated many examples in this area, and he recently utilized an enantioselective *N*-arylation[57] of **42** to synthesise atropisomeric anilide derivatives which were then used in the enantioselective synthesis of NET inhibitors (Scheme 7).[58]



Scheme 7: Taguchi's enentioselective synthesis of a NET inhibitor
(a) $Pd(OAc)_2$, (S)-BINAP, Cs_2CO_3, toluene, 80 °C
(b) i. Li-TMP; ii. Allyl-Br
(c) i. 9-BBN; ii. NaOH, H_2O_2
(d) $AlCl_3$, C_6H_6, 80 °C

1.4 Asymmetric Synthesis of Atropisomers

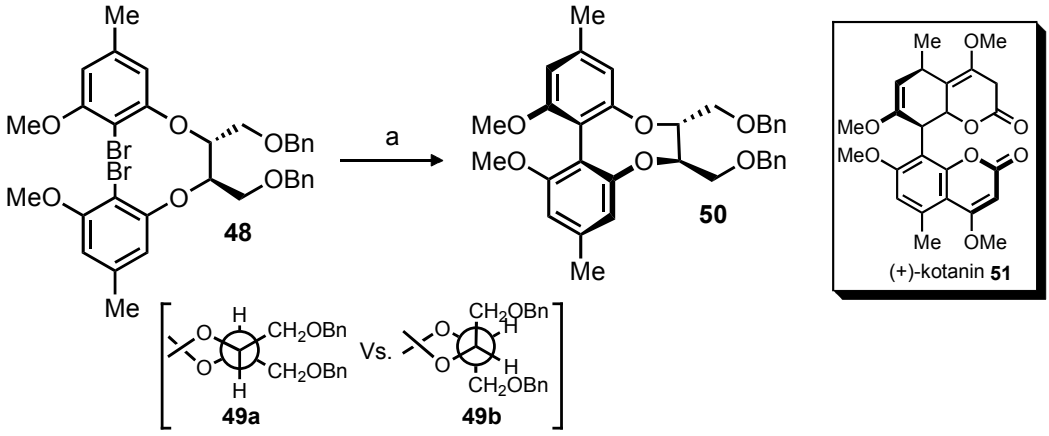
The asymmetric synthesis of atropisomers (of any sort) is a field which has been remarkably slow to develop, principally because of the difficulty of combining the formation of necessarily hindered biaryl couplings with stereochemical control.[59,60] While there are an increasing number of asymmetric methods for the construction of atropisomeric biaryls by asymmetric coupling methods, almost all practical syntheses of ligands rely on resolution.[61,62]

1.4.1 Asymmetric coupling methods

Asymmetric coupling methods involve the simultaneous joining of the two aromatic portions with asymmetric induction. This can either be diastereoselectivly – using a chiral tether / auxillary / or other traceless agent whose source of asymmetry is incorporated into the coupling and then removed – or enantioselectively via the use of a metal catalysed cross coupling reaction with a chiral ligand.

1.4.1.1 Use of a chiral tether

Lin used a tartaric acid derived chiral bridging unit in the total synthesis of (+)-kotanin **50** (Scheme 8).[35] The origin of the selectivity observed in this oxidative coupling reaction was proposed by Sargent,[36] who suggested that the cyano cuprate intermediate **49** adopts *gauche* conformation **49a** rather than a diaxial conformation, **49b**.

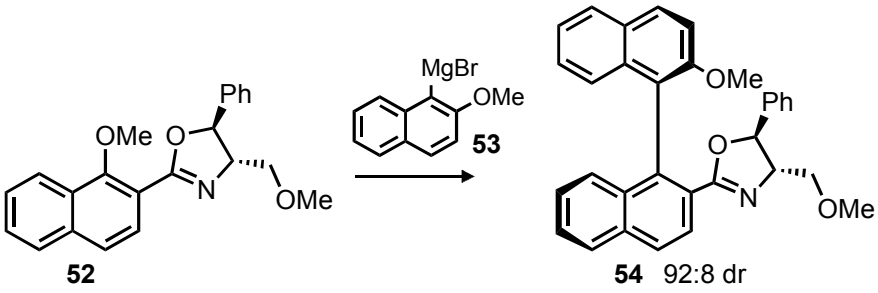


Scheme 8: Key step in the synthesis of (+)-kotanin[35]
(a) i. *tert*BuLi; ii. CuCN; iii. O2, THF -78 °C

1.4.1.2 Chiral auxilliaries

The use of chiral auxiliaries on one of the aromatic components, rather than a chiral link, in a biaryl coupling allows much more freedom of the substituents on the second aromatic unit. Better transfer of stereochemical information is achieved when the auxiliary is placed *ortho* to the coupling site.[7]

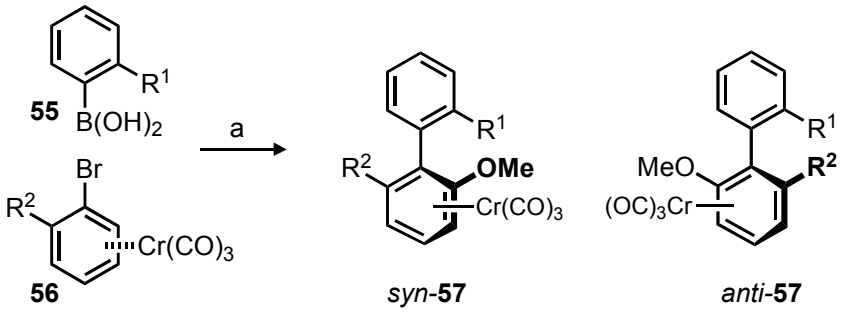
The first highly selective biaryl coupling using a non-bridging chiral auxiliary was reported by Meyers in 1982,[38] whereby an oxazoline derived from (+)-1-methoxy-2-amino-3-phenyl-3-hydroxypropanol activated an *ortho* methoxy group to nucleophilic aromatic substitution by a naphthyl Grignard reagent. This generated binaphthyl **54** with 92:8 dr and in 65 % yield (Scheme 9).[38]



Scheme 9: Meyers' oxazoline auxiliary in diastereoselective synthesis of binaphthyl[38]

The major disadvantages of using chiral auxiliaries are the added steps in synthesis required to introduce and remove the auxiliary. Also, as can be seen above, the auxiliary limits the substitution pattern in the *ortho* positions.

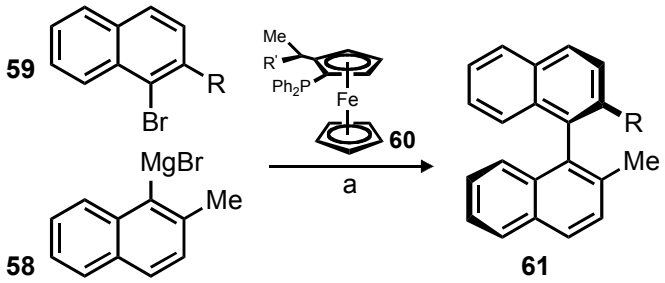
Transition metal – arene complexes, in which the metal is bound to the aromatic ring by η^6 coordination, have planar chirality. Uemura *et al.* exploited this in the synthesis of biphenyls by coupling planar-chiral bromoarenes **56** with boronic acids in a Suzuki coupling reaction (scheme 10). Cross coupling of the planar-chiral aryl bromides with aryl boronic acids was highly diastereoselective, achieveing at least 97: 3 selectivity for either the *syn* or *anti* atropisomer **57**, depending on the substitution pattern.[44]



Scheme 10: Diastereoselective Suzuki cross coupling of planar chiral aryl bromides with boronic acids[43]
(a) [$Pd(PPh_4)$], Na_2CO_3, MeOH / H_2O

1.4.1.3 Metal-catalysed asymmetric cross-coupling

Hayashi pioneered the use of chiral ligands in asymmetric cross coupling reactions. A nickel-catalyzed coupling of naphthyl Grignard reagents with naphthyl bromides (Kumada cross coupling) in the presence of the ligand **60** was achieved with enantiomeric ratios of up to 98:2 and excellent yields (Scheme 11, Table 1).[56]

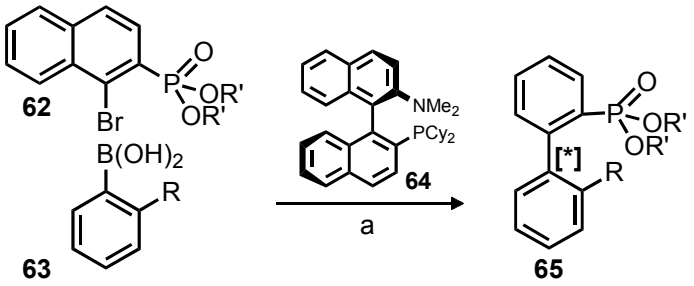


Scheme 11: Asymmetric Kumada cross coupling in the enantioselective synthesis of binaphthyls[56]
(a) **60** (4-10 mol%), $NiBr_2$ (2-5 mol%), Et_2O/toluene, -10 °C

R	Ligand (R')	Yield	er
H	H	81 %	51:49
H	OMe	92 %	91.5:8.5
Me	OMe	69 %	97.5:2.5

Table 1: Asymmetric Kumada cross coupling in the enantioselective synthesis of binaphthyls[56]

The most successful asymmetric synthesis of atropisomeric biaryls so far using a Suzuki coupling was published by Buchwald *et al.* (Scheme 12, Table 2).[60]



Scheme 12: Suzuki coupling in the asymmetric synthesis of biaryls.[60]
[*] configuration at axis unknown.
(a) **64** (0.8 – 3.3 mol%), $[Pd_2(dba)_2]$ (0.5 – 0.2 mol%), K_3PO_4, toluene, 60-80 °C

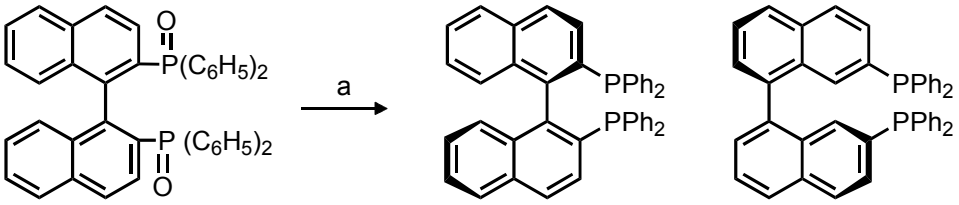
R	R'	Yield	er
Me	Et	98%	95.5:6.5
Et	Et	96%	96:4
i-Pr	Et	89%	92.5:7.5
Ph	Et	74%	87:13
Me	Me	91%	92:8
Me	Me	95%	93:7

Table 2: Yields and enantioselectivities for the asymmetric synthesis of Suzuki coupled biaryls.[60]

As little as 0.2 mol % of the catalyst can be used without any loss of enantiomeric excess in the products. The presence of the phosphonate group is not essential to achieve the high levels of enantioselectivity but it can be converted into a PPh_2 group thus allowing the synthesis of axially chiral monodentate ligands.[60]

1.4.2 Classic resolution

The enantiomeric synthesis of BINAP **4** employs a resolution of bis-phosphine oxide **66**. One enantiomer of the compound forms a much more crystalline 1:1 complex with di-*O*-benzoyl tartrate than the other, leading to the fortuitous synthesis of both the *R* and *S* forms [61] (Scheme 13).



66 **S-(–)-BINAP 4** ***R*-(+)-BINAP 4**

Scheme 13: Synthesis of BINAP by Classic Resolution
(a) i..(–)-di-*O*-benzoyl-L-tartrate or (+)-di-*O*-benzoyl-D-tartrate; ii. Fractional crystallisation, iii. Base; iv. $HSiCl_3$, Et_3N

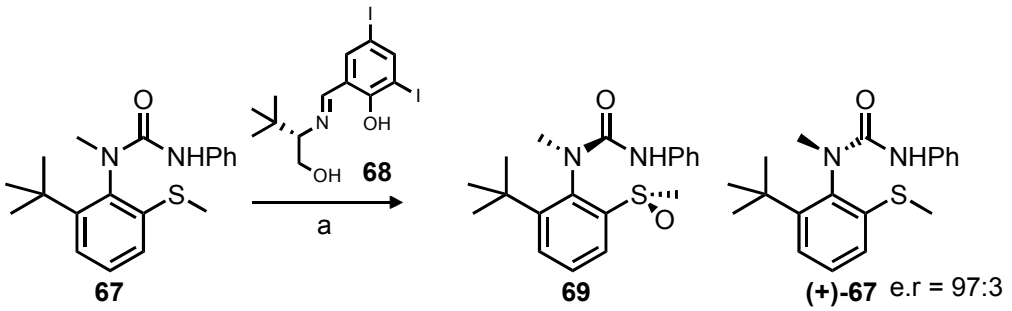
Classical resolution methods have also been utilised to publish the first total synthesis of Murrastifoline-F,[63] a naturally occurring member of the carbazole alkaloids, while Malkov and Kokovsky's technique of co-crystalising with *S*-(-)-BINOL afforded them their catalyst[64] for the asymmetric allylation of aromatic aldehydes.

Despite their common utility, however, there exist a number of drawbacks with the above-described methods, namely; (1) The acidic or basic groups required for resolution are rarely present in a final target ligand, placing constraints on the choice of synthetic route and therefore the ability to vary a single route to provide a range of ligands; and (2) often only one enantiomer of a particular syntheses is required, leading to a maximum 50% yield.

Recent approaches towards the synthesis of atropisomers have aimed to exploit the potential dynamic nature of axial chemistry and indeed progress has been made towards the synthesis of atropisomers via kinetic resolution[65,66] and dynamic resolution under kinetic[67,68] or thermodynamic[42,43,54,69,70] control.

1.4.3 Kinetic resolution methods

Kinetic resolution methods make use of the fact that when two enantiomers show different reaction rates, one enantiomer is converted while an excess of the less reactive enantiomer can be recovered in an enantioenriched form. Clayden recently employed such a strategy during the first asymmetric synthesis of an atropisomeric urea (Scheme 14). [65]



Scheme 14: Asymmetric Synthesis of an Atropisomeric Urea by Kinetic Resolution
(a) H_2O_2, $VO(acac)_2$, ligand **68**

This method for KR employed an asymmetric oxidation of **67** in the presence of a ligand to generate *anti*-**69** in good enantiomeric excess (86:14). The reaction reached no further than 50% completion, with the remaining sulfide (+)-67 isolated in 30% yield and with 97:3 er.

1.4.4 Dynamic Kinetic resolution

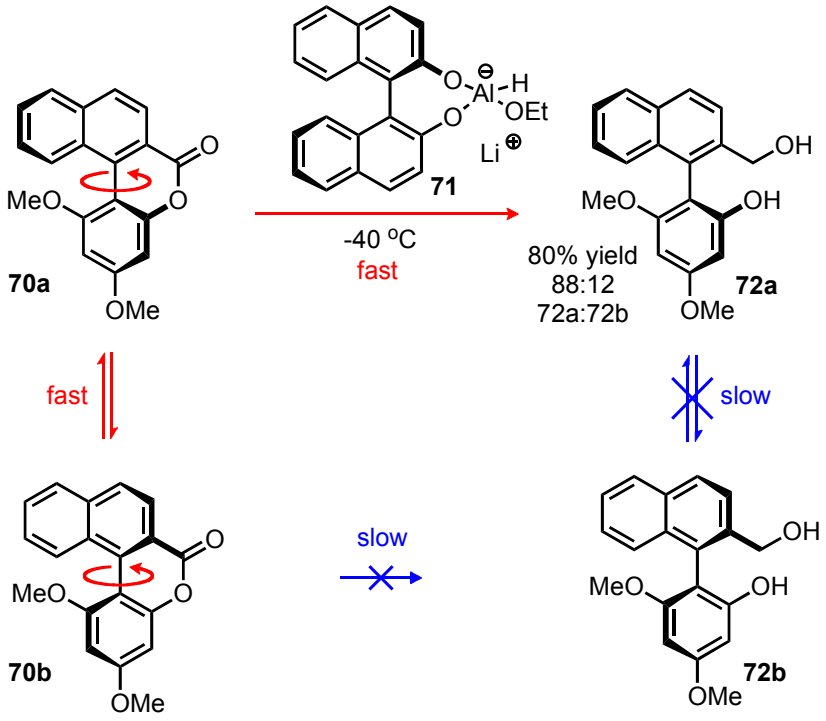
Dynamic resolution methods tackle the obvious drawbacks of the above-described system, namely that the maximum conversion in the reaction is only 50% and that the product has to be separated from the reactants. The inherent kinetic lability of atropisomers makes them especially suited to this process.

If a chirally labile substrate can interconvert faster than it can react, the reaction proceeds with one enantiomer reacting faster than the other but the equilibrium continually shifting to obtain a 50:50 mixture of the remaining starting material; the faster-reacting enantiomer is therefore continually replenished at the expense of the slower-reacting enantiomer, making it theoretically possible to convert the achiral reactant with 100% completion.

Both the Clayden[67] group and others[68] have exploited its use in synthesis, with Bringmann *et al.*[68a] utilising a DKR to yield either enantiomer of the natural product Mastigophorene.

In a simple example shown in scheme 15, two lactones **70a** and **70b** are enantiomeric conformers even at 240 °C, and interconvert rapidly on the timescale of their reduction by the BINAL reagent **71**. One of them (**70a**) reacts faster than the other, and generates a product **72a** which, because it lacks the bridging lactone linkage, is atropisomeric up to ambient temperature and beyond. As **70a** reacts, equilibrium with

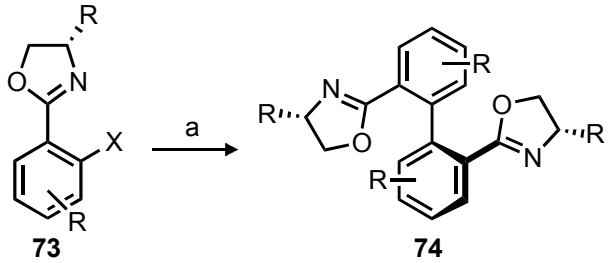
70b is continually restored, and eventually a product **72a** is formed in good yield (80%) and with good enantioselectivity (88:12).



Scheme 15: Bringmann's method for dynamic kinetic resolution

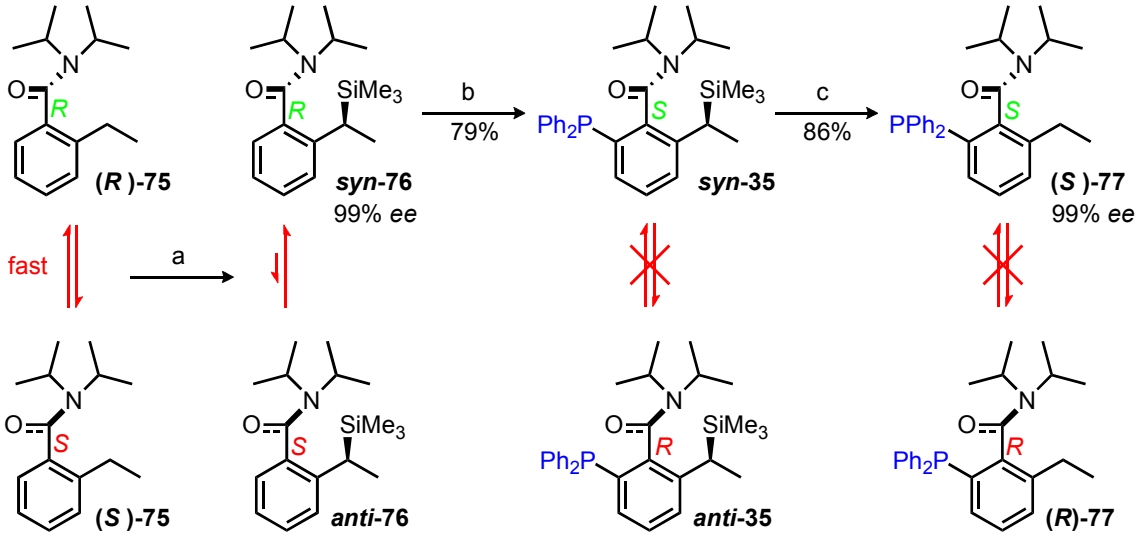
1.4.5 Thermodynamic Resolutions

Thermodynamic control is particularly suited to compounds for which stereoisomeric interconversion can be achieved via a simple mechanism — thermally induced bond rotation in the case of atropisomers. This concept has been realised by Meyers who demonstrated that thermodynamic control can be used in the asymmetric synthesis of chiral biaryls **74**[71] via copper mediated Ullmann coupling of *o*-bromoaryloxazolines **73** (Scheme 16).



Scheme 16: Meyers thermodynamic resolution of *o*-bromoaryloxazolines
(a) Cu, solvent, heat

Thermodynamic resolution was also the method of choice for the enantioselective synthesis of the atropisomeric chiral amide ligand **35**, the application of which was seen in section 1.3.4. Moreover, the procedure became the first instance of an amide being made enantioselectively (Scheme 17).



Scheme 17: Thermodynamic resolution in the synthesis of ligand **35**
(a) i. *s*-BuLi, (–)-sparteine; ii. Me_3SiCl
(b) (a) i. *s*-BuLi; ii. Ph_2PCl
(c) TBAF

A stereogenic centre was constructed enantioselectively adjacent to an otherwise freely rotating (i.e. kinetically unconstrained) axis, leading to the synthesis of **76**. The benzamide, which prefers to adopt principally conformation *syn*-**76** has only a low kinetic barrier to rotational interconversion between its conformers, but this changes when the major conformer is trapped as a major atropisomer by increasing the steric hindrance to rotation about the axis. Lithiation and substitution of **76** introduces a kinetic barrier to conformer (now atropisomer) interconversion, thus allowing the major atropisomer *syn*-**35** to be obtained, after purification, enantiomerically and diastereoisomerically pure.

Finally, removal of the stereogenic centre (by desilylation in this case) provides a single atropisomeric enantiomer of the phosphine **(*S*)-77**, which, despite the loss of a thermodynamic preference for one atropisomer over the other, was unable to relax to thermodynamic equilibrium with **(*R*)-77** because of the residual kinetic barrier to rotation provided by the Et and PPh_2 groups.

1.4.5.1 Thermodynamic resolution: application to the first asymmetric synthesis of Vancomycin

Vancomycin **12**[18,19] (the biological benefits of which were discussed in section 1.2), remains the only natural product thus far published where the atropisomeric diaryl ethers contained within its framework are synthesised asymmetrically. Its *aglycon* is considered to consist of three interlocking cyclic tripeptides that collectively give rise to a conformationally rigid cup-shaped structure; these are usually referred to as the AB, C-O-D and D-O-E ring systems (Figure 11). Construction of each of the constituent macrocycles must be carried out in such a way that this skeleton is produced in only one of eight possible atropdiastereomers; the magnitude of this challenge is testified by the fact that more than 40 years passed between the first isolation of vancomycin and its first successful total synthesis.[18a]

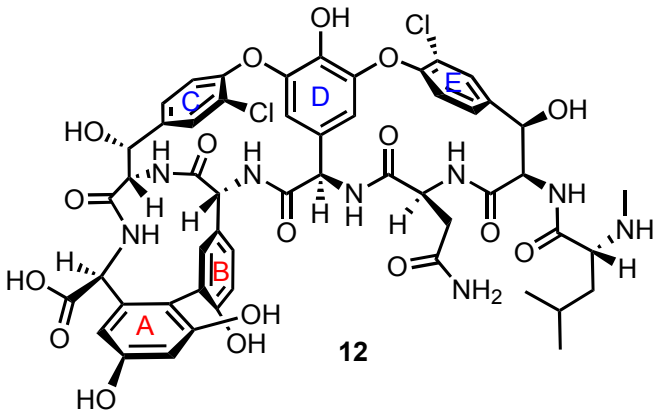
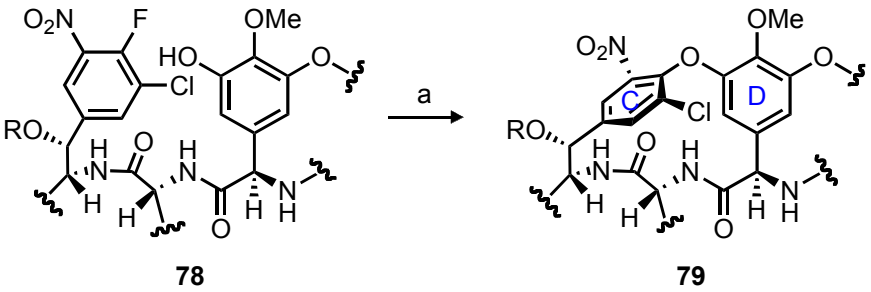


Figure 11: Structure of Vancomycin aglycon

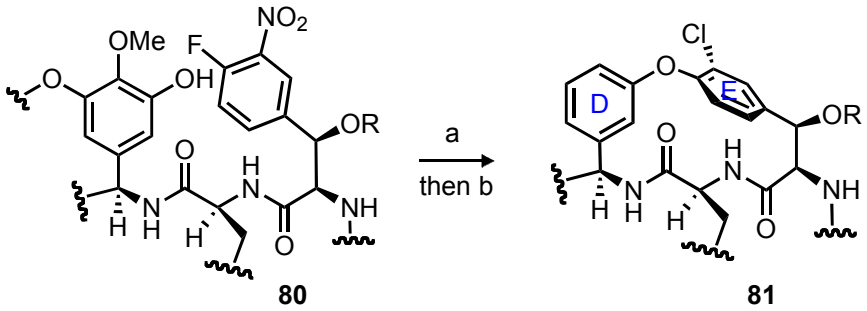
Much literature has delved into the diversity of synthetic approaches that can be applied to its synthesis, most notably the review by Nicolaou,[18] however for the purposes of this report only the synthesis of the diaryl ether containing rings will be discussed.

Of the three reported syntheses, that of Evans[19b] is chronologically the first. Here, Evans found that S_NAr ether formation (and subsequent macrocylisation) with a nitro group *meta* to the chlorine in **78** afforded the desired atropisomer as a 5:1 mixture, although no explanation for the observed selectivity was given (scheme 18). It was then a simple task to diazotise the nitro group followed by reduction to yield the desired monochloride in enantiomerically enriched form.



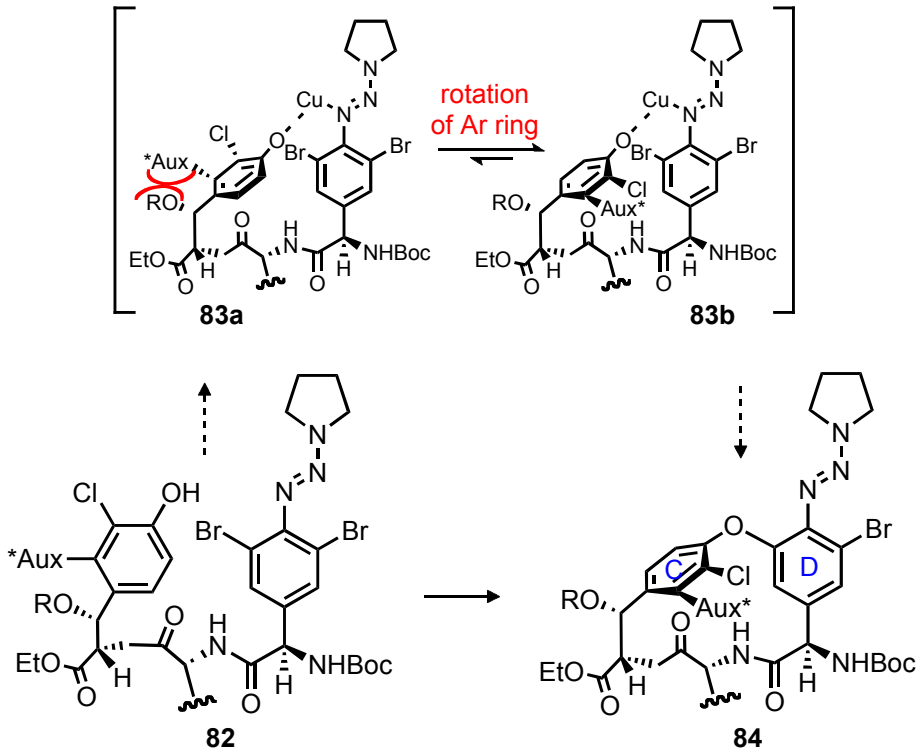
Scheme 18: Selective ring closing of C-O-D ring system
(a) Na_2CO_3, DMSO, rt, 1.5h

The substitution pattern of the aromatic ring was found to play a key role in determining the atropisomer bias in the C-O-D macrocycle in **79**; if a non-chlorinated analogue of **78** was cyclised in the same way - via S_NAr - the predominant product became the undesired atropisomer in a ratio of 10:1. Evans therefore utilised this strategy in the similar intramolecular S_NAr ring closing of the D-O-E cycle by placing a single nitro group on the ring, which preferentially sat on the back face of **81** and was then later converted to the naturally present chloro derivative (scheme 19).



Scheme 19: Selective ring closing of D-O-E ring system
(a) CsF, DMSO, rt, 1.5h
(b) i. Zn(0), HOAc, EtOH, 40 °C; ii. $NaNO_2$, H_3PO_2, *cat.* Cu_2O, THF/H_2O, 0 °C; iii. CuCl, $CuCl_2$

Nicolaou *et al.*[18b] published a rather more elegant synthesis employing a bulky auxiliary designed to direct the chlorines into the desired orientation by minimising unfavourable steric interactions. The strategy relied on attaching a bulky substituent onto ring "C" ring of **82** that would cause an unfavourable interaction with the hydroxyl moiety on the neighbouring amino acid as in **83a** (Scheme 20). Rotation of the aromatic ring to **83b** to reduce steric clashes coupled with a chelating group on the hydroxyl of central ring D, ensured stereoselective ring formation. Metal triazine mediated ring closure then formed the macrocyclised product **84** as a single atropisomer in excellent yield.



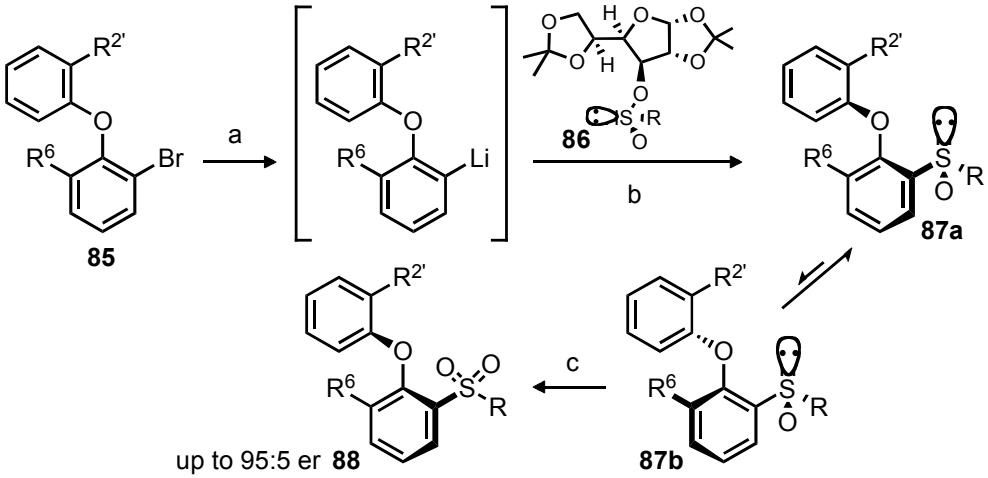
Scheme 20: Nicolaou's Asymmetric synthesis of the C-O-D ring system of Vancomycin

Boger's synthesis[19] utilised similar S_NAr ether formation to that used by Evans for ring closure of both the C-O-D and D-O-E macrocycles. However, while Evans controlled the conformation of the ether axis during the formation of the linkage, Boger formed the ring systems in racemic form, separated the diastereoisomers, equilibrated the "wrong" isomer back to the equilibrium mixture and then repeated the steps in order to afford the desired atropisomer in enriched form.

1.4.6 Dynamic Thermodynamic Resolutions

Dynamic thermodynamic resolution is a practically more straightforward method than described above, and makes use of the potential thermal lability of the atropisomeric axis. In the example illustrated in scheme 21 - the first enantioselective synthesis of an atropisomeric diaryl ether – the synthesis began with racemic atropisomer **85.** This compound was converted to a diastereomeric (and therefore energetically non-equivalent) mixture of atropisomers, each enantiomerically pure, by reaction with an enantiomerically pure "resolving agent". In this case a sulfoxide (**68**) was used, although centres such as proline-derived aminals and ephedrine derived oxazolidines have been utilised in similar chiral syntheses.

Resolution is then achieved not by discarding 50% of the material, but simply by heating. The "near atropisomers" are equilibrated to gain the thermodynamically favoured conformation, which can itself be isolated in enantioenriched form by means of addition of a bulky substituent to prevent rotation, followed by removal of the auxiliary. In this case, the chirality of the sulfoxide was destroyed by oxidation to the corresponding sulfone to provide atropisomer **88** in up to 95:5 er.[43]



Scheme 21: Synthesis of enantiomerically enriched atropisomeric diaryl ethers by dynamic thermodynamic resolution using an *ortho* sulfoxide auxiliary
(a) *n*BuLi, THF, -78 °C, 1 min
(b) sulfoxide **86** , -78 °C to +20 °C, 16h
(c) *m*CPBA, CH_2Cl_2, 0 °C

The observed stereochemical control in the diaryl ether series is proposed to arise from a combination of steric and electronic effects. Dipole repulsion between the S-O bond and the proximal Ar-O bond of the ether, in combination with steric repulsion between the aryl and alkyl substituents of the sulfoxide group, favors conformations in which a lone pair of electrons of the sulfoxide group eclipses, or lies gauche to, the proximal Ar-O bond (Figure 12).

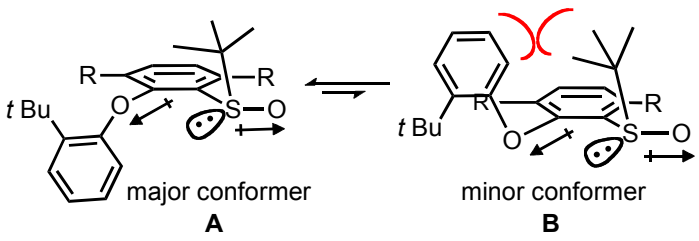


Figure 12: Conformational preference in sulfinyl ethers

Steric repulsion between the ether substituents (the upper ring) and the alkyl substituent on the sulfoxide group then favor Ar-O-Ar' conformer **A** over conformer **B**. Such a rationale is in accordance with the observed increased selectivity afforded by bulkier substituents α and *ortho* to the sulfoxide group (Table 3).

Entry	$R^{2'}$	R^6	R^3	R	Ratio 87a:87b
1	^{t}Bu	CN	H	^{i}Pr	57:43
2	^{t}Bu	CN	Et	^{i}Pr	66:34
3	^{t}Bu	CH_2OMe	H	^{t}Bu	86:14
4	^{t}Bu	CH_2OMe	Me	^{t}Bu	95:5
5	^{t}Bu	CH_2OMe	Me	$C(Me)(CH_2)_5$	94:6
6	^{t}Bu	CH_2OMe	Et	$C(Me)(CH_2)_5$	93:7
7	^{i}Pr	CH_2OMe	H	^{t}Bu	98:2
8	^{i}Pr	CH_2OMe	H	^{i}Pr	83:17

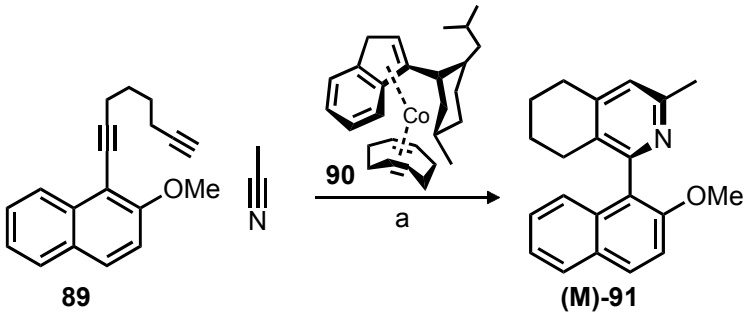
Table 3: Diastereoselectivities in *ortho* sulfoxide substituted biaryl ethers

Overall, resolution is achieved dynamically (no material is wasted) and under *thermodynamic* and not *kinetic* control. Using this highly versatile procedure, Clayden *et al.* have enantioselectively synthesised a variety of atropisomers including atropisomeric amides,[42,54,69] ethers,[43] sulfones, and even the binapthyl ligand QUINAP[70] **5**.

1.4.7 Aromatic ring construction

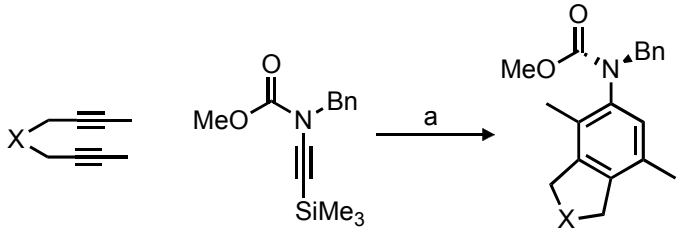
A fundamentally new strategy has recently emerged in the construction of chiral biaryl compounds in which a preformed aryl-C bond is transformed atropselectively into the biaryl axis upon construction of the second aromatic ring.

The groups of Gutnov and of Heller synthesised axially chiral 2-aryl pyridines by a catalytic asymmetric [2+2+2] cycloaddition.[72] The reaction of the 1-naphthyl diyne **89** with alkyl or aryl nitriles in the presence of the cobalt catalyst **90** gave the pyridines **91** in good yields and up to 88% *ee* (Scheme 22).



Scheme 22: Asymmetric synthesis of a biaryl by construction of an aromatic ring
(a) 1 mol % **90**, *hv* (wavelength = 420 nm), THF, 3 °C

This work has recently been extended by Tanaka *et al.* who have developed hindered, axially chiral anilides[73] **94** in >99% *ee* using $Rh^{(I)}$-catalysed cycloaddition of 1,6-diynes **92** with trimethylsilylynamides **93** to control the conformation of the chiral axis during the ring closing step (Scheme 23).



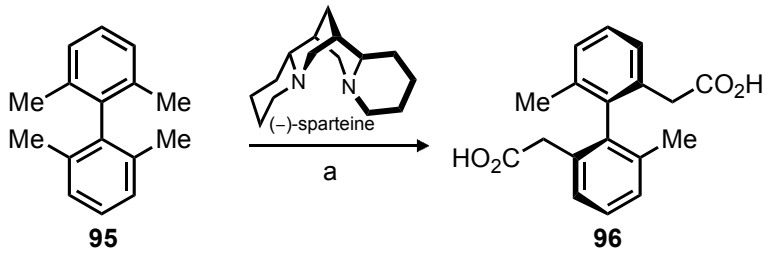
Scheme 23: Atroposelective formation of anilides by construction of an aromatic ring
(a) 10 mol% $[Rh(COD)_2]BF_4$, (*S*)-xyl BINAP, DCM, rt, 16h
X = $NSO_2(4\text{-}BrC_6H_4$

1.4.8 Desymmetrisation methods

The desymmetrisation of symmetric compounds consists of a modification that eliminates one or more elements of symmetry from the starting compound. In the case of the biaryls, desymmetrisation introduces asymmetry to the molecule and leads to an axially chiral product.

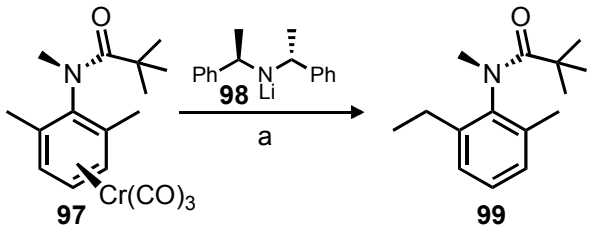
1.4.8.1 Chemical Desymmetrisation

Raston *et al.*[83b] (scheme 24) performed an enantioselective dilithiation of the axially prostereogenic tetra-*ortho*-methylated biphenyl **95** in the presence of the chiral ligand (–)-sparteine. An electrophilic quench with carbon dioxide followed, and lead to the synthesis of diacid **96** with moderate stereocontrol (40% ee).



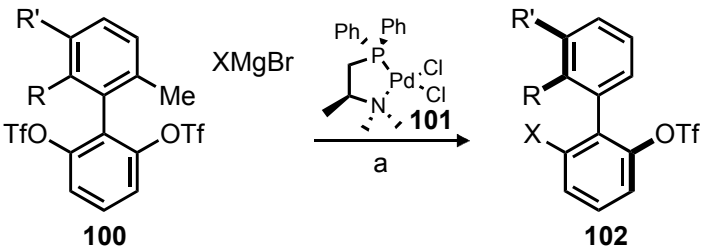
Scheme 24: Desymmetrisation via enantioselective dilithiation
(a) i. *n*Buli, (–)-sparteine; ii. CO_2

As with the biaryls, axial chemistry in atropisomeric amides may be introduced by stereochemical control in the atroposelective reactions of planar chiral complexes. [74] Enantioselective lithiation was reported in this context by Uemura[75] who showed that the achiral complex **97** could be enantioselectively deprotonated by treatment with a chiral lithiumamide base **98** (Scheme 25). The stereogenic C-C and C-N axes in these compounds were orientated such that the larger NR_2 and acyl groups were directed away from the chromium, and after decomplexation returned atropisomer **99** in excellent yield and enantioselectivity.



Scheme 25: Atroposelective reactions of planar chiral complexes
(a) i. **98**, THF, -78 °C to -30 °C; ii. MeI; iii. *hv,* O_2

Harada[83d] desymmetrised tetra-*ortho*-hydroxybiphenyl through a diastereoselective formation of an eight-membered diether bridge while, more recently, Hayashi[83c] has developed a remarkable enantio-differentiating cross coupling reaction of ditriflates. Here he used Grignard reagents in the presence of an enantiomerically pure palladium complex **101** to form desymmetrised axially chiral biaryl **102** in good yield with high enantioselectivities (Scheme 26, Table 4).

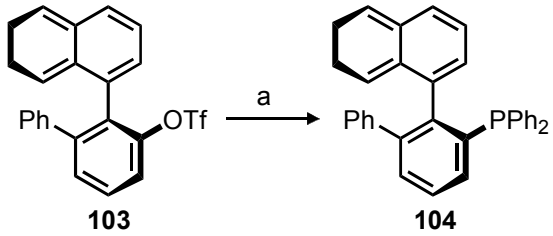


Scheme 26: Enantioselective desymmetrisation of ditriflates by Palladium catalysed cross coupling (a) LiBr or LiI, 5 mol % **101**

R	R'	X	Yield / %	er
Benzo	Benzo	Ph	92 %	97:3
Benzo	Benzo	*m*-tol	90 %	97.5:2.5
Benzo	Benzo	Ph_3Si—≡	88 %	96:4
Ph	H	Ph	80 %	97:3
Ph	H	Ph_3Si—≡	88 %	>99:1
Me	H	Ph	85 %	97.5:2.5
Me	H	Ph_3Si—≡	87 %	92.5:7.5

Table 4: Yields and enantioselectivities for desymmetrisation of ditriflates

The triflate group remaining in the product can be subjected to a further cross coupling reaction allowing the synthesis of a wide range of biaryls, including monophosphine **104** (Scheme 27) which was demonstrated to be useful as a ligand in the hydro silylation reaction of styrene giving 85 % yield and 95:5 er. [67]



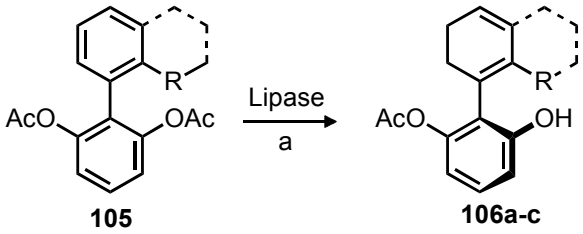
Scheme 27: Further manipulation to desymmetrised triflate, synthesis of atropisomeric phosphine[67] (a) i. $Ph_2P(O)H$, Pd $(OAc)_2$/dppp, *i*-Pr_2NEt; ii. $HSiCl_3$, MeOH

1.4.8.2 Atroposelective Enzymatic Desymmetrisation

The Enzyme Commisson has classified enzymes in six main groups according to the type of reaction they catalyse[76]: (1) Oxidoreductases; (2) Transferases; (3) Hydrolases; (4) Lyases; (5) Isomerases; (6) Ligases. Enzymes from groups 1 through 4,

especially hydrolytic enzymes, have found broad application in organic transformations.[77]

In an approach by Matsumoto *et al.*[78], the enzymes *Candida antarctica* lipase (CAL) and *Pseudomonas cepacia* lipase (PCL) were used to enantiselectively monohydrolyse (and therefore desymmetrise) the prochiral diacetoxy biaryls **105**. The axially chiral 2-acetoxy-6-hydroxy biaryls **106** were obtained in moderate to high yields (51-94%) and excellent enantioselectivities (≥96% *ee*), even for derivatives bearing small substituents (e.g. R=Me). In all cases, the *M* atropisomer predominated, although no stereochemical rationale was given (Scheme 28, Table 5).



105 **106a-c**

Scheme 28: Enzymatic desymmetrisation of axially chiral biaryl **105**
(a) Lipase, phosphate buffer (pH = 7), 30-35 °C, 1-7 days

R	**Me**		**Et**		**CH_2OBn**		**2,3-benzo**	
Lipase	Yield	er	Yield	er	Yield	er	Yield	er
Candida antarctica	80 %	98:2	57 %	>99:1	68 %	>99:1	72 %	98:2
Pseudomonas cepacia	86 %	>99:1	67 %	98:2	51 %	99:1	94 %	99:1
Pseudomonas fluorescens							82 %	89:11

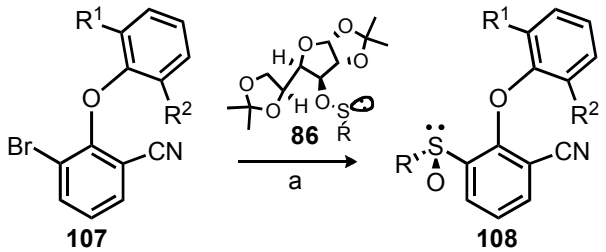
Table 5: Yields and enantioselectivities for the enzymatic desymmetrisation of axially chiral biaryl **105**

1.5 Aims of the Project

Members of the diaryl ether family of compounds[79] have diverse functions as mammalian hormones (thyroxine),[80] powerful antibiotics (vancomycin, teicoplanin, ristocetin),[18,81] and ligands for transition-metal-promoted hydroformylation (bis(2-diphenylphosphinophenyl)ether; DPEphos).[52] They are also present in a range of natural products including the bastadins, perottetines, riccardin B, and cyclic peptide K3.[20,82]

Their synthetic utility is limited however, until these compounds can be synthesised efficiently in a stereoselective fashion. Unfortunately (with the notable exception of vancomycin) this has been an area that has seen relatively little success. The main obstacle preventing their development seems to be the difficulty of combining the formation of necessarily hindered biaryl couplings with an aspect of stereocontrol.

Although the synthesis of enantiomerically enriched diaryl ethers based on a *tert*-butyl substituted aryl ring was successful (as described in the enantioselective synthesis in section 1.4.1), the barrier to rotation was still slightly lower than would be desirable for stable chirality. Synthesis of sulfoxides based on the bulkier *i*-propyl-methyl substituted ring were attempted, however the yields were extremely poor compared with the singly substituted analogues (Scheme 29, Table 6).



Scheme 29: Increasing the barrier to rotation in the diaryl ethers
(a) *n*BuLi, -78 °C, THF, 1 min, then **86**

108	**Substitution**			**Yield / %**
	R	**R^1**	**R^2**	
a	^{i}Pr	^{i}Pr	Me	0
b	Cychex	^{i}Pr	Me	4
c	Tol	^{i}Pr	Me	4
d	CycHex	^{t}Bu	H	66

Table 6: Increasing the barrier to rotation in the diaryl ethers

An alternative and relatively undeveloped approach towards the asymmetric synthesis of diaryl ether atropisomers would be to use desymmetrisation methods. As discussed in section 1.4.8, if at least one of the two aromatic rings is symmetrically substituted, then an enantioposition-differentiating transformation of one substituent will reduce the symmetry and lead to an axially chiral compound.

The main strategies; those of enantioselective lithiations and enantioselective enzymatic reactions, have proved to work well with biaryl atropisomers and with organic molecules in general, but few examples exist as to their utilisation in non-biaryl systems and the use of desymmetrisation for the synthesis of single atropisomers is rare.[83]

It is therefore the aim of this report to utilise the methodologies outlined above in order to synthesise enantiomerically enriched diaryl ethers. Their requirements for chirality have recently been established, so it is envisaged that once a method for their enantioselective synthesis is in hand, further evaluations into their synthetic utility (either as ligands or as units in natural product synthesise) can be made.

Previous work carried out by the Clayden group has already established that the diaryl ether and diaryl sulfide linkage can form a chiral axis, and that the stereochemistry of this axis can be controlled by a neighbouring chiral auxiliary such as a sulfoxide (see section 1.4.6). However, this work did not investigate the ability of achieving stereocontrol via the controlling influence of the axis. Utilising similar strategies to those discussed in section 1.3 for the benzamide class of atropisomers, we also aimed to explore the stereoselectivity of the reactions of atropisomers based on this Ar-X-Ar framework.

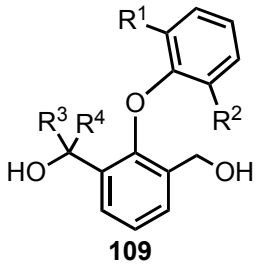
2. Results and Discussion

2.1 Synthesis of Diaryl Ethers

Multi-gram quantities of diaryl ether linked compounds were required for use in a number of the stereoselective reactions and investigations contained within this thesis. A synthetic strategy was therefore sought in which to sythesise analogues of these compounds on a large scale.

2.1.1 Diaryl ether synthesis and requirements for chirality

The preconditions for axial stability in the diaryl ethers were fully elucidated by Clayden *et al.*[26] in 2006, where it was observed that atropisomerism in this class of compound can be exhibited provided certain structural conditions are fulfilled (Table 7). A comprehensive investigation into the mechanism of interconversion suggested that the potential for chirality depended less on the number of substituents than the substitution pattern.[26] Atropisomerism was exhibited when one of the substituents was as large as a *t*-butyl and when there were at least 3 substituents *ortho* to the ether axis. Ethers based on this framework were therefore the targets for synthesis.



109

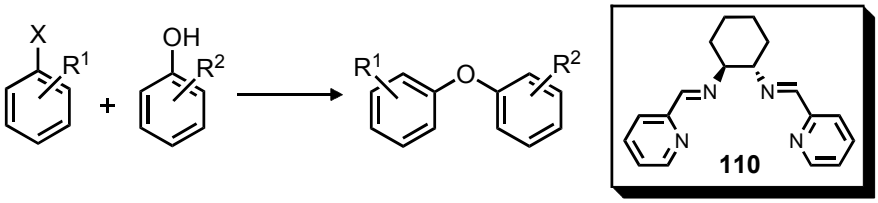
Entry	R^1	R^2	R^3	R^4	$\Delta G^{\neq}$kJmol^{-1}	$t_{½}$25°C
1	^{i}Pr	H	Me	H	epimerisation	< 1 μS
2	^{i}Pr	^{i}Pr	H	H	< 37	< 1 μS
3	^{i}Pr	^{i}Pr	Me	Me	< 37	< 1 μS
4	^{i}Pr	H	Me	Me	90.9	8 mins
5	^{t}Bu	H	Me	H	105	20h
6	^{t}Bu	H	Me	Me	113.5	50 days

Table 7: Barriers to rotation in diaryl ethers

The classic approach to diaryl ether synthesis is the metal catalysed Ullman coupling reaction. Initial synthetic work done by Boger[19c] during the synthesis of

vancomycin utilised an Ullman macrocyclisation to form the diaryl ether linkages of the final product. However, the harsh conditions of the traditional Ullmann coupling are not applicable to a wide variety of functional groups and so the search for a milder method of forming diaryl ethers has taken many forms.

Ullmann couplings of phenols and aryl halides under milder conditions have been reported by Cristau *et al.*[84] who reported high yielding reactions of aryl halides with phenols in acetonitrile using Cs_2CO_3 and catalytic copper (I) oxide in the presence of ligand **110** (Table 8).

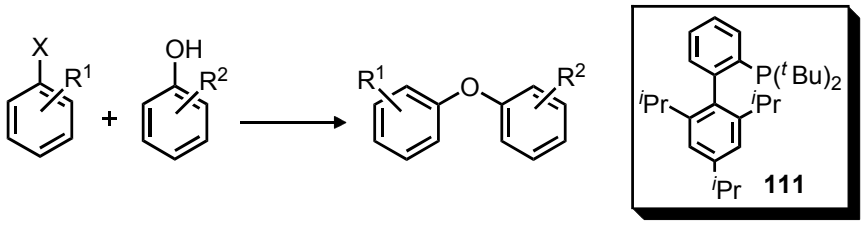


Entry	R^1	R^2	X	Time / h	T /°C	Yield / %
1	H	H	Br	90	110	100
2	H	H	I	24	82	100
3	H	2-Me	I	40	82	93
4	2-Me	2-Me	I	35	110	98

Table 8: Ullmann coupling results published by Cristau[84]

Although yields for the couplings were excellent the most hindered ether synthesised was di-*ortho*-methyl (entry 4), making this approach inappropriate for installing the large degree of hindrance around the axis required to observe atropisomerism.

The Buchwald group has also developed a series of ligands that promote the coupling of phenols with aryl halides, and have recently reported[85] the use of ligand **111** to aid the formation of a variety of *ortho*-substituted diaryl ethers in excellent yield (Table 9).

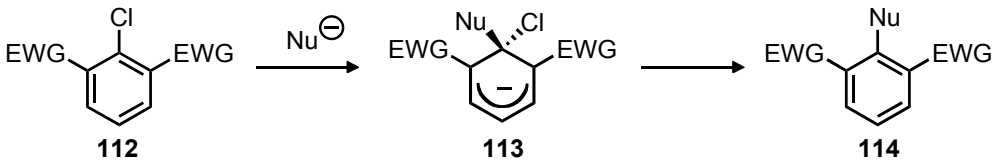


Entry	R^1	R^2	X	T / °C	Yield / %
1	4-CN	H	Br	100	94
2	4-CN	2-iPr	Br	100	84
3	3-NMe2	2-tBu	Cl	100	88
4	2-CO2Me	2-iPr	Br	100	78
5	2,5-di-Me	2-Me	Br	100	92
6	2-Me	2-iPr	Br	100	84

Table 9: Pd-catalysed coupling results published by Buchwald

Again, although Buchwald and co-workers managed to install a greater degree of steric hindrance *ortho* to the axis than in the corresponding Ullmann coupling, it can still be seen that as substituent size in this position increases, yields for the etherification invariably decrease. The publication also reported that it was not possible to synthesise ethers with greater than two *ortho*-substituents thus making this method inappropriate for the installation of high degrees of steric hindrance.

An alternative approach to the formation of hindered diaryls is the employment of an S_NAr reaction. Simple aryl halides do not undergo S_N1 or S_N2 reactions however the installation of strongly electron-withdrawing substituents in the *ortho* and/or *para* positions can promote S_NAr. The electron withdrawing groups (EWG) of compound **112** reduces the electron density of the π-system and allows the nucleophile (Nu^-) to approach the ring and form a negatively charged sigma complex, stabilised by de-localisation of the negative charge onto the electron withdrawing groups. The forward reaction then eliminates the chloride anion and reforms the aromatic ring (Scheme 30).



Scheme 30: S_NAr facilitated by ortho-electron withdrawing groups

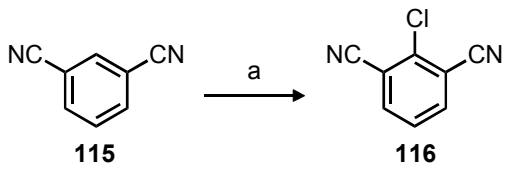
Mazzocchi *et al.*[86] reported forming diaryl ethers by substitution of aryl bromides

with Group I metal phenoxides. They synthesised a range of diaryl ethers as models of thyroid hormones for conformational studies. Both sodium and potassium stabilised phenoxides were utilised as reacting partners for the aryl bromides. This method avoids the requirement for expensive catalysts and was thought to be versatile enough to be used for the desired application.

S_NAr is generally less sensitive to steric hindrance than the metal catalysed coupling reactions and was therefore the method selected for the construction of the diaryl ethers described in this work.

2.1.2 Synthetic Strategy

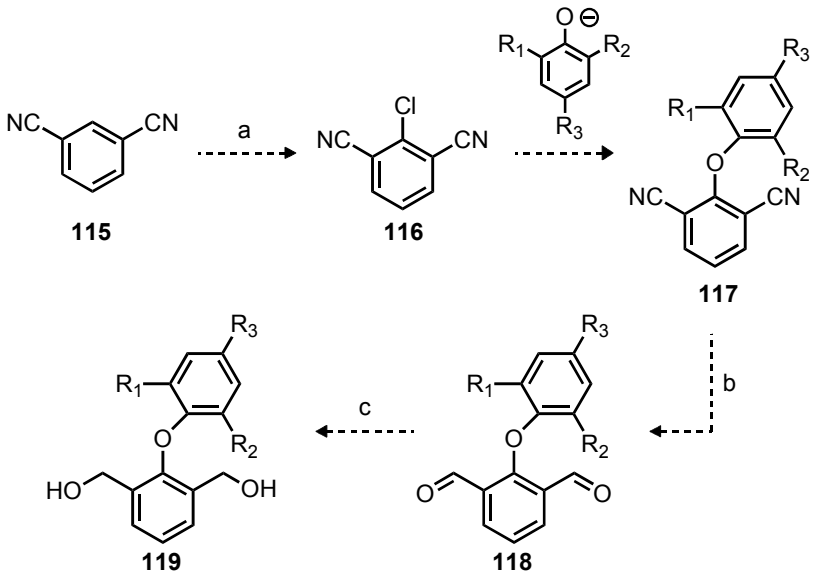
Krizan and co-workers[87] reported the selective lithiation and subsequent chlorination of isophthalonitrile **115** to yield **116** in excellent yield (Scheme 31), thus providing a reliable route to an activated aryl chloride partner that could undergo the required S_NAr.



115 **116**

Scheme 31: Chlorination of isophthalonitrile as reported by Krizan
(a) i) LDA, THF, –95 °C, 1 h. ii) Cl_3CCCl_3, –78 ºC - 20 °C, 16 h

These methods were therefore selected to afford a viable route to a range of *pro*-atropisomeric diaryl ethers, as outlined in Scheme 32.

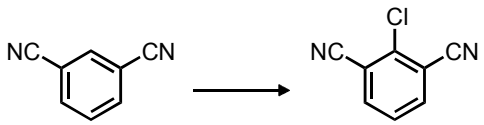


Scheme 32: Synthetic route towards potentially atropisomeric diaryl ethers
(a) i. LDA, THF, –95 °C, 1 h; ii. Cl_3CCCl_3, –78 ºC - 20 °C, 16 h
(b) i. DiBAL-H, –78 °C ,16 h; ii. HCl, H_2O, 1 h
(c) $NaBH_4$, THF, 16 h

The chlorinated compound **116**, prepared via selective lithiation with LDA at -98 °C followed by a Cl_3CCCl_3 quench, can be coupled with an appropriate phenoxide to give the dinitrile ether **117**. Reduction to the di-imine with DiBAl-H followed by acid hydrolysis will yield dialdehyde **118**, which on treatment with $NaBH_4$ will generate the final synthetic target **119**.

2.1.3 Chlorination

Directed lithiation of 1,3-dicyanobenzene **115** using LDA at -95°C followed by a hexachloroethane quench yielded the desired chloride **116** in up to 89% yield (Table 10).



115 **116**

Entry	Temp[a] / °C	Scale[c]	Temp[b] of C_2Cl_6 / °C	Solvent	Yield / %
1	–78	5g	RT	THF	15
2	–95	5g	RT	THF	70-89
3	-95	5g	RT	Toluene	49
4	–95	10g	RT	THF	48
5	-95	10g	-5	THF	70
6	-95	20g	RT	THF	69[d]
7	-95	20g	10	THF	36

Table 10: Yields and conditions of chlorination

[a] Temperature of reaction taken as the temperature of the solution of LDA before and during the addition of **115** and C_2Cl_6 [b] Taken as the temperature of the dissolved C_2Cl_6 before addition to deprotonated **115** [c] Scale based on the amount of **115** used in the reaction [d] Reaction carried out in a completely sealed reaction vessel with slow, controlled addition of reagents under vacuum

The reaction was seen to be extremely temperature dependent: lithiation and quench at -78°C resulted in only a 15% conversion to the product (entry 1). Furthermore, increasing quantities of starting materials above a 5g scale resulted in the mass recovery of **116** remaining the same (entries 2 → 4). Thus in order to obtain the quantities required for bulk synthesis, we were required to synthesise **116** in batches.

It was envisaged that a scale up of the reaction could be achieved by cooling both substrate **115** and the C_2Cl_6 quench to -95°C before the addition to LDA. However, attempts at cooling **115** were completely unsuccessful owing to its insolubility in THF below rt. Attempts to find a suitable solvent in which **115** could show improved solubility were also unsuccesful.

Improved success was observed on cooling the hexachloroethane quench, which remained in solution at -10°C when adequately diluted. Unfortunately, on a scale of 30g

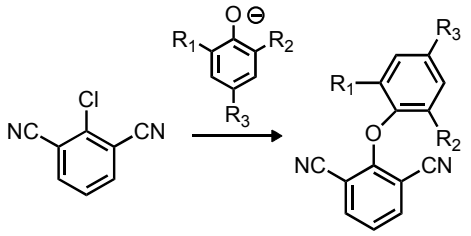
it was not possible (owing to the limiting size of the reactant cooling vessel) to achieve the necessary dilution at lower temperatures, and precipitation occurred.

Greater success was achieved by conducting the experiment using Schlenk apparatus and by using a vacuum assisted dropwise addition of both **115** and the hexachloroethane quench (entry 6).

The importance of purification was also highlighted during this synthesis: both flash column chromatography (where elution of **116** from its close running impurities was slow) and crystalisation of **116** from IPA appeared to provide similar levels of purification by ^{1}H NMR analysis. However, excess C_2Cl_6 (not visible on ^{1}H NMR) was found to crystallise out in IPA and contaminate large batches of product.

2.1.4 Diaryl ether formation

Formation of the *ortho*-substituted ethers was initially conducted via a two-step procedure (Method A). The reaction of phenol with KOH in toluene under Dean-Stark conditions followed by refluxing the formed phenoxide salt (after solvent removal) in DMF with **116** for 16 hours yielded **117** with varying success (Table 11).



116 **117**

Entry	117	Substituent R¹	R²	R³	Temp °C	Solvent	Base	Method	Yield[c] %
1	**a**	^{i}Pr	H	H	130	DMF	KOH	A	23
2					reflux	DMF	KOH	A	80-86
3	**b**	^{t}Bu	H	H	130	DMF	KOH	A	61
4					reflux	DMF	KOH	A	83
5					reflux	DMF	NaH	B	82
6	**c**	^{i}Pr	Me	H	reflux	DMF	KOH	A	69-71
7	**d**	^{t}Bu	Me	H	130	DMF	KOH	A	0
8					reflux	DMF	KOH	A	28[d]-52
9					reflux	MEG	KOH	A	0
10					reflux	DMF	KOH	B	7 + [b]
11					reflux	DMF	NaH	B	51
12						DMF	K_2CO_3	B[a]	54
13						DMSO	K_2CO_3	B[a]	0
14	**e**	^{t}Bu	Me	Me	reflux	DMF	KOH	A	49-62
15						DMF	K_2CO_3	B[a]	51

Table 11: Yields and conditions of diaryl ether formation

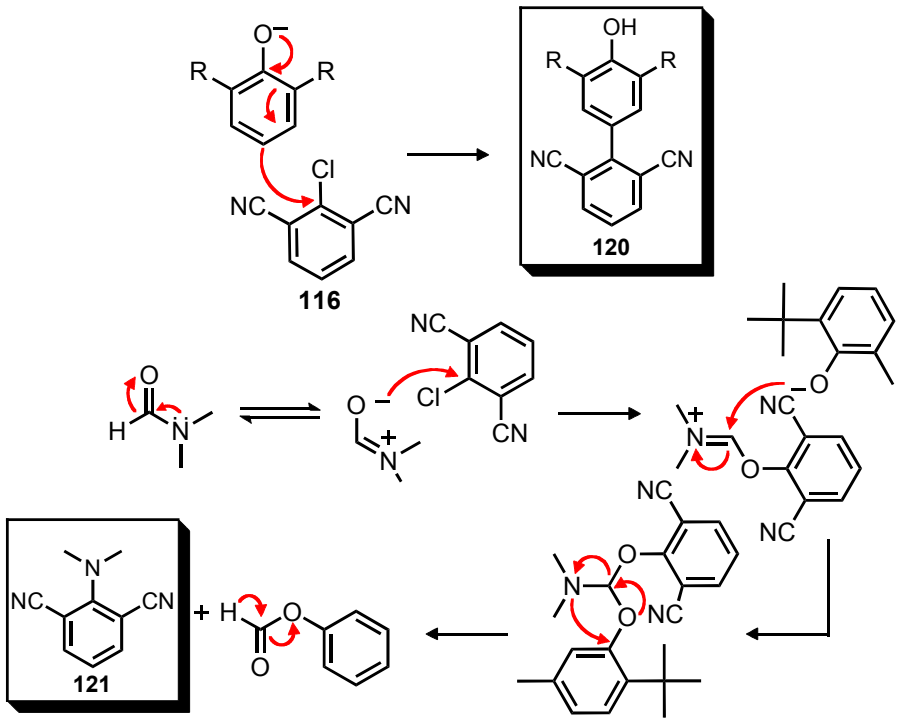
Method A: Phenol refluxed in toluene with KOH under Dean-stark conditions, toluene removed and replaced with DMF, then **116** added. Method B: Base added directly to phenol in solvent, stirred for 30 mins then **116** added
[a] Reaction carried out in the presence of 3 Å mol. sieves [b] Impurity **121** observed, yield not determined [c] Yield based on the scale of the reaction using ≤ 0.5g of **116**, unless otherwise stated [d] Yield carried out on a large scale based on using > 0.5g of **116**

Attempts at non-refluxing temperatures gave back either starting material or low yields of the desired product (entries 1, 3 and 7).

As expected, yields were found to be highly dependent on the nature of the *ortho* substituents; increased steric bulk resulted in decreased yields (entry 3 → entry 8).

Given the seemingly high dependance of the reaction on temperature, attempts at refluxing in the higher boiling point solvent ethylene glycol were made. However this resulted in only the starting phenol being returned, possibly due to the hygroscopic nature of the solvent. An attempt at employing DMSO as the reaction solvent returned large quantities of DMS under the harsh and long reaction times (entry 13).

Isolation and analysis of some of the major impurities of the reaction mixture provided some useful insights into the possible reasons behind the low yielding couplings of sterically encoumbered **117d.** Amino benzene **121** was thought to have been isolated due to the decomposition of DMF to Me_2NH or by the mechanism outlined in Scheme 33. In the case of biaryl impurity **120**, placing a substituent in the *para* position of the starting phenol led to an increased conversion to the ether (compare yields of **117d** with **117e**, entries 8 → 14).



Scheme 33: Possible reaction mechanisms for the formation of impurities **120** and **121**

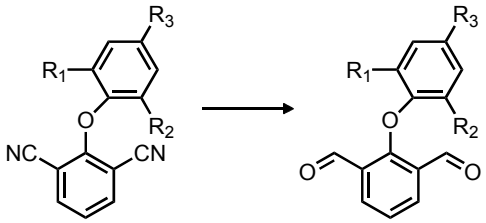
With respect to reducing reaction times and thus the possibility of solvent degradtion products, a microwave assisted coupling reaction was attempted. However,

complete return of starting materials coupled with the limited capabilities regarding the scales achievable resulted in this method being abandoned.

Atempts at combining phenoxide formation with the coupling step and negating the need to change reaction conditions succesfully reduced a step in the procedure with comparable results in yield, and for a range of bases (Method B, entries 5, 10-13 and 15 in Table 11).

2.1.5 DiBAl-H reduction

Addition of an excess (2.5 equivalents) of DiBAl-H in either toluene or DCM to **117** at various temperatures for between 12 and 16 hours followed by acid hydrolysis of the intermediate imine, yielded dialdehyde **118** (Table 12).



Entry	118	Substitution			Temp (°C)	Solvent	Yield (%)
		R^1	R^2	R^3			
1	a	^{i}Pr	H	H	-78	Toluene	62
2					-40	Toluene	47
3					0	Toluene	42
4					RT	Toluene	63
5	b	^{t}Bu	H	H	-78	Toluene	67
6					-40	Toluene	45[a]
7					-40	Toluene	[b]
8					RT	Toluene	54
9	c	^{i}Pr	Me	H	RT	Toluene	25
10					50	Toluene	9.4
11					-78	Toluene	75
12	d	^{t}Bu	Me	H	RT	Toluene	33-64
13					-40	Toluene	52-74[c]
14					-40	DCM	44-72[c]
15	e	^{t}Bu	Me	Me	-40	Toluene	65
16					50	Toluene	62

Table 12: Yields and conditions of DiBAL-H reduction
[a] DiBAL-H added dropwise through pressure equalised dropping funnel [b] Methanol quench before acid hydrolysis resulted in mainly acetal product [c] Addition of 6M HCl after work-up

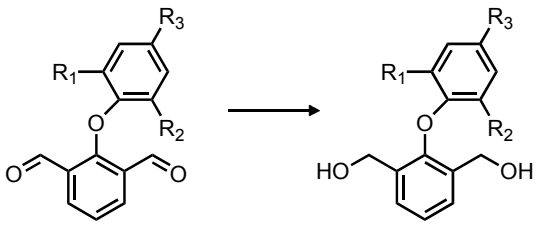
Optimum reaction temperatures appear to be between -40 °C and -78 °C, employing either toluene or DCM as the solvent. A large excess of the hydride reagent is also required to ensure formation of the di-aldehyde (the mono-aldehyde is almost inseparable from the desired di-aldehyde by column chromatography). In an attempt at reducing the exothermic nature of the acid hydrolysis, methanol was employed as a

DiBAl-H quench before addition of HCl. However this resulted in acetal formation, presumably via nucleophilic attack of the methanol.

The main problem regarding scale-up of the reaction seemed to be the formation of a large amount of insoluble sticky filtrate produced in the hydrolysis step. This filtrate was difficult to break down using various methods. A number of attempts were made to reduce its prevalence; slowing the addition of DiBAl-H, diluting the reaction mixture, reducing the temperature at the hydrolysis step and changing the reaction solvent to DCM. However, none were successful. It was eventually discovered that the addition of 6M HCl dissolved the filtrate after work-up, and after further work-up and purification, yields increased by as much as 63% (entries 13 and 14).

2.1.6 Borohydride reduction

Addition of a large excess of sodium borohydride to dialdehyde **118** at room temperature for 12-16 hours led to the formation of **119** with excellent reliability. The substituent patterns did not appear to have any effect on the yields of **119** and proceeded in up to 95% (Table 13).



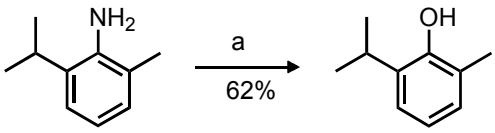
118 **119**

119	**Substitution**			**Yield (%)**
	R^1	**R^2**	**R^3**	
a	^{i}Pr	H	H	81
b	^{t}Bu	H	H	92
c	^{i}Pr	Me	H	88
d	^{t}Bu	Me	H	95
e	^{t}Bu	Me	Me	81

Table 13: Yields of $NaBH_4$ reduction

2.1.7 Routes to the commercially unavailable phenol

Of the four starting phenols utilised in the diaryl ether formation outlined in section 2.1.4, all but one, 2-*iso*-propyl-6-methylphenol, were commercially available. Given that the analogous aniline **122** was commercially available, it was proposed that a transformation to the diazonium salt by the method of Jones[88] followed by a Shine[89] transformation to the alcohol would yield the desired product **123**.



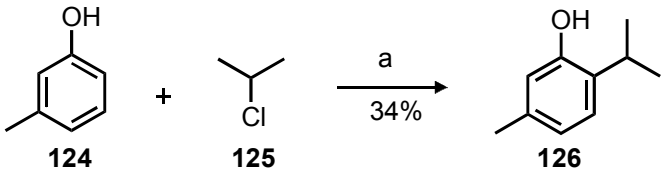
122 **123**

Scheme 34: Synthesis of phenol **123** via its diazonium salt
(a) i. *conc.* HCl, H_2O, dioxane, $NaNO_2$; ii. H_2SO_4, 50 °C

By the method of Jones,[88] **122** was dissolved in *conc.* HCl and dioxane and treated with sodium nitrite to form the diazonium salt. By the method of Shine[89] the diazonium salt was then added to *conc.* H_2SO_4 and heated for 16 h to yield **123** in overall 62% yield. However, having performed the reaction on a small scale the commercially available aniline became unavailable to repurchase for large-scale throughput.

A new method for the synthesis of a 2-*iso*-propyl-6-methyl substituted phenol **123** was therefore sought. As discussed in section 2.1.4, the *para*-substituted phenol ether used in the coupling of **117e** increased yields in the step by up to 10% compared to its 2,6-disubstituted analogue **117d** (entries 8 → 14, table 11, section 2.1.4). Given the difficulty outlined above in forming **123**, an alternative synthesis of a trisubstituted (2-*iso*-propyl-4-6-dimethyl) phenol **129** was planned in order to afford a *para*-substituted analogue of **123.** This could then be utilised in the S_NAr coupling step to effect higher yields than the 2-*iso*-propyl-6-methyl analogue **117c**.

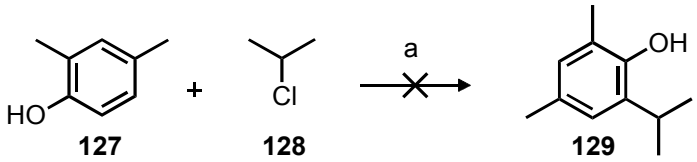
A 1936 patent[90] reported the *iso*-propyl alkylation of a number of substituted phenols utilising Fridel Crafts chemistry. One example included the conversion of *m*-cresol **124** into thymol **126** in 34% yield (Scheme 35). It was therefore envisaged that *iso*-propyl choride could react at the *ortho* position of commercially available 2,4-dimethyl xylene **127** in a similar fashion, to afford the required phenol **129**.



124 **125** **126**

Scheme 35: Reported synthesis of *ortho*-substituted phenol via Friedel Crafts chemistry[90]
(a) $AlCl_3$, 1,2-DCE

The commercially available xylene **127** was added to a solution of $AlCl_3$, before cooling to -10°C and adding isopropyl chloride **128** (Scheme 36).

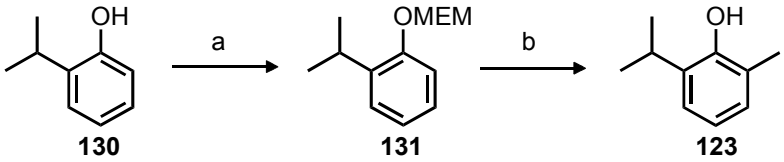


127 **128** **129**

Scheme 36: Attempted synthesis of **129** via Friedel Crafts chemistry
(a) $AlCl_3$, 1,2-DCE

However, the desired product **129** was not formed. The ^{1}H NMR appeared to show formation of a number of products that were not cleanly isolable either by flash column chromatography or distillation.

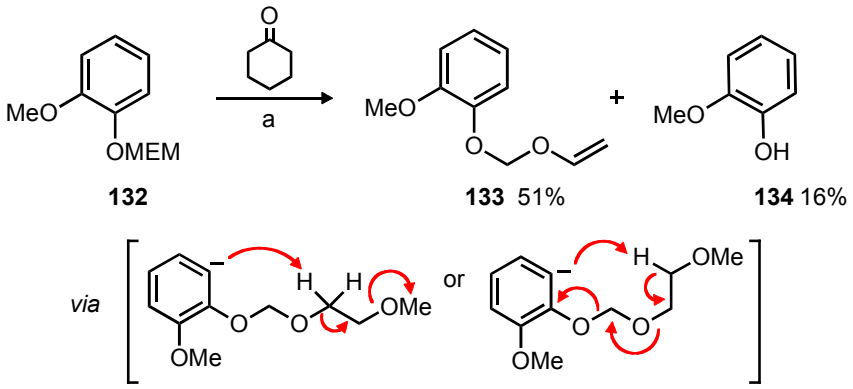
A new method was therefore derived from a method by James *et al.*[91] and is shown in Scheme 37.



130 **131** **123**

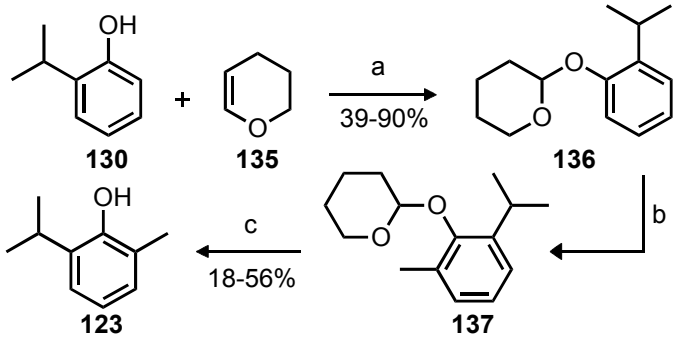
Scheme 37: New route to commercially unavailable phenol **127**[91]
(a) i. NaH; ii. MEMCl
(b) i. *n*BuLi; ii. MeI; iii. H^+ deprotection

Where James *et al.*[91] used methoxymethyl (MOM) chloride to protect the phenol, it was proposed to use methoxyethoxymethyl (MEM) chloride as a less toxic and more readily available protecting group. However, Moskowitz[92] reported the difficulty of using MEM as a protecting group for phenolic hydroxyl, as *ortho*-lithiation can lead to an intramolecular attack on the MEM group instead of the desired condensation (Scheme 38).



Scheme 38: Difficulty of ortholithiating in the presence of MEM
(a) *n*BuLi

Consequently, an alternative protecting group in the form of a 2-tetrapyranal (THP) ether was employed. A viable route to the commercially unavailable phenol **123** was therefore developed (Scheme 39).

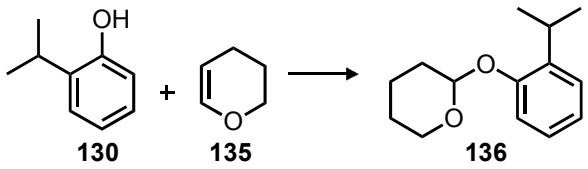


Scheme 39: Synthetic strategy towards commercially unavailable phenol
(a) H_2SO_4 on SiO_2, C_2CL_6
(b) i. *n*BuLi; ii. MeI
(c) AcOH deprotection

THP ether protected compound **136** was prepared via sulphuric acid adsorbed SiO_2 catalysis with phenol **130** (39-90%). This was then *ortho*-lithiated with *n*BuLi and quenched with MeI to afford **137**. Deprotection in AcOH/H_2O/THF afforded the final product **123** (18-56%).

2.1.7.1 THP ether protection

THP ether protected compound **136** was prepared via sulphuric acid adsorbed SiO_2 catalysis[93] with phenol **130** (Table 14).



130 **135** **136**

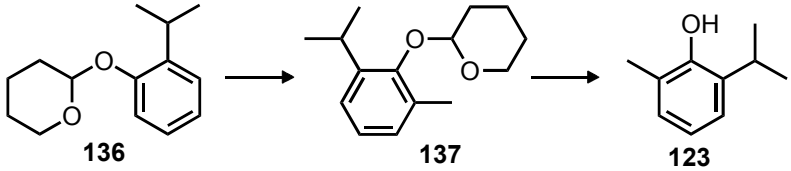
Entry	Scale (based on 130) / cm^3	Yield / %
1	1	89
2	20	57-90
3	30	39

Table 14: Yields and conditions of THP ether protection

The decline in yield (entries 1 → 3) was attributed in part to a loss in activity over time of the acidified silica gel.

2.1.7.2 Ortho-*lithiation, quench and deprotection*

Formation of the doubly *ortho*-substituted phenol was conducted via addition of the mono alkylated THP ether **136** to a stirring suspension of *n*BuLi and TMEDA in an ice bath, followed by an electrophile quench and then a deprotection in AcOH to yield **123** (Table 15)**.**



136 **137** **123**

Entry	Scale (based on 136) / g	Conditions	Quench	Yield[a] / %
1	1	[b]	MeI	56
2	27.5	[b]	MeI	28
3	1.45		MeI	18
4	10		MeI	12[c]
5	9.5		Me_2SO_4	-

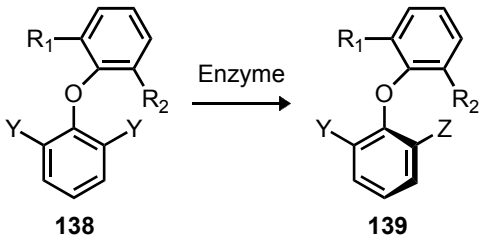
Table 15: Yields and conditions of *ortho*-lithiation and methylation
[a] yield calculated from **136** [b] **136** added slowly to a stirring suspension of *n*BuLi/TMEDA through a pressure equalised dropping funnel [c] calculated yield was an inseperable mixture of **123** and **130**

Isolated yields of **137** were unavailable due to the product being inseparable from the starting material **136**. The crude mixtures were therefore reacted without further purification to yield **123**. Eventual purification of **123** also proved to be problematic, thought in part to be attributable to phenols **123** and **130** (from the deprotection of unreacted **136**) being soluble in one another. A number of purification techniques were attempted; separation on acidified silica, recrystallisation of the phenoxide salts of the compounds and distillation - all of which were unsuccessful.

An NMR study of a deuterated quench of the lithiated species of **136** with MeOD demonstrated that there was a 75% conversion to product, indicating that the electrophilic quench and not *ortho*-lithiation was the problematic step. To this end, a different form of electrophilic methyl was sought in the form of Me_2SO_4. However, this was seen to give a complex reaction mixture on deprotection (entry 5). Consequently, the highest yields were obtained by adding the substrate slowly to *n*BuLi/TMEDA via a pressure-equalising dropping funnel up to a 1g scale (entry 1).

2.2 Biocatalytic Desymmetrisation of Diaryl Ethers

With large quantities of *pro*-atropisomeric compounds **118** and **119** now available, we turned our attention towards a strategy for desymmetrisation. As previously mentioned, Matsumoto[78] had employed an enzyme to effect an enantiopos-differentiating transformation of a biaryl with excellent success (section 1.4.8.2), and the added ecological benefit of such a process seemed appealing.



138 **139**

Scheme 40: Desymmetrisation of an atropisomeric achiral ether

From a synthetic viewpoint, one of the most appealing features of enzymes is their specificity; they only touch the functional group corresponding to their active site and in most cases will only react with or produce a single enantiomer of a given compound. Indeed, by far the best asymmetric syntheses are achieved in nature by enzymes and their ability as chiral host molecules to discriminate between enantiomers of a racemic substrate is of well-recognised preparative value. For example, the resolution of racemic mandelate by pig liver esterase was published by Dakin[94] as early as 1903.

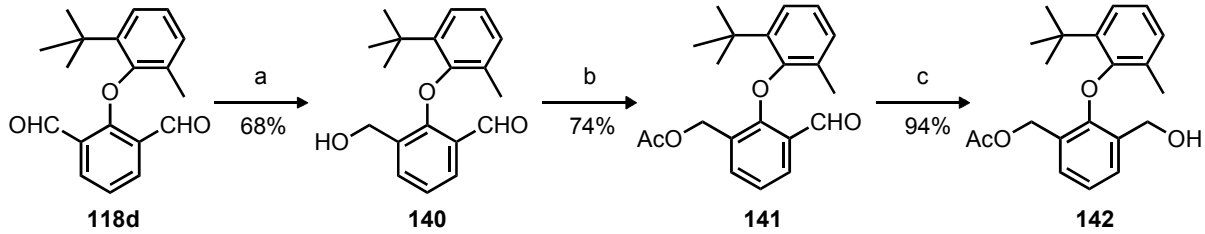
Against this background, we decided to investigate a biocatalytic approach to the enantioselective synthesis of atropisomeric diaryl ethers, based on the desymmetrisation of appropriately achiral substrates containing a pair of enantiotopic functional groups (Scheme 40).

2.2.1 Enantioselective acylation and deacylation

The selective enzymatic acylation and deacylation of alcohols has become a powerful technique for the preparation of optically enriched compounds and is practiced both in laboratory and large-scale production.[95,96] Initial screens of our compounds were therefore undertaken with the readily available enzymes shown to be effective by

Matsumoto;[78] *Pseudomonas fluorescens* lipase (PFL) and *Pseudomonas cepacia* lipase (PCL).

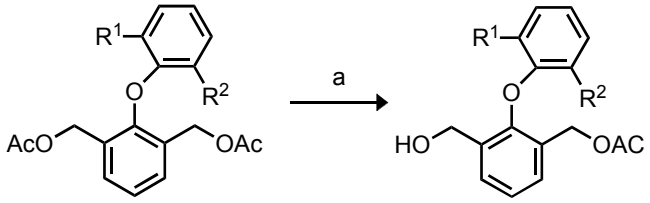
A racemic reference was first synthesised in order to effectively measure the enantioselectivity of the reaction by HPLC. Dialdehyde **118d** was selectively reduced with 0.25 equivalent of $LiBH_4$ (68% yield) before acylating via an NaH deprotonation followed by an acetic anhydride quench in refluxing diethyl ether (74%). Further reduction in $NaBH_4$ afforded the mono acylated product **142** in 92% yield (Scheme 41).



118d **140** **141** **142**

Scheme 41: Synthesis of a mono-acylated racemic reference
(a) 0.25 eq. $LiBH_4$, 0 °C, EtOH
(b) i. NaH; ii. Acetic anhydride
(c) $NaBH_4$, THF

The results of the incubation of our substrates with both PCL and PFL are shown in Table 16, where unfortunately very little activity was displayed towards the ethers and the selectivity in all cases was nil.[97]

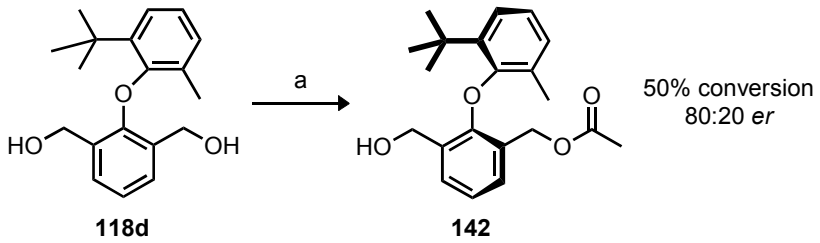


143 **142**

Entry	Substitution R^1	Substitution R^2	Enzyme	Temp	Time	Yield / % 143	Yield / % 142	er
1	^{i}Pr	H	PCL	40 °C	10 d	100	0	-
2	^{i}Pr	H	PFL	40 °C	10 d	47	30	-
3	^{t}Bu	H	PFL	RT	4 wk	100	0	-
4	^{t}Bu	H	PCL	40 °C	7 wk	100	0	-
5	^{t}Bu	H	PFL	40 °C	7 wk	82	12	-
6	^{t}Bu	Me	PCL	40 °C	7 wk	100	0	-
7	^{t}Bu	Me	PFL	40 °C	7 wk	100	0	-
8	^{t}Bu	Me	PFL	50 °C	22 d	100	0	-

Table 16: Activity and selectivity of deacylation with lipase enzymes
(a) Lipase, 1:2 acetone:0.1 M phosphate buffer solution (pH 7) in water

An enantioselective acylation was therefore undertaken using *Candida antartica* lipase B and vinyl acetate (Scheme 42).



118d **142**

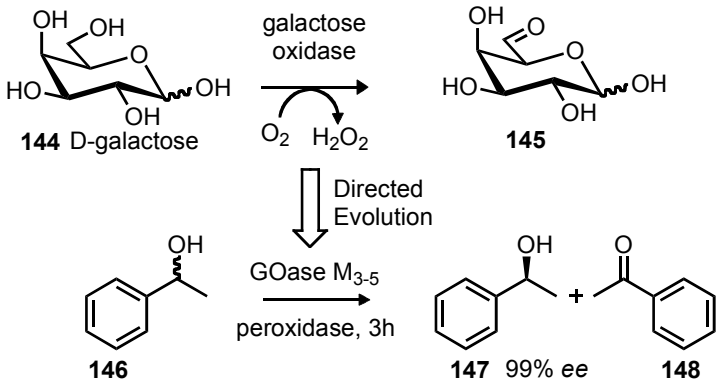
Scheme 42: Acylation with CAL-B and vinyl acetate
(a) CAL-B, vinyl acetate

In this case slow acylation of **118d** was observed with approximately 50% conversion after 24 hours and modest enantioselectivity of 80:20 er. Consequently, our attention turned towards the application of a different class of enzyme.

2.2.2 Kinetic resolution by enantioselective oxidation

Kinetic resolutions of atropisomers offer the added benefit of being able to recover, racemise and recycle the unreactive enantiomer. Despite this, their application in synthesis is rare,[65,98] and the enzymatic kinetic resolutions of both biaryl[78,99] and non-biaryl atropisomers[100] are a relatively recent development.

Galactose Oxidase (GOase) is a soluble, copper-dependent enzyme that catalyses the O_2 dependent oxidation of the C6-OH of D-galactose **144** to the corresponding aldehyde **145** (Scheme 43). Turner *et al*[101] successfully changed this specificity from a 1º to a 2º alcohol oxidase capable of enantioselective oxidation and with the ability to bind nonpolar, rather than polar substrates. The groups directed evolution approach through random mutagenesis and screening identified a varient of the enzyme, GOase $M_{3\text{-}5}$, which possessed good activity towards a range of 1-phenylethanol templates, and with high enantioselectivity (99% ee). We therefore hoped to apply this enantiodiscriminating oxidase enzyme to our diols.



Scheme 43: Directed evolution of GOase

2.2.2.1 Initial screening and method development

Our initial focus was to investigate what, if any, effect the substitution pattern of our diaryl ethers had on the oxidative ability of the GOase M_{3-5} enzyme. In collaboration with Bo Yuan and Prof. Nick Turner[102] at the Manchester Interdisciplinary Biocentre, diaryl ethers **118a-d** (synthesis described in section 2.1) were screened for their activity using a peroxidase based assay. Oxidase-catalysed H_2O_2 formation (intrinsically linked to the enzmes activity) was used in conjunction with a peroxidase enzyme and the substrate ABTS (2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) to produce a green pigment (Figure 13). The reaction kinetics were then indirectly measured by following the absorbance increase at 420 nm (Figure 14).

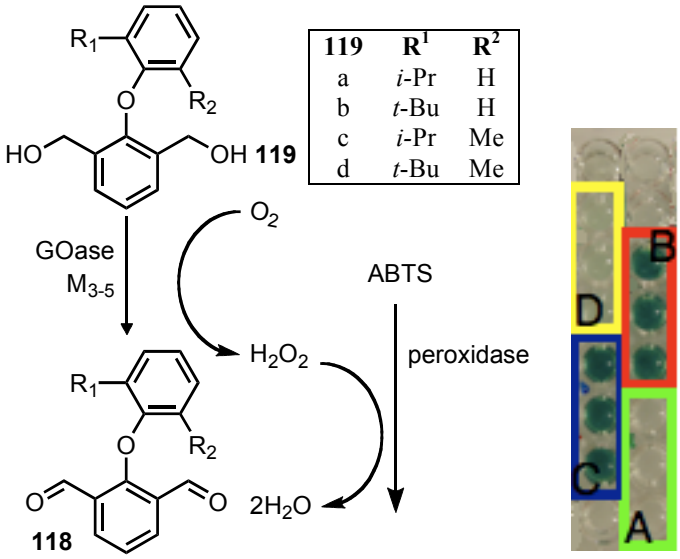


Figure 13: ABTS peroxidase assay to measure activity of GOase towards substrates **119a-d**

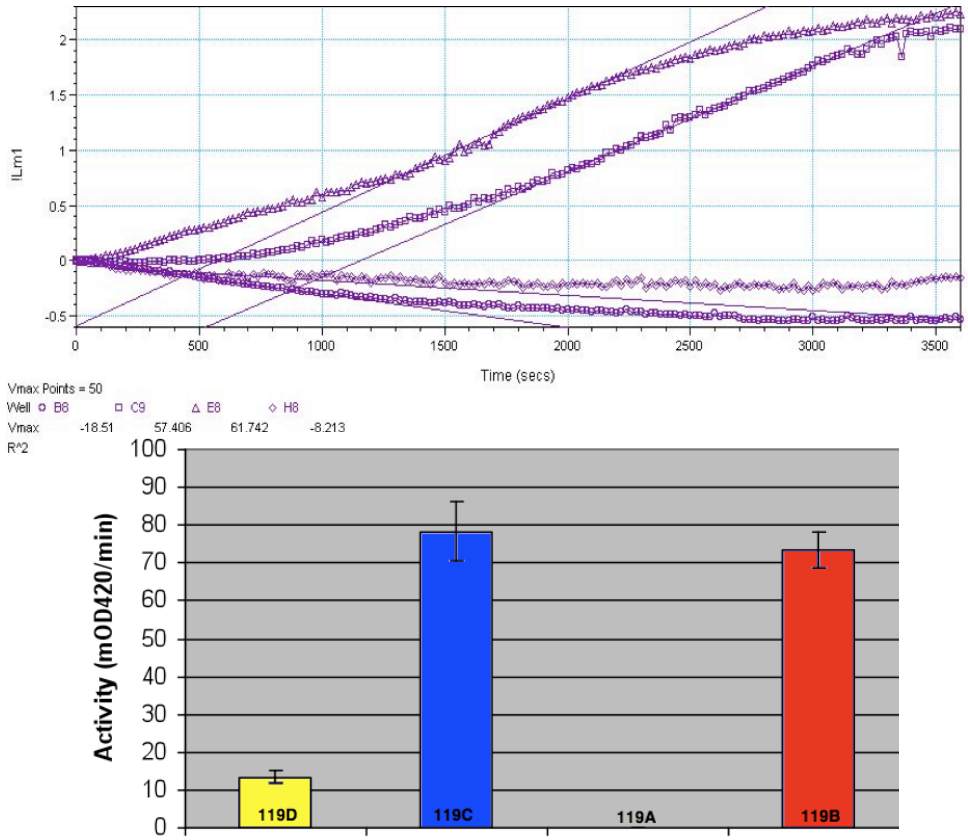
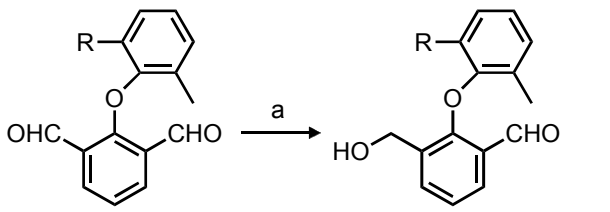


Figure 14: Activity screening of diols **119a-d** with GOase M_{3-5}

Despite the insolubility of the diols in the assay mixture, it was possible to measure activity for compounds **119b-d**. The highest activity was observed for compounds **119b** and **119c** with some activity observable for **119d**. However no activity was observed for compound **119a**.

The most promising diols **119c** and **119d** (based both on their activity and their potential for being stable chiral atropisomers) were then taken through for enantioselective studies with the enzyme. As a result, racemic references for their monoreduced analogues were synthesised (Scheme 44).



118c R = ^{i}Pr
118d R = ^{t}Bu

149 R = ^{i}Pr 72%
140 R = ^{t}Bu 68%

Scheme 44: Synthesis of racemic references for GOase M_{3-5} enzyme study
(a) 0.25 equivalent $LiBH_4$, 0 °C, EtOH

Diadehydes **118c** and **118d** were treated with 0.25 equivalents of lithium borohydride at 0 ºC for 1 hour in ethanol to yield the monoaldehydes **140** and **149** in up to 72% yield. HPLC analyses were then taken of the monoreduced products in order to find suitable conditions and retention time references for their enantiomer seperation.

The inherent insolubility of diols **119a-d** under the aqueous conditions of the study lead us to screen a number of water-miscible solvents. It was found that MBTE and DMSO gave the largest degree of solubility while still remaining compatible with the enzyme's activity. However, a large degree of variation between the selectivity of GOase M_{3-5} towards our substrates in MTBE under seemingly identical conditions made the low volatility of the solvent an unsuitable choice. Although the initial screens were undertaken in an assay mixture of 10%, the enzyme was found to tolerate assay mixtures of up to 30%, overcoming our solubility issue.

Initial method development was undertaken on quantities of monoaldehyde **140** by Bo Yuan (Table 17). The preferential oxidation of one monoaldehyde enantiomer was monitored by HPLC, and found largely to depend on enzyme quantity (entries 1 → 3) and assay component (entries 3 → 5).

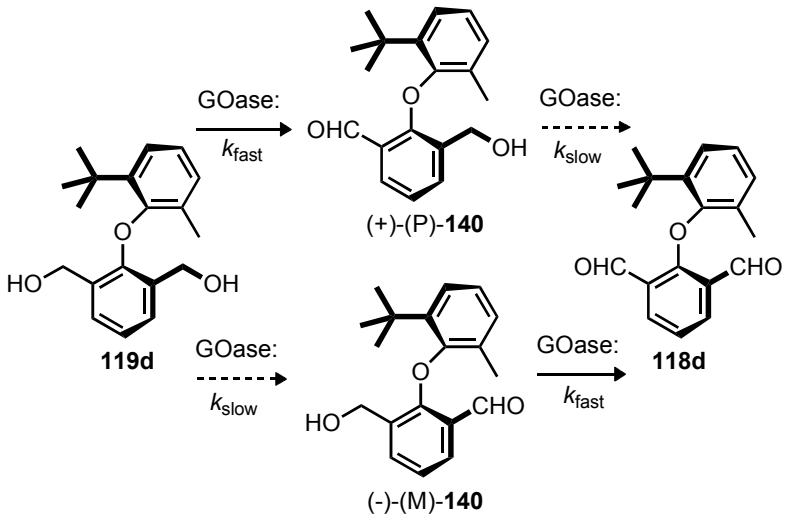
Entry	Assay component	Enzyme Quantity	Reaction Time	er
1	30% MTBE (aq)	28.9 µl	3 hours	50:50
2	30% MTBE (aq)	28.9 µl	6 hours	51:49
3	30% MTBE (aq)	57.8 µl	3 hours	65:35
4	30% MTBE (aq)	57.8 µl	21 hours	61:39
5	30% DMSO (aq)	57.8 µl	3 hours	98:2

Table 17: Selectivity enhancement of GOase M_{3-5}

2.2.2.2 Results of incubating 119 c and 119d with GOase M_{3-5}

Diols **119c** and **119d** were incubated with the GOase M_{3-5} enzyme under the optimised conditions and the course of the reaction followed by HPLC analysis (Scheme 45, Figure 15). Unfortunately, the attempted kinetic resolution of the less hindered diol **119c** (with an *ortho* isopropyl in place of the *ortho tert*-butyl of **119d**) returned a racemic compound. This was thought to be most likely as a result of racemisation of the compound on the timescale of the reaction. Although **119c** is resolvable by HPLC, our

work with related compounds[26] featuring similarly low barriers to racemisation seems to corroborate this theory.



Scheme 45: Enantioselective oxidation of pro-atropisomeric diarl ethers

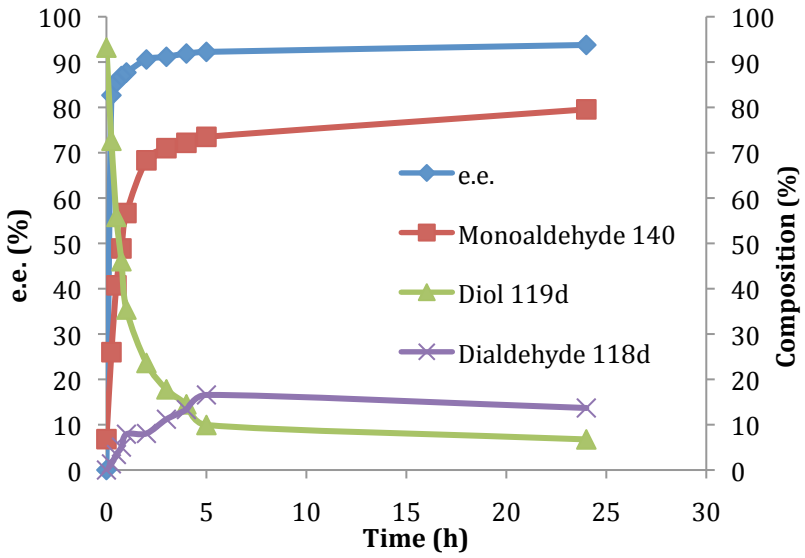


Figure 15: Enantioselective desymmetrisation of **119d** using GOase $M_{3\text{-}5}$ variant

Incubation of diol **119d** with the enzyme rapidly produced the oxidised ***P*-140** (see section 2.2.2.3 for assignment of configuration) in approximately 88% ee after just 1 hour. This was followed by a seemingly slower increase to a maximum ee of 94% after 24 hours.

This increase in ee, along with the formation of dialdehyde **118d** (14% after 24h), suggests that the minor enantiomer *M*-**140** produced in the enantioselective oxidation of **119d** is preferentially being removed by a secondary oxidation process to the dialdehyde

118d. Thus the final enantiomeric purity of *P*-**140** is determined by a combination of enantioselective desymmetrisation and kinetic resolution, as has been noted before in other systems.[77]

2.2.2.3 Assignment of configuration

The absolute sense of the enantioselective oxidation was established by comparing the experimental and modelled circular dichroism spectra of the remaining starting material from the kinetic resolution, (+)-*P*-**140** (Figure 16).

The modelled spectra was obtained by Dr. J. McDouall using density functional calculations at the B3LYP/6-311G(d,p) level, with the Gaussian suite of programs.[103] Favoured conformations of **140** were identified by taking the X-ray crystal structure of **118d**[104] and modelling the replacement of firstly the pro-*M* and secondly the pro-*P* formyl group with a CH_2OH group. Minimization of these starting structures led to two diastereoisomeric conformations differing in energy by 2 kJ mol^{-1}.

Taking the enantiomer of the lower energy conformation having *P* stereochemistry at the stereogenic axis, time-dependent density functional (TD-DFT) calculations of the lowest 100 electronically excited states were obtained. These data were then used to simulate the CD spectra of both conformations with the GaussSum package.[105]

The CD spectra are simulated by overlapping Gaussian functions for each transition using the excitation energies and rotatory strengths (using the dipole length representation).[106] The quality of the fit may be controlled by specifying the width of the bands and we found that a width of 0.4 eV produced the CD spectrum of *P*-**140** illustrated by the pink line (Figure 16).

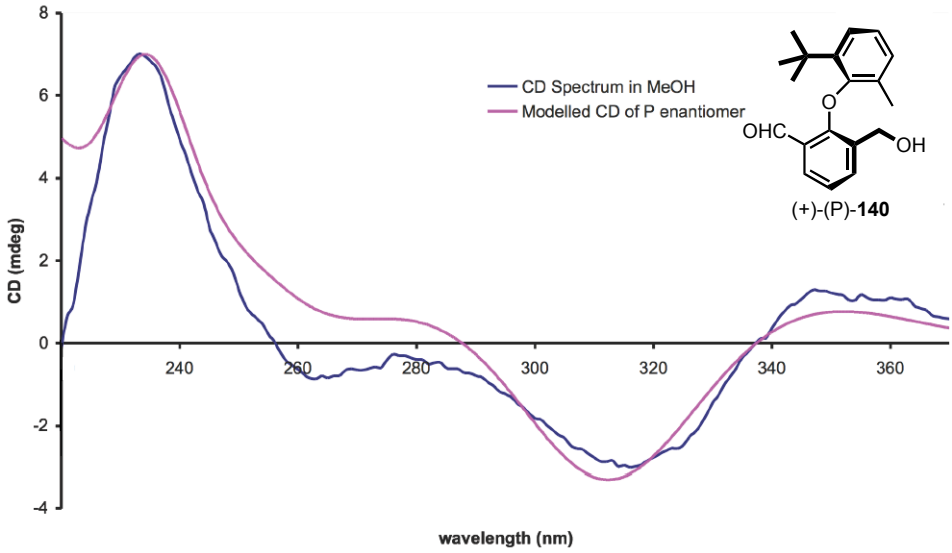


Figure 16: CD spectra of (+)-P-**140**: (blue line) observed for the slower reacting enantiomer of **140**; (pink line) modelled for the lowest energy conformer of P-**140**

The modelled spectrum matches the experimental CD spectrum (Figure 16, blue line) very closely, with positive maxima aligning at 234 (observed) and 235 (modelled) nm and at 348 (observed) and 353 (modelled) nm. A negative maximum at 313 (observed) and 316 nm (modelled) nm also practically align, while a shoulder in both observed and modelled spectra appear at 280 nm. The match confirmed that the slower reacting enantiomer of **140**, and hence also the product of the desymmetrisation of **119d**, has *P* stereochemistry (Scheme 45).

Further confirmation of our assignment of configuration came from modelling the active site of GOase, which is characterised by a bowl-shaped cleft near the surface of the protein.[107] The $M_{3\text{-}5}$ variant contains a mutation at position 330 compared to the wild-type (Lys →Met) and this residue has previously been identified as important in controlling substrate recognition. A homology model of the GOase $M_{3\text{-}5}$ was therefore created using the crystal structure of the E1 mutant (PDB code ZWQ8) as a template, which consists of two amino acid changes from the $M_{3\text{-}5}$ mutant. Docking the two enantiomers of **140** into the binding site of GOase using the CHARMm forcefield implemented in Accelrys Discovery Studio 2.5, revealed that the bulky *tert*-butyl group of the substrate is forced to occupy a position in which it is pointing away from the cleft and towards the surface of the protein. In such a binding mode, the hydroxymethyl group of *M*-**140** is placed close to the copper-containing reactive centre poised for oxidation to the aldehyde (Figure 17).

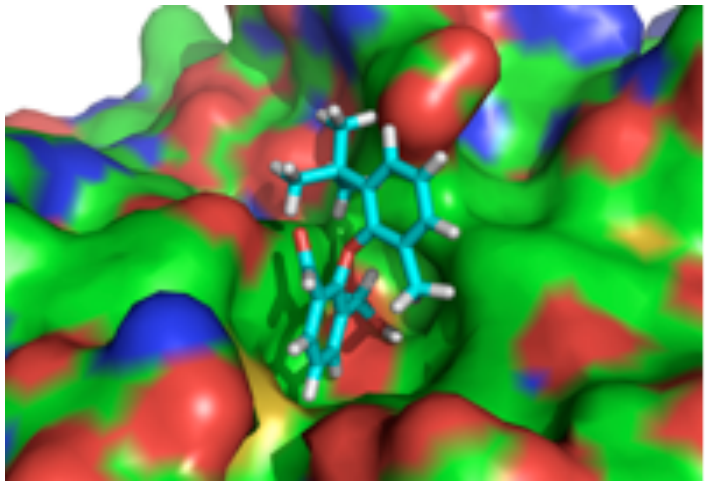


Figure 17: Docking model of the faster reacting enantiomer (M)-**140** into the active site of GAose M_{3-5}

This model therefore predicts that *M*-**140** is the faster reacting enantiomer in the kinetic resolution process and thus the opposite enantiomer to the enantioenriched sample left behind by the enzyme. This observation is in agreement with the assignment of absolute configuration based on circular dichroism.

2.2.2.4 Determining the enantioselectivity and E-value

As kinetic resolutions invariably involve a trade-off between yield and enantiomeric excess, their reactions are best characterised by an enantioselectivity factor *(E)*. This value quantifies the treatment of biochemical data and allows the synthetic chemist to make useful predictions by relating the parameters of conversion (c) and optical purity (ee).

To investigate the enantioselectivity of the kinetic resolution process, racemic monoaldehyde (±)-**140** was incubated with the GOase M_{3-5} variant resulting in 89% conversion after 24h (Figure 18).

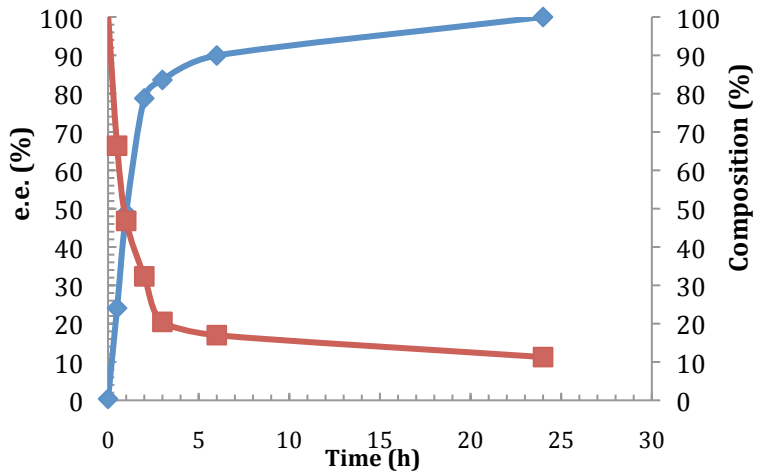


Figure 18: Kinetic resolution of (±)-**140** using GOase M_{3-5} variant: Composition ■ = monoaldehyde **140**; ♦ = ee%.

As expected, the remaining atropisomer was of *P*-configuration with an ee of 99%. This also confirmed that the resolution process proceeds more slowly than the desymmetrisation reaction (incubation of the diol returned an 88% ee within an hour).

Entry	Time / h	Conversion / %	ee / %	E
1	0.5	34	24	3.54
2	1	53	49	3.95
3	2	68	79	4.89
4	3	80	84	3.47
5	6	83	90	3.60
6	24	89	99	4.54

Table 18: Kinetic resolution of GOase M_{3-5} and determination of E number

The relationship between the extent of conversion *(c)* and the enantiomeric excess of the recovered substrate fraction (ee(S)) for various values *(E)* was calculated using:

$$E = \ln[(1-c)(1-ee(S))]/\ln[(1-c)(1+ee(S))]$$ [108]

The kinetic resolution under these conditions has a selectivity (*E*) value of approximately 4 (Table 18).[109]

2.2.2.5 Determining the the configurational stability

The half-life to racemisation and thus the barrier to rotation about the chiral axis of the enantiomerically enriched (+)-(*P*)-**140** (obtained from the kinetic resolution) was established by incubation in heptane at 90 °C, with the decay in ee measured by HPLC (R,R-whelk-o1) as a chiral stationary phase, eluting with hexane: IPA 97:3 at 0.5 ml/min. The relative concentration of the enantiomers was measured regularly (Table 19).

Time / mins	% A	% B	ee / %
0	19	81	62
690	19	81	62
1440	21	79	58
3335	23	77	54
4895	32	68	36
6735	33	67	34

Table 19: Racemisation of monoaldehyde (+)-*P*-**140** by incubation in heptane at 90 °C

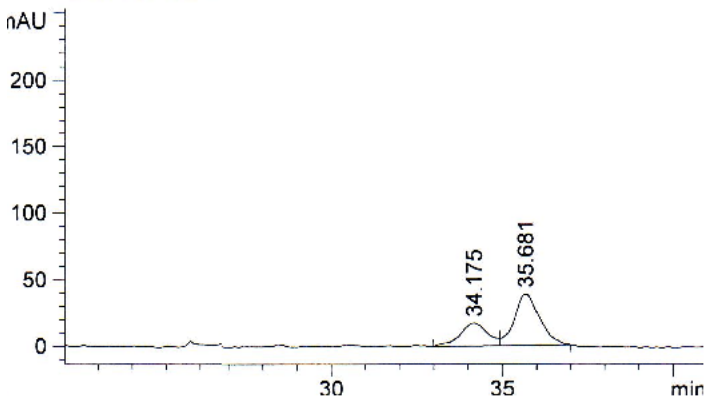


Figure 19: HPLC trace of monoaldehyde (+)-*P*-**140** (Chiralcel R,R-Whelk column running 97:3 hexane:IPA at 0.5 ml/min)

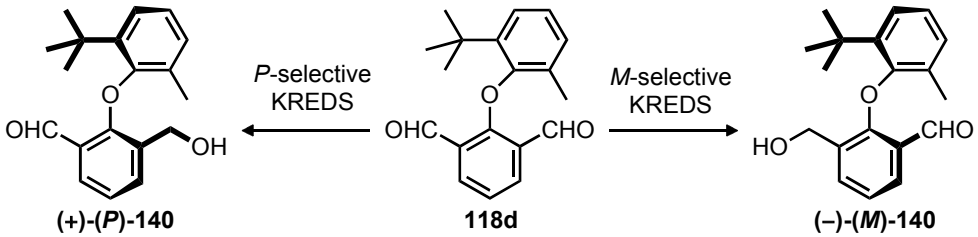
A slow first order decay in the ee value from 62 to 34% was observed over a period of several days. Fitting to the equation ee = ee(t=0) • e^{-kt} gave the first order rate constant, $k = 1.605 \times 10^{-6}$ s.

The Half-life for racemisation was then calculated using the equation: $t_{½} = \ln 2 / k$ from which we deduced the half-life for racemisation at this temperature to be 120 h. This in turn gives an estimation of a barrier to enantiomerisation greater than 130 kJ mol^{-1} at 90 °C.[110]

2.2.3 Desymmetrisation with Ketoreductases

We also examined an alternative approach to the synthesis of enantiomerically enriched monoaldehyde **140**, via asymmetric reduction of the symmetrical dialdehyde **118d** using ketoreductases (KREDs).

KREDs have been widely applied to the asymmetric reduction of ketones, particularly benzylic ones,[111] but to our knowledge had not previously been used for the desymmetrisation of *pro*-atropisomeric substrates. A panel of 17 different KREDs[112] were therefore screened and the conversions and ee value of the product determined after 24 hours (Scheme 46, Table 15).



Scheme 46: Reduction of **118d** with ketoreductases (KREDs)

Entry	Enzyme	Conversion[b] / %	ee / %	Configuration[c]	R / S[a]
1	KRED101	53	24	*P*	*R*
2	KRED103	6	22	*P*	-
3	KRED104	3	75	*M*	-
4	KRED105	2	99	*M*	-
5	KRED106	3	11	*P*	-
6	KRED108	39	78	*M*	*S*
7	KRED109	3	54	*M*	-
8	KRED110	1	99	*M*	-
9	KRED114	95	40	*M*	-
10	KRED115	33	9	*M*	*R*
11	KRED116	23	79	*M*	-
12	KRED117	7	79	*M*	-
13	**KRED118**	**91**	**77**	***P***	***S***
14	KRED119	99	71	*P*	*S*
15	KRED120	22	87	*M*	*S*
16	**KRED121**	**84**	**61**	***M***	***R***
17	KRED124	3	99	*M*	*R*

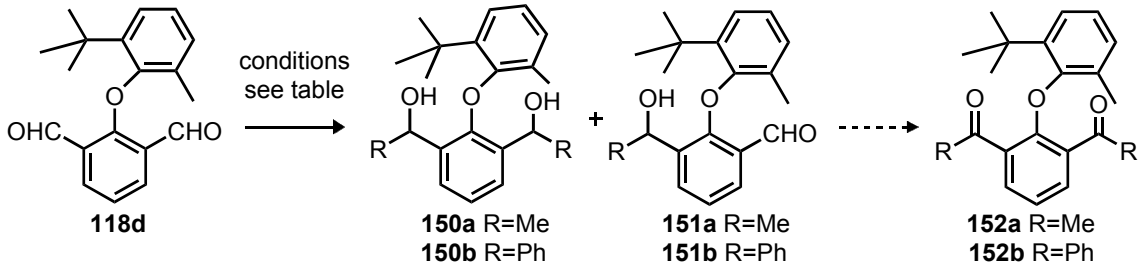
Table 20: Reduction of **118d** with ketoreductases (KREDs)
[a] The typical selectivity of the KRED in the reduction of nonsymmetrical diaryl ketones is shown (when known).[111] [b] Conversion after 24 h. [c] Major enantiomer produced by reduction

All of the enzymes showed activity and often high enantioselectivity (Entries 4, 8 and 17) although some with low conversion. Notable successes were achieved with KRED118 (91% conv., 77% ee *P*-enantiomer) and KRED121 (84% conv., 61% ee *M*-enantiomer). These KREDs have previously been classified as either (*S*)- or (*R*)-selective based upon their stereoselectivity in the reduction of non-symmetrical diaryl ketones.[111]

Interestingly, this trend is not always followed for the reduction of **118d**, *i.e.* enantiomerically enriched *P*-**140** was obtained from both an (*R*)-selective KRED101 and (*S*)-selective KRED118. Similarly, *M*-**140** was obtained from both (*R*)- (KRED121) and (*S*)- (KRED108) selective enzymes. These results suggest that dialdehyde **118d** binds at the active site of the ketoreductases in a different mode to that adopted by more conventional benzylic ketones.

2.2.3.1 Towards the desymmetrisation of a diketone

In order to assess the KRED activity against a ketone analogue of our compound, diketone **152** became a target for synthesis. It was envisaged that the diketone could be synthesised by a double Grignard addition to dialdehyde **118d**, owing to the large stocks of this compound, followed by an oxidation to afford **152** (Scheme 47).



Scheme 47: Synthetic strategy towards diketone **150** from aldehyde **118d**

However, attempts to make the diol **150** from dialdehyde **118d** with this organometallic species were low yielding at the second addition (Table 21). The main products of the reaction were the monoaddition product **150** and an unidentified impurity, **X**. Sequential addition: taking the mono addition product and resubjecting it to the same reaction conditions also failed.

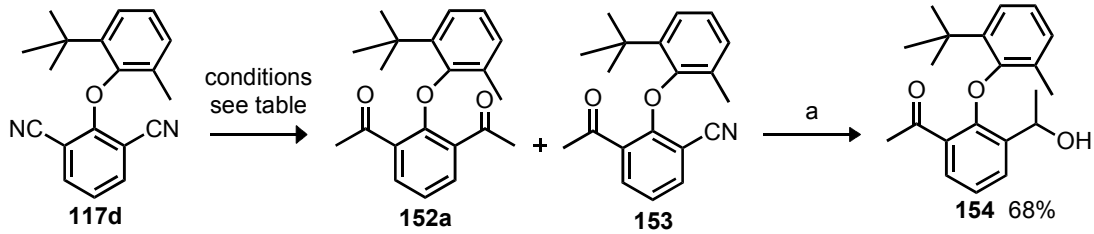
Bartoli[113] reported enhancing the electrophilicity of carbonyl groups (and therefore the subsequent addition of the organomagnesium reagent), by carrying out the

addition in the presence of an organocerium reagent. However, although addition of this product suppressed the formation of the unidentified side product (entries 10 and 11), neither monoaddition **151** or product formation **150** occurred. The diol was eventually reached however by addition of 6 equivalents of (non-coordinating) PhLi at -78 ºC in ether (entry 14).

Entry	Conditions[a]	RLi / RMgBr	Eq	Yield / %			
				118d	**151**	**X**	**150**
1	-78 ºC, 4 h → RT 12 h	MeMgBr	3	82	9	3	5
2	0 ºC, 4 h → RT 12 h	MeMgBr	10	-	20	50	13
3	0 ºC, 4 h → RT 12 h	PhMgBr	4	-	31	-	4
4	Benzene, -78 ºC, 8 h	MeMgBr	6	-	53	14	20
5	RT, 12 h	MeMgBr	3	34	42	7	12
6	RT, 16 h	MeMgBr	6	34	42	7	12
7	65 ºC 7 h	MeMgBr	3	15	51	7	15
8	65 °C 7 h	MeMgBr	10	-	4	38	28
9	65 ºC, 12 h, 1:1Benzene:THF	MeMgBr	3	7	68	/	/
10	0 ºC, 4 h	MeMgBr + $CeCl_3$	3	90	2	-	-
11	0ºC, 4h	MeMgBr + $CeCl_3$	6	84	8	-	1
12	-78 ºC, 4 h	PhLi	3	55	38	2	5
13	-78 ºC, 4 hrs → RT 12 h	PhLi	3	26	56	5	11
14	-78 ºC, 4 h → RT 12 h, ether	PhLi	6	-	15	-	62

Table 21: Attempted alkylation of **118d** with organometallic reagents
[a] All reactions carried out in anhydrous THF unless otherwise stated

Formation of the diketone was also directly reached from dinitrile compound **117d** (Scheme 48, Table 22). Grignard addition again failed (entries 1 and 2) although the addition of 6 equivalents of MeLi at -78 °C in ether afforded **152a** in 72% yield (entry 4). As expected, the racemic reference mono reduced product **154** was then reached via a reduction of **152a** with $LiBH_4$ in EtOH at 0 ºC for 1 hour (68%) to afford the product as mixture of diastereomers (70:30).



Scheme 48: Synthesis of diketone **152a** and racemic reference **154** from dinitrile **117d**
(a) 0.25 equivalent $LiBH_4$, EtOH, 1 h

Entry	Conditions	MeLi / MeMgBr	Eq.	Yield / %		
				117d	153	152a
1	0 ºC → 60 ºC 12 hours, THF	MeMgBr	3	10	56	-
2	0 ºC → 60 ºC 12 hours, THF	MeMgBr	5	-	70	
3	-78 ºC 4 hrs, ether	MeLi	3	72	2	-
4	-78 °C, 90 mins, ether	MeLi	6	-	-	72

Table 22: Diketone synthesis from **117d**

Study of the activity of the KREDS towards our benzyl ketones is currently ongoing. However, our results so far suggest that biocatalytic redox reactions may be more widely applicable to the asymmetric synthesis of atropisomers by desymmetrisation.

2.2.4 Ongoing and future work: Toward ligand synthesis

The large impact of phosphine ligands became evident by the important discovery of the Wilkinson hydrogenation catalyst, $RhCl(PPh_3)_3$.[114] Substitution at the aromatic ring of the ligand revealed an electronic effect on the reaction rate, illustrating the distinct ligand effect on the reactivity of a transition metal complex. Since then, an impressive number of phosphine and phosphite ligands have been applied in many catalytic reactions, and it became obvious that the steric and electronic properties of the ligands have an enormous effect on the reactivity of metal complexes.

The capability for our diaryl ethers to demonstrate potential as hemi-labile ligands in catalytic applications has been alluded to in section 1.3.4, where the application of DPEPhos and Xantphos in (non-asymmetric) catalysis was discussed. In this case, the potential to combine the architecture and reactivity profile of DPEPhos with the stereochemical opportunities offered by atropisomeric ligands might be realised

if we can make the bisphosphines more heavily encumbered and thus able to exhibit atropisomerism. Similarly, although no diaryl ether P,N-donor ligands are known, other axially chiral bidenate ligands have drawn attention due to their high efficiency in catalytic asymmetric synthesis (Figure 20). The non-biaryl wide bite-angle P,N-ligand **157** was used in the enantioselective hydroboration of vinylarenes in up to 94% ee.[115] A route towards being able to incorporate phosphine and/or nitrogen into our ligands in order to assist metal chelation was therefore investigated.

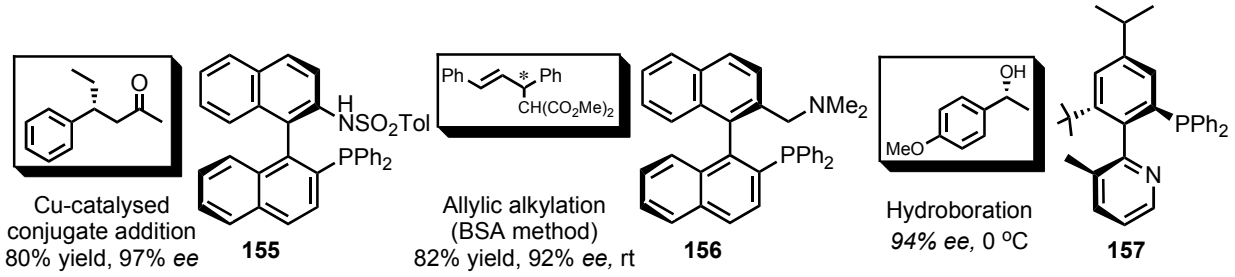
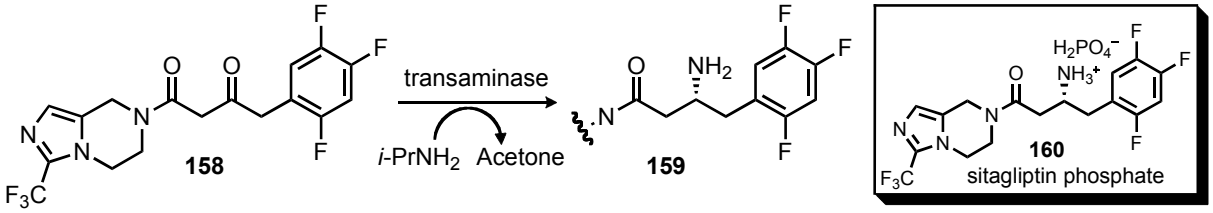


Figure 20: Examples of P,N-ligands and their use in synthesis.[115,116]

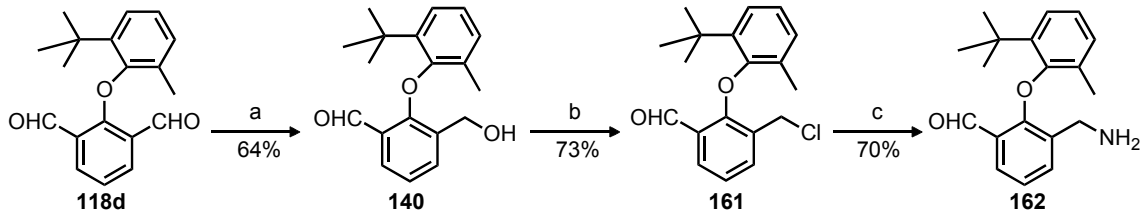
2.2.4.1 Transaminases

The emergence of transaminases, which catalyse the direct amination of ketones to chiral amines using ammonia, are providing an alternative and highly attractive additional option towards the synthesis of chiral amines.[117] Such a process was recently employed in the asymmetric synthesis of Sitagliptin[118] **160** (an anti-diabetic drug) where the chiral amine present in its struture was biocatalytically transformed from ketone **158** (Scheme 49).



Scheme 49: Synthesis of Sitagliptin phosphate via a transamination

This could prove a feasible route towards the synthesis of the "N" part of a chiral P,N ligand. Consequently, a racemic reference was synthesised in order to screen our original dicarbonyl compounds for selectivity against these enzymes (Scheme 50).



Scheme 50: Synthesis of monoaminated diaryl ether
(a) 0.25 equivalent $LiBH_4$, EtOH, 1h
(b) $SOCl_2$, reflux
(c) NH_4OH, reflux

Attempts to selectively reduce one of the two functional groups present in either the dinitrile **117d** (via a selective reduction with $LiAlH_4$) or the dialdehyde **118d** (via a selective reductive amination) both failed under a number of conditions. Therefore dialdehyde **118d** was monoreduced with 0.25 equivalents of $LiBH_4$ before being treated with $SOCl_2$ at reflux to afford the chlorinated analogue **161** in good yield. **161** was then refluxed in NH_4OH to afford the monoaminated product **162** in 70% yield.

Dialdehyde **118d** was incubated with Transaminase-113 in DMSO and the reaction followed by HPLC over the course of 24 h (Figure 21 and Figure 22).

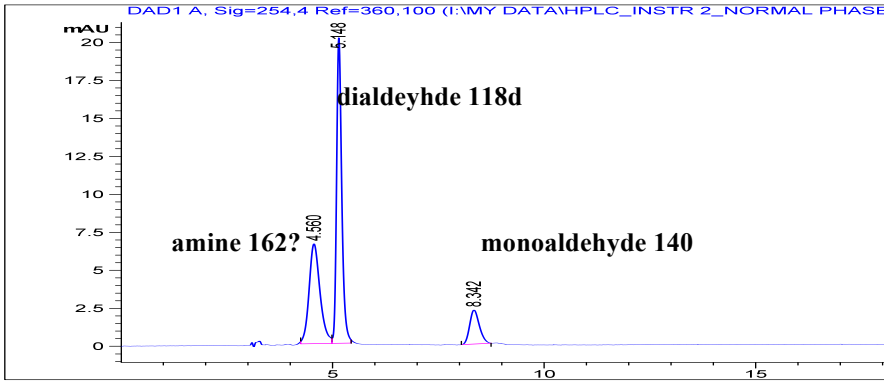


Figure 21: HPLC trace of transaminase reaction mixture after 24 h
Chiralcel ASH column running 97:3 hexane:IPA at 1.0 ml/min

The Initial results from incubation with TA113 shows the formation of a new peak at 4.56 (Figure 21) that increases during the course of the reaction over a period of 24 h (Figure 22), although a cross-reference with racemic compound **162** is yet to be performed. This peak was not found in the control reaction (run without the presence of transaminase-113).

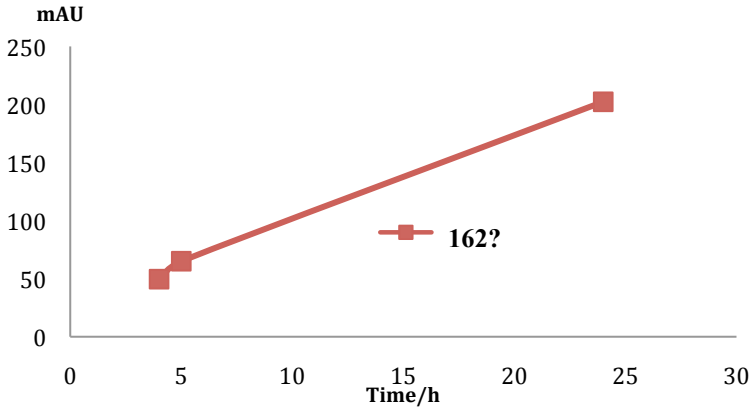
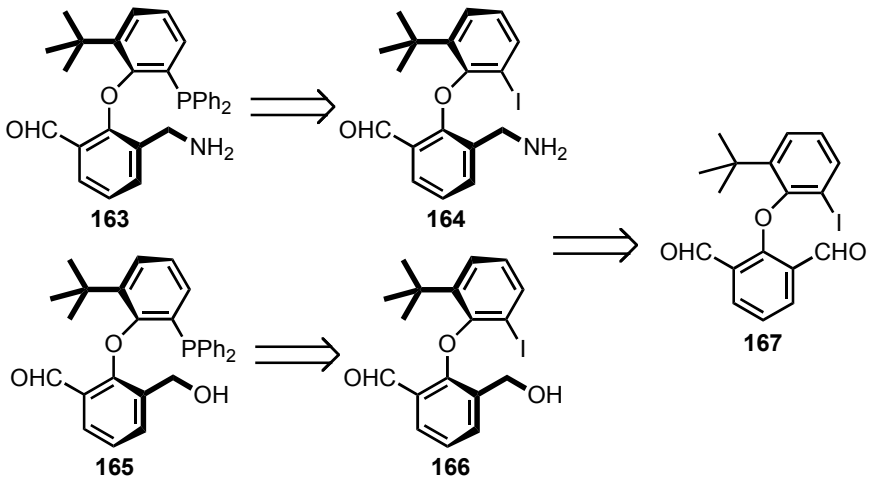


Figure 22: Increase of product over time for the transamination of **118d** with TA-113
Reaction conditions: 118d 5 mM in DMSO, TA113 5 g/l, GDH 1 g/l, LDH 1 g/l, NAD+ 1g/l, PLP 0.5 g/l, D/L-alanine 45 g/l, glucose 10 g/l, potassium phosphate buffer (pH 8-8.5) 100 mM

However the control reaction also showed a reduction in **118d** along with the formation of monaldehyde **140**, suggesting that LDH in the assay mixture could be responsible for the reduction. Synthesis of a diaminated analogue is currently underway, and further optimisation with this class of enzyme is ongoing.

2.2.4.2 Incorporation of an iodine substituent

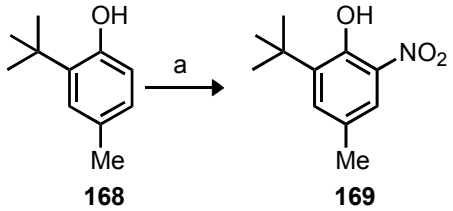
Phosphination of a potential diaryl ether based ligand could be carried out by iodine-lithium exchange followed by trapping with chlorodiphenylphosphine (or a phosphite derivative) (Scheme 51). This method has previously seen success in the synthesis of phosphinophenyl ethers.[119]



Scheme 51*:* Synthesis of a phosphinophenyl ethers based ligand

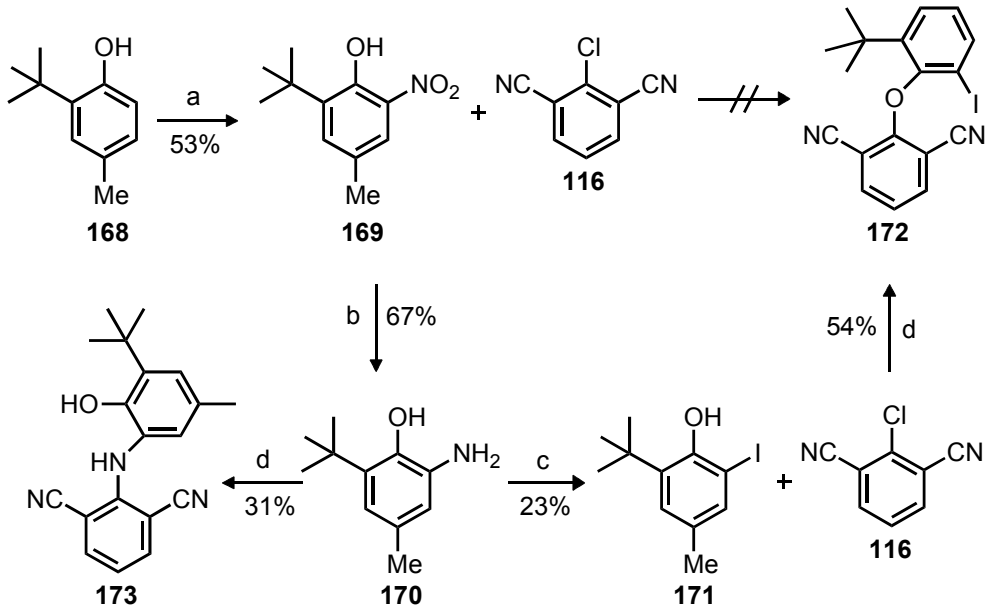
As such, a phenol incorporating an iodine substituent in the 2-position and a *tert*-buytl group in the 6-position was synthesised.

The group of G.-Choghamarin has published an efficient method for the mononitration of a variety of phenols.[120] Their procedure included the nitration of commercially available phenol **168** which displayed a nitro in position-6 and a *tert*-butyl group in position-2 (Scheme 52).



Scheme 52*:* Nitration of phenol **168**
(a) SiO_2-OSO_3H, $Al(NO_3).9H_2O$, wet SiO_2, CH_2Cl_2,

Based on this observation, and utilising the diaryl ether synthesis described in section 2.1, a route towards the iodine substituted d iaryl ether **172** was undertaken (Scheme 53).



Scheme 53*:* Synthesis of a potential ligand
(a) SiO_2-OSO_3H, $Al(NO_3).9H_2O$, wet SiO_2, CH_2Cl_2, rt
(b) Fe powder, HCl
(c) i. *conc.* H_2SO_4, $NaNO_2$; ii. KI
(d) K_2CO_3, DMF, 3Å mol sieves, 156 ºC, **116**

Nitrated phenol **169** was prepared via the literature described procedure[120] in 53% yield. Attempted coupling with **116** failed, returning only starting material and

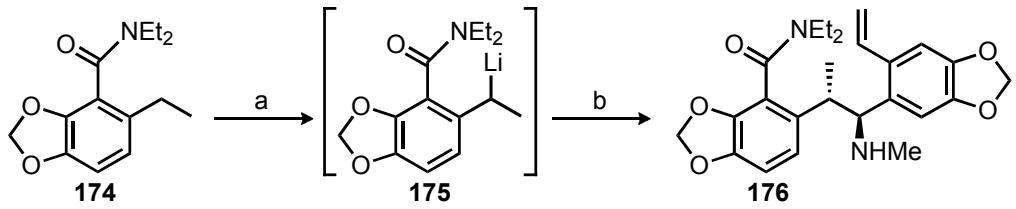
suspected degradation products. This is most likely due to the strongly deactivating nature of the nitro group in position-6 of the aryl ring. **169** was therefore reduced to the corresponding aniline **170** with Fe powder and HCl (67 %) before being converted to a diazonium salt and quenching with KI to afford iodo-phenol **171** in 23% overall yield. The coupling of **171** and **116** then proceeded in moderate yield (54 %). An attempt to couple the aniline compound **170** to **116** produced compound **173 (**tentatively assigned as the amine shown) in 31 % yield.

With **172** in hand, this compound will be converted to the dialdehyde **167** and either screened for activity against the above described transaminase (in the hope of achieving an enantioenriched species that can be transformed into a P,N-ligand), or treated with either of the GAOase $M_{3\text{-}5}$ (after converting to a diol) or the KRED enzymes that have previously worked well (sections 2.2.2 and 2.2.3).

2.3 Enantiopos-Differentiatiation and Stereoselectivity of Laterally Lithiated Diaryl Ethers

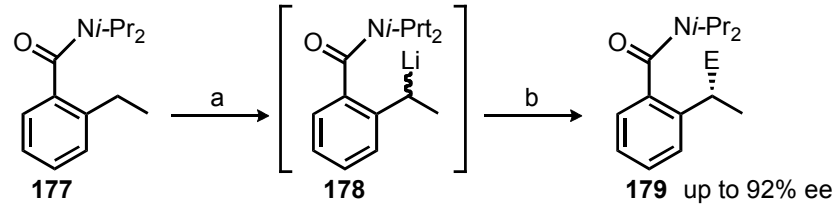
Much work has been done within the Clayden group on the ability of tertiary aromatic amides to direct lateral lithiation *i.e* to deprotonate at the more acidic benzylic sites of alkyl groups located *ortho* to an amide axis.

Complexation of the butyllithium coupled with the strong acidifying effect of the electron withdrawing carbonyl group are thought to account for the regioselecective nature of these lithiation reactions, and their stereoselectivity has also been extensively studied. For example, lateral lithiation of amide **174** gave organolithium **175** which, on addition to an imine, generated only a single diastereoisomer of the amine **176** (an intermediate in a synthesis of corydalic acid methyl ester) (Scheme 54).[121]



Scheme 54*:* Diastereoselective lateral lithiations of amides
(a) LDA
(b) ArCH=NMe

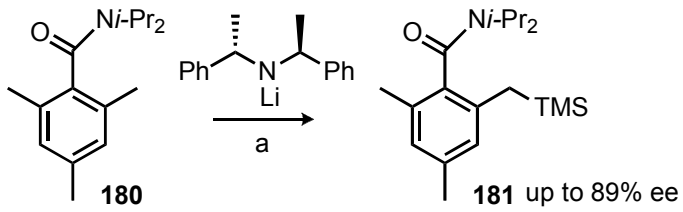
Similar reactions lead to enantiomerically enriched products in the presence of sparteine.[122] Lateral lithiation of **177** gave organolithium **178** which was configurationally labile at the lithium-bearing centre but which reacted enantioselectively in the presence of (–)-sparteine to produce laterally functionalised products **179** in up to 92% ee (scheme 55).[123,124]



Scheme 55*:* Absolute stereocontrol via lateral lithiations of amides
(a) *sec*BuLi
(b) E^+, (–)-sparteine

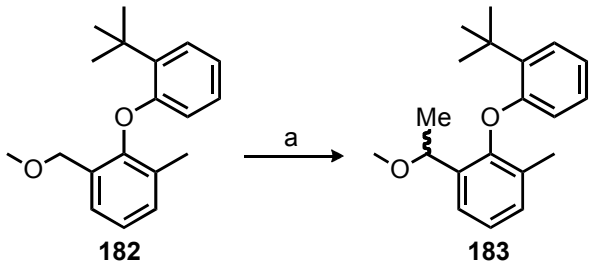
A chiral lithium amide base also governed the selective desymmetrising lateral lithiation of one of the pair of enantiotopic methyl groups of **180**, leading to the

enantiomerically enriched atropisomers of **181** (Scheme 56). [125]



Scheme 56*:* Desymmetrising lateral lithiation of a benzamide
(a) i. -78 °C, THF; ii.TMSCl

Lateral lithiation in the diaryl ethers, however, remains relatively unexplored. We therefore aimed to explore the possibility that, when quenched with a bulky substituent, the chiral centre at the lateral position could be efficient at controlling the conformation of the diaryl ether axis. An initial investigation[126] thus looked at the ability of this class of compound to undergo directed metallation and simple unsymmetrical compound **182**, left over from a previous study, was subjected to the lateral lithiation conditions outlined in Scheme 57**.**



Scheme 57*:* Lateral lithiation of non-symmetrical diaryl ether **182**
(a) i. *n*BuLi, (–)-sparteine, -78 / 0 °C, ether; ii. MeI

Diaryl ether **182** (in ether) was added to a stirred solution of *n*BuLi, both with and without (–)-sparteine, at –78 °C or 0 °C, stirred for 1 hr and then quenched with MeI. The results from these reactions are summarised in Table 23, and show good yields and moderate diastereoselectivity (entries 2-4). The enantioselectivity of the reaction was unable to be measured on chiral HPLC owing to the low barrier to rotation.

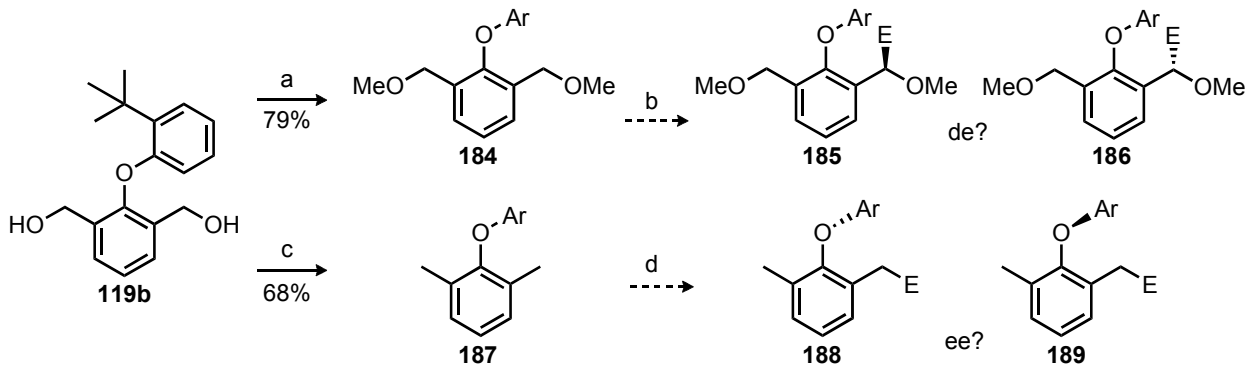
Entry	Conditions	Yield / % 182	183	dr
1	–78 °C	92	0	-
2	–78 °C / (–)-sparteine	38	49	66:34
3	0 °C	0	88	66:34
4	0 °C / (–)-sparteine	5	80	66:34

Table 23: Results from the lateral lithiation of **182** with *n*BuLi

The consistent ratio of diastereomers in this case suggests that the dr is controlled through a thermal equilibration of the products **183**, and is not a result of a stereoselective deprotonation / reaction of the intermediate organolithium.

However, with the success of these lithiations, and with quantities of diols **119** in hand, it was envisaged that our substrate could be employed as a precursor for the enantiopos-differentiating lateral lithiation strategies outlined in Scheme 58 (section 2.3.1). The *pro*-atropisomeric compounds **184** and **187** were therefore our initial targets for synthesis, and it was hoped that we could obtain high kinetic selectivity in the lateral lithiation of our ethers with bulkier compounds.

2.3.1 Strategy and synthesis of *pro*-atropisomers



Scheme 58: Lateral lithiation strategy
(a) i. NaH; ii. MeI
(b) i. R-BuLi, ii. E^+
(c) H_2, PdC
(d) i. R-BuLi, (–)-sparteine; ii. E^+

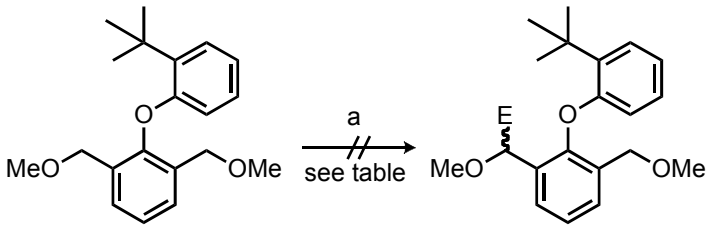
For our initial studies, the singly *ortho*-substituted **119b** was chosen given the far greater ease of its synthesis compared to its 2,6-substituted analogue (see diaryl ether synthesis, section 2.1). Therefore, diol **119b** was reacted with a large excess of NaH

followed by an electrophile quench with MeI. This gave **184**, a candidate for lateral lithiation investigations, in 79% yield.

Similarly, one analogue of **187** was made by hydrolysing the diol **119b** with 10% Pd/C on a continuous flow system. The reaction to generate **187** was carried out on the H-cube in ethanol at a concentration of 0.02M, a temperature of 25°C, a pressure of 1 ATM and in 68% yield. Although the yield appears to only be moderate, the sole by-product in the reaction mixture was starting **119b.** It is therefore believed that higher yields might be reached by conducting another cycle on the H-cube.

2.3.2 Lateral lithiation of *meso*-dimethoxy analogues

Initial studies of **184** sought to assess the diastereoselectivity of its reaction with a range of electrophiles, and thus lateral lithiations of **184** followed by an electrophile quench were attempted utilising the same conditions found to be successful in the deprotonation of the analogous but unsymmetrical **182** (Scheme 59, Table 24).



184 **190**

Scheme 59: Lateral lithiation of dimethoxy compound **184**
(a) i. R-BuLi; ii. E = TMSCl or MeI

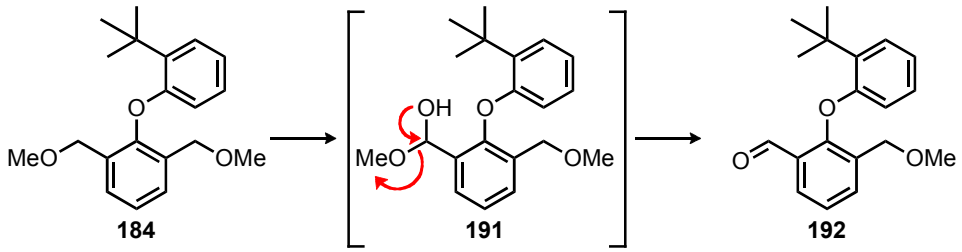
Entry	RLi	Eq[f]	Temp (°C)	Solvent	Addition[d]	Colour change[e]	Time to Quench	E^+	Yield / %
1	*s*Bu	1.5	-78	THF	RLi to **184**	None	1 hr	MeI	[a]
2	*n*Bu	1.5	-78	THF	RLi to **184**	None	4 hr	MeI	-
3	*n*Bu	1.5	0	THF	RLi to **184**	None	1 hr	MeI	-
4	*n*Bu	1.5	0	THF	**184** to RLi	None	1 hr	TMSCl	-
5	*n*Bu	1.5	0	THF	**184** to RLi	Green	1 hr	TMSCl	-
6	*n*Bu	1.5	0	Ether	**184** to RLi	Green	1 min	MeI	-
7	*n*Bu	1.5	0	Ether	**184** to RLi	Green	1 hr	MeI	-
8	*n*Bu	1.5	0	Ether	**184** to RLi	Green	1 hr	TMSCl	-
9	*n*Bu	1.5	0	Ether	**184** to RLi *	None	1 hr	MeI	-
10	*n*Bu	1.5	0	Ether	**184** to RLi	Green	1 min	MeI	[b]
11	*t*Bu	1.5	0	Ether	**184** to RLi	None	1 hr	MeI	-
12	*n*Bu	4	0	Ether	**184** to RLi	Green	1 min	MeI	[c]

Table 24: Conditions for attempted lateral lithiation of **184**
* reaction carried out in the presence of (–)-sparteine
[a] small amount of monoaldehyde by-product on NMR, yield not determined [b] minium amount of desymmetrised product on crude NMR, purification unsuccesful [c] small amount of dimethylated product seen on ^{1}H NMR, yield not determined [d] order of addition in the reaction taken as either adding dissolved **184** to a solution of cooled RLi (**184** →RLi) or adding RLi to a cooled solution of **184** (RLi→**184**) [e] colour change observed immediately after addition of RLi to **184** / **184** to RLi [f] Equivalents taken as the excess of RLi compared to **184**

However, despite a number of attempts a route towards desymmetrised **190** was unsuccessful.

A number of reaction conditions were explored but unfortunately varying solvent, temperature, order of addition, reaction times and the electrophile did not yield **190** in any isolable form. More powerful bases in the form of both *tert* and *sec*-BuLi were employed in the hope that the acidity of the benzylic protons was the problem. Unfortunately, neither were successful at yielding **190**.

It was noted that a number of attempts at deprotonation led to the observance of a colour change, usually indicative that a lithiation is occuring. Furthermore, under certain conditions it was seen that **184** appeared to have undergone an electrophilic quench with atmospheric oxygen, resulting in the formation of the monoaldehyde product **192** (Scheme 60). This in itself is a desymmetrisation reaction, and with further optimisation could prove synthetically useful.

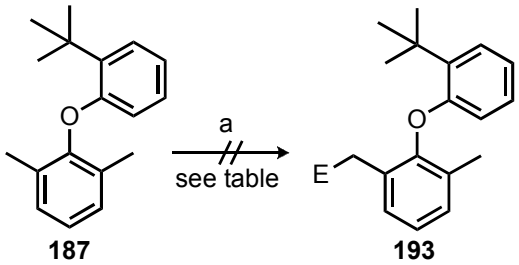


Scheme 60: Possible mechanism for mono-aldehyde biproduct formation **192**

In order to ascertain if any lithiation was indeed possible, the methods thought to be most effective were employed to try and force the lithiation of **184**. Ether **184** was therefore added to a large excess of *n*BuLi (entry 12) at 0 °C followed by the addition of MeI as the electrophile. The crude ^{1}H NMR showed a small amount of conversion, with two quartets corresponding to a double lithiation and quench, indicating that desymmetrisation in this set of compounds is not a viable strategy.

2.3.3 Lateral lithiation of *meso*-dimethyl analogues

The attempted lithiation of **187** with 1.5 equivalents of R-BuLi at varying temperatures to yield desymmetrised **193** also failed. (Scheme 61, Table 25).



Scheme 61: Lateral lithiation of dimethyl compound **187**
(a) i. R-BuLi; ii. E = TMSCl or MeI

Entry	RLi	Temp (°C)	Solvent	Yield
1	*sec*Bu	-78	THF	-
2	*t*ertBu	-78	THF	-
3	*n*Bu	0	Ether	-

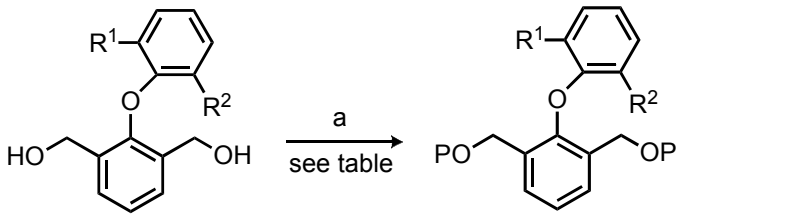
Table 25: Conditions for attempted lateral lithiation of **187**
(a)i.R-BuLi, ii. TMSCl or MeI

These results are perhaps unsurprising given our failed attempts at lithiating **184**. Work with this type of compound was therefore abandoned in favour of incorporating a

directing group on the benzylic carbon known to favour coordination to Li, such as MEM or carbamate. The benefit here would be two fold; firstly, these groups have a larger coordinating power to lithium and would therefore direct lateral lithiation to a greater extent, and secondly they would be much easier to cleave than an OMe group once desymmetrisation occurs.

2.3.4 Synthesis and lateral lithiation of *meso*-carbamate analogues

The search for a strongly coordinating protecting group in order to complex the lithium and direct lateral deprotonations led us in the obvious direction of the widely available MEM and diisopropyl-carbamate protecting groups.



119
b R^1 = *t*-Butyl, R^2 = H
d R^1 = *t*-Butyl, R^2 = Me

194 R^1 = *t*-Butyl, R^2 = H, P=Cb
195 R^1 = *t*-Butyl, R^2 = Me, P=Cb
196 R^1 = *t*-Butyl, R^2 = H, P=MEM
197 R^1 = *t*-Butyl, R^2 = Me, P=MEM

Scheme 62: Protection of diol **119** with MEM or diisoptopylcarbamate
(a) i. Base; ii. MEMCl or diisoprpylcarbamoylCl

Diol **119** was therefore dissolved in solvent at various temperatures and then subjected to the addition of a protecting group, ***P***, utilising a number of bases in order to reach the protected compounds **194-197**, candidates for further lithiation studies (Scheme 62, Table 26).

Entry		Protecting Group (Eq.)	Base (Eq.)	Temp (°C)	Solvent	Yield / %
1	196	MEM (2 eq)	Hunigs (2.5eq)	RT	DCM	-
2	196	MEM (3 eq)	Hunigs (4eq)	Reflux	DCM	-
3	196	MEM (3 eq)	NaH (6eq)	RT	THF	-
4	197	MEM (3 eq)	NaH (4 eq)	Reflux	THF	-
5	194	Cb (3 eq)	Net_3 (5eq)	RT	DCM	-
6	194	Cb (3 eq)	NEt_3(5eq)/DMAP	RT	DCM	-
7	194	Cb (3 eq)	NEt_3(5eq)/DMAP	Reflux	DCM	-
8	194	Cb (5 eq)	NEt_3(5eq)/DMAP	RT	DCM	-
9	194	Cb (10 eq)	NEt_3(5eq)/DMAP	RT	DCM	-
10	194	Cb (20 eq)	NEt_3(5eq)/DMAP	RT	DCM	[a]
11	194	Cb (4 eq)	Pyridine	Reflux	Pyridine	67
12	194	Cb (20 eq)	NaH (6 eq)	RT	THF	38
13	194	Cb (4 eq)	NaH (4 eq)	Reflux	DCM[b]	47
14	194	Cb (4 eq)	NaH (4 eq)	Reflux	DMF	-
15	194	Cb (4 eq)	NaH (4 eq)	Reflux	Toluene	33
16	194	Cb (4 eq)	NaH (6 eq)	80	Toluene[c]	37
17	194	Cb (4 eq)	NaH (4 eq)	Reflux	THF	35
18	194	Cb (4 eq)	NaH (6 eq)	80	THF[c]	61
19	194	Cb (4 eq)	NaH (6 eq)	Reflux	Ether	8
20	194	Cb (4 eq)	NaH (6 eq)	Reflux	Ether[c]	98
21	195	Cb (4 eq)	NaH (6 eq)	Reflux	Ether[c]	75
22	195	Cb (4 eq)	NaH (6 eq)	Reflux	Ether[d]	72
23	194	Cb (4 eq)	NaH (6 eq)	Reflux	Ether[d]	87

Table 26: Conditions for attempted protection of diol **119**

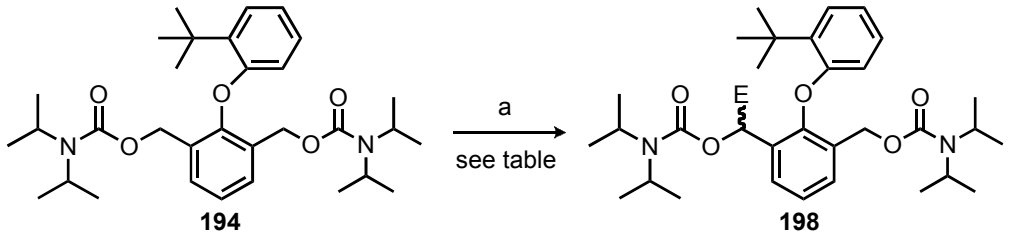
[a] Minimal conversion to product by crude ^{1}H NMR, yield not determined [b] Cb added instantaneously after NaH to avoid any radical reactions in DCM [c] Products of reaction left for 1 week open to the air before work-up [c] Product intentionally left open to air for 16 h before work-up [d] catalytic amount of 18-crown-6 ether added to reaction mixture

An unexpected difficulty occurred during the attempted protection of diols **119,** with a propensity for the diols to only monoprotect, if at all, even with large excesses of electrophile. NaH deprotonation of **119b** followed by a carbamate protection of the diol in refluxing ether was only found to proceed in a high yield after a fortuitous discovery that complete evaporation of the volatile ether solvent from the reaction vessel over a period of 16 hours led to the reaction yield increasing from 8 → 75% (entries 19 → 21).

This seemed to imply that the Na+ counter ion was complexing to the deprotonated substrate in solution and affecting its nucleophilicity towards the

carbamoylCl electrophile. Thus addition of a catalytic amount of 18-crown-6 ether was added to the reaction vessel in order to chelate the problematic Na+ counter ion, and the reaction proceeded in up to 87% yield (entries 22 and 23).

With the *pro*-atropisomeric protected compounds **194** and **195** now in hand, it was decided that before any enantioselective or diastereoselective lithiations could take place, a working set of reaction conditions should be found. Carbamate **194** was therefore subjected to a lithiation followed by quench under a number of conditions (Scheme 63, Table 27).



Scheme 63: Conditions for attempted lateral lithiation of carbamate protected **194**
(a) i. R-BuLi in ether; ii Electrophilic quench

Entry	RLi	Eq.	Temp (°C)	Conditions	Time to Quench	E^+	Yield / %	d.r.[d]
1	*n*Bu	1.5	0	[a]	5 mins	MeI	-	-
2	*sec*Bu	2.4	-78 to 0	[b]	[b]	$(CH3)_2CO$	-	-
3	*sec*Bu	1.1	-78	[c]	1 h	PhCHO	-	-
4	*sec*Bu	1.1	-78 to 0	[b]	[b]	PhCHO	-	-
5	*sec*Bu	1.6	-78	[c]	0.5 h	$(CH3)_2CO$	63	>95:5
6	*sec*Bu	1.6	-78	[c]	5 mins	$(CH3)_2CO$	43	>95:5

Table 27: Conditions for attempted lateral lithiation of **194**
[a] **194** added to RLi [b] RLi added to **194** at -78 °C for 1 hr, warmed to 0 ºC for 1 hr, then cooled to -78 ºC and electrophile added [c] RLi added to **194** [d] Taken as the ratio of diatereomers seen by ^{1}H NMR

The most favoured conditions were those described by Beak[37] for analogous diisopropylcarbamate protected compounds. Therefore, *sec*BuLi (1.6 eq) was added to a stirring suspension of **194** in ether at -78 ºC, stirred for half an hour and then quenched with acetone and warmed to RT over night, yielding up to 63% of **198**. However, the reaction proved to be highly capricious with seemingly identical reaction conditions often proceeding to fail.

This, coupled with the observation that the yields of **198** and its analogues appeared to decrease the longer they were left in solution (ie longer times before

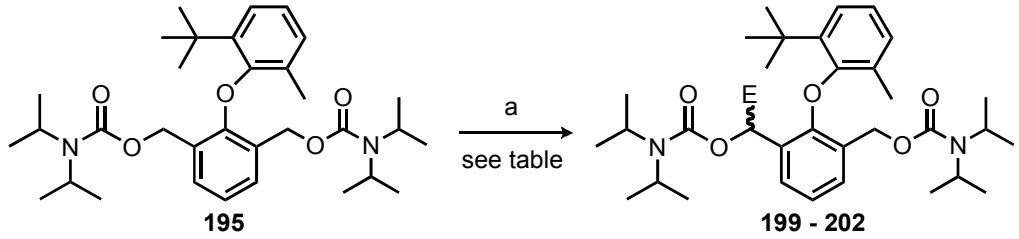
quench), led us to switch our inert atmosphere from nitrogen to argon. All subsequent lithiation reactions were carried out with freshly distilled (no longer than 2 hours old) electrophiles and freshly redistilled (–)-sparteine (also obtained commercially as reported 99% purity). The solvents, substrates and (–)-sparteine were also freeze-thaw degassed in order to avoid the problems of oxidation and reprotonation.

Additionally, all future lithiation strategies utilised the doubly *ortho* substituted 2-*tert-butyl,6-methyl* analogue **195**, the atropisomers of which (owing to the results from our enzyme studies) were expected to show a higher propensity for being chiral at useful temperatures, and for longer periods of time.

2.3.5 Desymmetrisiation and stereoselectivity of laterally lithiated diaryl-ethers

With quantities of **195** in hand, and with the conditions required for lateral lithiations established, the next step was to investigate if this class of compound could exert control over the formation of a new chiral centres via lateral lithiation.

Carbamate protected diaryl ether **195** was therefore dissolved in ether, subjected to a freeze–thaw degass technique and cooled to -78 °C. 1.6 equivalents of *sec*BuLi was added dropwise and the lithioderivative was allowed to stir for half an hour before being quenched with a variety of electrophiles (Scheme 64, Table 28).



195 **199 - 202**

Scheme 64: Lateral lithiation and electrophilic quench of carbamate protected **195**
(a) i. *sec*BuLi , -78 °C, ether; ii. Electrophilic quench

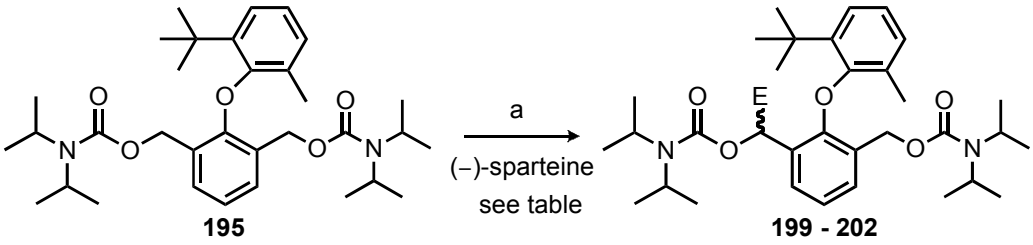
Entry		E^+	Yield / %	d.r.[a]
1	199	$(CH3)_2CO$	75	95:5
2	200	Cyclobutanone	56	85:15
3	201	TMS-Cl	70	95:5
4	202	$(CH_3CO)_2O$	69	85:15

Table 28: Diastereoisomeric ratios of laterally lithiated **195** with a variety of electrophiles
[a] Taken as the ratio of diastereomers seen by ^1H NMR

The diastereo-controlling ability of the axis appears to be very good, with one main diastereomer being evidenced in the ^{1}H NMR in each case, regardless of whether E is an alcohol (as in the addition of acetone and cyclobutanone, entries 1 and 2), a carbonyl (when E = acetic anhydride, entry 4) or a silyl (entry 3). A number of other quenches were attempted including DMF, benzaldehyde, acetaldehyde, DIAD, and propionaldehyde. However, despite a number of attempts all returned starting material or a mixture of unidentifiable products.

The next stage was to see if this control could be extended to the enantioposelective desymmetrisation technique we had intended from the outset. **195** was therefore subjected to the same conditions but in the presence of the chiral ligand, (−)-sparteine. It was hoped that this would bias the formation / reaction of the organolithium itself, which when combined with the diastereocontrol demonstrated above could (after removal of the unwanted chiral centre) instill asymmetry at the axis and offer a route to atropisomerically pure diaryl ethers.

Diaryl ether **195** in ether, and (–)-sparteine were subjected to a freeze–thaw degass technique, before cooling the mixture to -78 °C and adding *sec*BuLi. The reaction was then allowed to stir for half an hour before being quenched with a variety of electrophiles (Scheme 65, Table 29).



Scheme 65: Lateral lithiation of daryl ether **195** in the presence of (–)-sparteine
(a) i. *sec*BuLi , -78 °C, (–)-sparteine, ether; ii Electrophilic quench

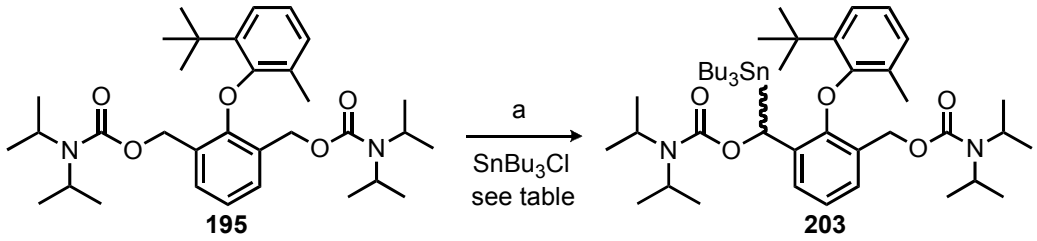
Entry		E^+	Yield / %	dr[a]	er[b]
1	199	$(CH3)_2CO$	86	>97:3	75:25
2	200	Cyclobutanone	26	>97:3	73:27
3	201	TMS-Cl	72	95:5	78:22
4	202	$(CH_3CO)_2O$	66	95:5	81:19

Table 29: Lateral lithiation of **195** with attempted absolute stereocontrol
[a] Taken as the ratio of diastereomers seen by ^{1}H NMR [b] Taken as the ratio of enantiomers measured on chiral HPLC, first eluted peak reported first

The enantioselective lithiations in each case afforded desymmetrised **199-202** with uniformally moderate e.r.'s, and (–)-sparteine improved diastereoselectivity in the case of **200** and **202** (entries 2 and 4). This might imply that (–)-sparteine accelerates the reaction, and that if left to react for longer, the d.r.'s of entries 2 and 4 from Table 28 could improve.

2.3.5.1 Stereoselectivity with the electrophile $SnBu_3Cl$

An interesting case occurred when **195** was subjected to the lateral lithiation conditions already described, with or without (–)-sparteine, and quenched with $SnBu_3Cl$ (Scheme 66). It appeared in this case to be the first example of a non-diastereoselective reaction of **195** depending on the reation conditions (Scheme 67, Table 30).



Scheme 66: Lateral lithiation and quench of daryl ether **195** with $SnBu_3Cl$
(a) i. *sec*BuLi , -78 °C, (–)-sparteine / no (-)-sparteine, ether; ii Electrophilic quench

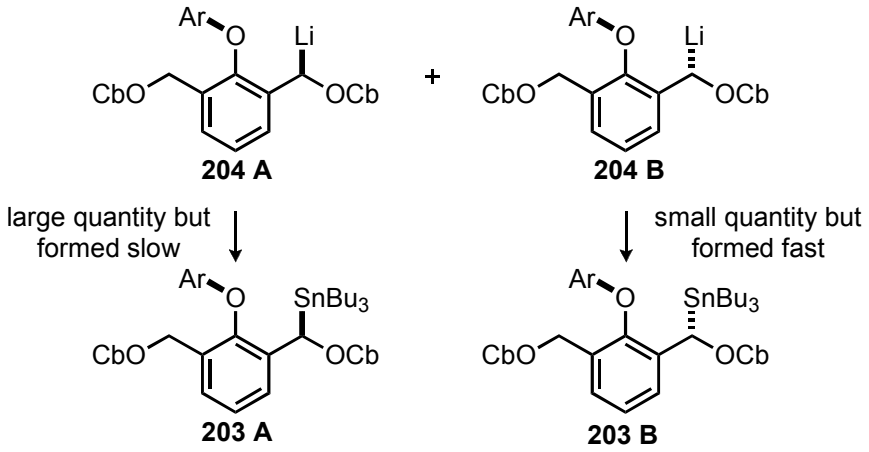
Entry	(–)-sparteine	Reaction time of organolithium with $SnBu_3Cl$	Yield / %	dr[a]	er[b]
1	No	90 mins	9	2:1	-
2	No	6 hrs	42	5:1	-
3	No	16 hrs	58	9:1	-
4	Yes	16 hrs	62	95:5	20:80
5	Yes	26 hrs	59	95:5	20:80

Table 30: Lateral lithiation of **195** followed by quench with $SnBu_3Cl$
[a] dr's measured as a ratio of of diastereotopic signals in ^1H NMR [b] er's measured as a ratio of signals on chiral HPLC, first eluted peak reported first

Revealingly, the enantiomeric ratio of the reaction while remaining similar in value to the previous examples, appears to have been reversed (compare each entry 4 in Tables 29 and 30) and the favoured diastereomer now elutes second on HPLC, compared to the favoured diastereomers of **201** and **202** which elute first. The CH_2Ph AB system of the more prevalent diastereomer of **203** has a chemical shift that appears further downfield in ^1H NMR compared to the CH_2Ph AB system of the less prevalent

diastereomer **203**, and compared to the CH_2Ph AB system of **199** – **202**. In the case of the enantioenriched products, **203** rotates circular polarised light in the opposite sense to **199** - **202**. This suggests that the opposite diastereomer has been formed, and given our experience with trialkyl tin compounds, that the mechanism of the reaction has switched from one of retention to one of inversion (discussed in section 2.3.6). However, as each compound is not structurally identical we cannot presume to know which diastereomer is favoured, and this theory is completely speculative.

Diastereomeric ratios in the case of **203** heavily depend on the incubation time of the organolithium with the electrophile, and on whether (–)-sparteine is used. Longer reaction times (90 minutes compared with 16 hours) increases the dr from 2:1 to 9:1, (entries 1 → 3) and the presence of (–)-sparteine improves the ratio from 9:1 to 95:5 for the same reaction times (entries 3 → 4). In each case the prevalence of what we assume to be the inversion product diastereomer is increased. The favoured diastereomer in this case was proven not to be under thermodynamic control as heating the 2:1 mixture at 55 ºC for 24 hours afforded no change in the diastereomeric ratio.



Scheme 67: Proposed reaction mechanism leading to the diastereotopic ratios of **203**

The appearance of the lowest diastereomeric ratio (2:1) occurring with the least amount of conversion (9%, entry 1) is thought to be more indicative of what is occurring during the reaction. This theory, as illustrated in Scheme 67, proposes that the d.r. is a reflection of the respective reaction rates between $SnBu_3Cl$ and the intermediate organolithiums **204**A and **204**B. Organolithium A is the more prevalent diastereomer, but reacts slower than the less prevalent diastereomer B. Therefore, at low conversions, **203**B appears to be more highly represented in the ratio of diastereomers.

If this is the case, it would imply a configurational stability of the intermediate organolithium species, and this hypothesis could be investigated utilising a tin-lithium exchange,[127] which will be discussed in section 2.3.6.1.

2.3.6 Configurational stability and stereoselectivity in the reaction and synthesis of laterally lithiated diaryl ethers

We went on to investigate the mechanism of the stereoselective reaction of the lateral lithiation – electrophilic quench of diaryl ether **195** and, given that the stereochemistry of organolithiums is intimately associated with the configurational stability of the lithium-bearing centre, to study the configurational stability of the intermediate organolithium.

Figure 23 shows the stereochemical possibilities available to the organolithium after deprotonation. Once formed, any epimerisation of the C-Li bond would lead to equilibration of the diastereomeric intermediates, whereas racemisation would require an unlikely rotation of the sterically hindered O-Ar axis and Li migration. The stereochemical outcome of the product can then be further influenced by the stereoselectivity of its reaction with electrophiles.

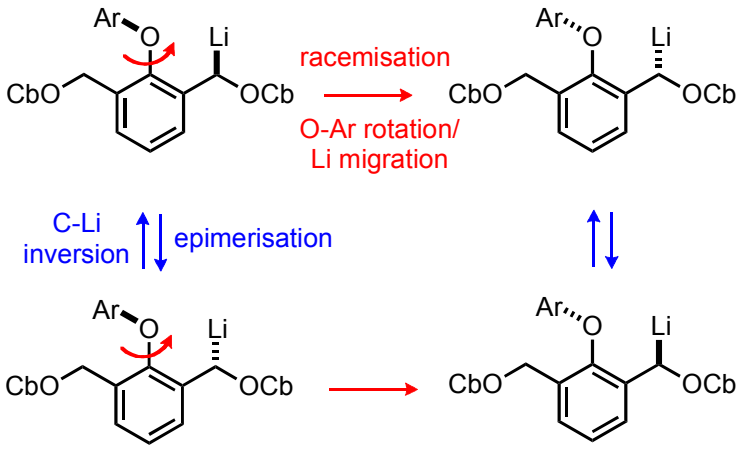


Figure 23: Stereoisomers of intermediate organolithium and pathways of epimerisation or racemisation

The group of Hoppe have placed huge significance on the origin of the electrophile in determining the mechanism of the reaction of benzylic organolithiums. Unlike the general reaction of organolithiums with electrophiles, which proceed with

retention of configuration*, stabilised organolithiums – compounds in which the lithium finds itself in an allylic or benzylic position – can react with either retention or inversion of configuration. The adjacent π-system of these conjugated organolithiums gives the C-Li bond more p-character, increasing the planarity of the organolithium and making the rear lobe of the C-Li σ-bond more susceptible to attack. Gawley[128] has proposed the terms S_E2ret and S_E2inv to distinguish between the two possibilities (Figure 24).

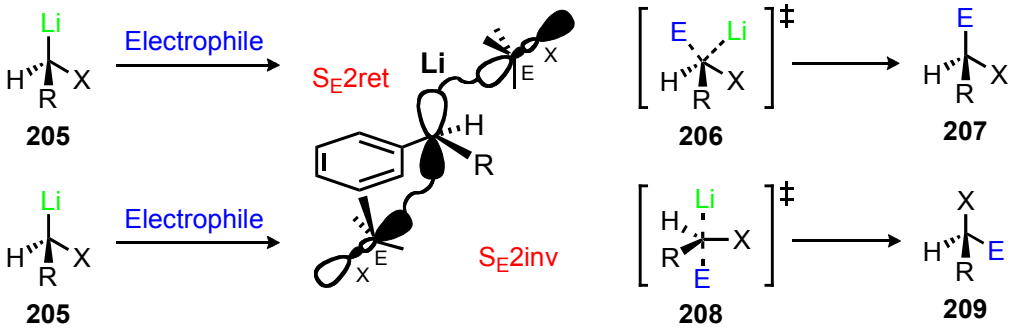
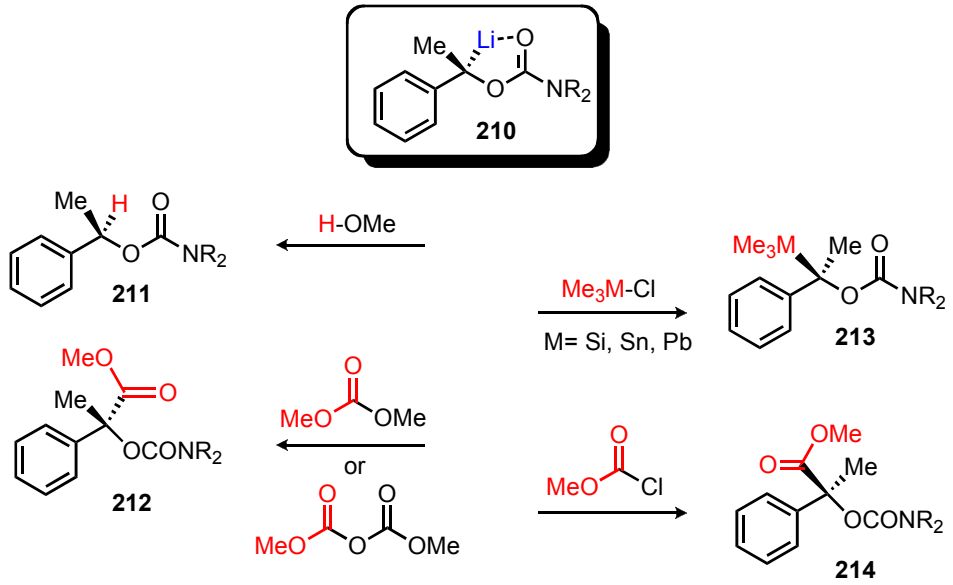


Figure 24: Reaction mechanism of organolithiums – S_E2ret or S_E2inv

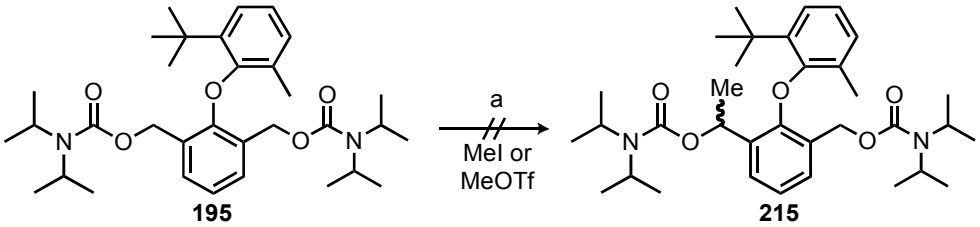
It is now well known that the stereospecificity of the reaction of a number of organolithiums with electrophiles is erratic, with many reported examples of organolithiums reacting with some electrophiles with retention and with others with inversion. Hoppe studied the stereochemical course of some reactions of a benzylic organolithium **210** with a variety of electrophiles. Retention of configuration was observed where the leaving group of the electrophile was able to coordinate to the lithium, for example MeOH (MeO^-) **211** and $MeCO_2COMe$ ($MeCO_2^-$) **212** whereas halide leaving groups gave inversion (Scheme 68).

* There are only two specific and one general exception to this rule



Scheme 68: Stereospecificity in the electrophilic substitution of benzylic organolithium **200**

We intended to investigate whether there would be any bias towards the formation of a new chiral centre when E was the same group but the source of the electrophile differed. Attempts were made to synthesise **215** via a lateral lithiation followed by quench with both MeI and MeOTf (Scheme 69). However, the reaction product was not reached.



Scheme 69: Lateral lithiation and quench of diaryl ether **195** with MeI or MeOTf
(a) i. *sec*BuLi , -78 °C, (–)-sparteine / no (–)-sparteine, ether; ii Electrophilic quench

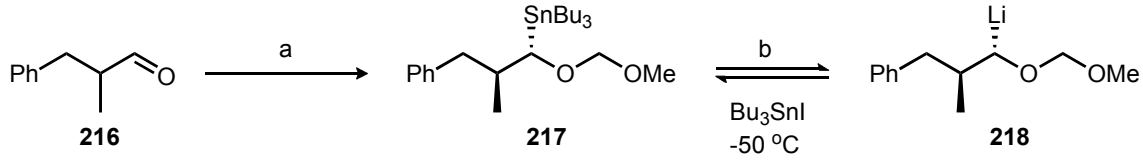
Consequently, we turned our attention towards investigating the possible retentive / invertive mechanism by utilising tin-lithium exchange chemistry. We also aimed to use a tin-lithium exchange in order to determine the configuational stability of the intermediate organolithiums **204**.

2.3.6.1 Tin-lithium exchange

The conversion of C-Sn to C-Li bonds by electrophilic substitution (tin-lithium exchange) is the most important general way of making configurationally defined

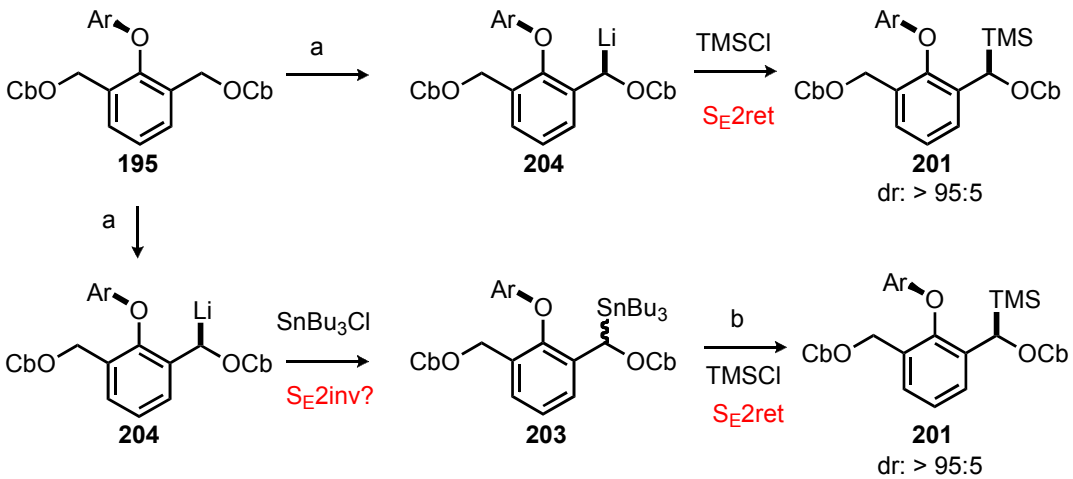
organolithiums.[127] These transmetallations are always assumed to proceed with reliable retention of configuration, although the Clayden group have presented a tin-lithium exchange that did not proceed stereospecifically.[35]

The first demonstration of this specificity was put forward by Stille in 1980, where his sequence of reactions started with stannane (±)**217** formed from the nucleophilic addition of of Bu_3SnLi to aldehyde **216**. The stannane transmetalates stereospecifically to an organolithium presumed to be (±) **218** which reacts stereospecifically with electrophiles, and the *overall* course of the reaction was proved to proceed with retention by re-stannylation with Bu_3SnI (Scheme 70).



Scheme 70: Stereospecificity in tin-lithium excahnge
(a) i. Bu_3SnLi; ii. $MeOCH_2Cl$; iii. Separate
(b) *n*BuLi, -78 °C, THF

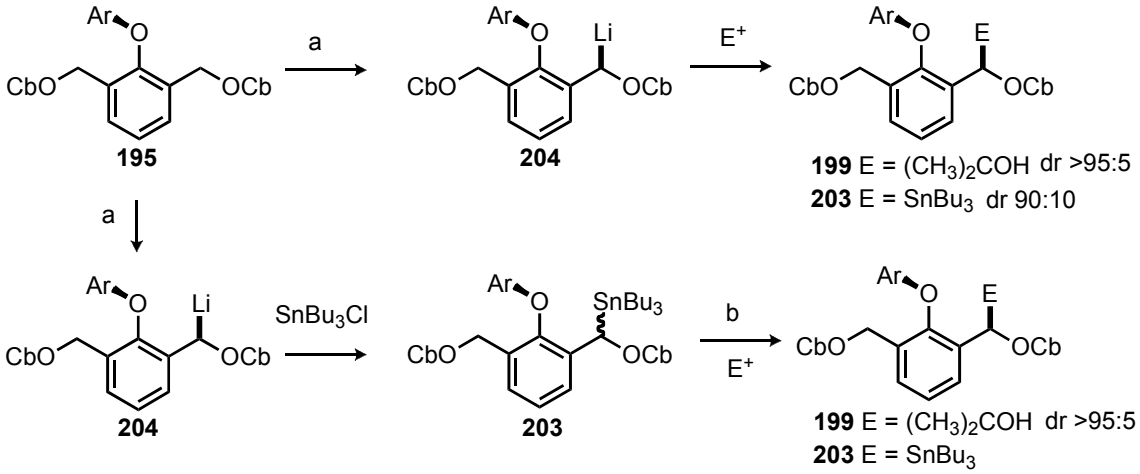
From the results we obtained in section 2.3.5, we suspected our organolithium to be reacting via an invertive process with the $SnBu_3Cl$ electrophile and with retention when TMSCl was used. In order to ascertain if indeed our compounds were reacting by retentive and invertive mechanisms, we synthesised **201** by two different routes. The first by deprotonation of **195** followed by a quench with TMSCl and the second by tin-lithium exchange of stannane **203** and a quench with TMSCl (Scheme 71).



Scheme 71: Complimentary syntheses of **201**
(a) *sec*BuLi, -78 °C, ether, 0.5 h
(b) *n*BuLi, -78 °C, ether, 2 h

It was hoped that the different origin of organolithiums of **204** would be reflected in the different stereochemical properties of **201**. The deprotonation of **195** followed by direct addition of TMSCl led to the synthesis of **201** as a single diastereomer. Synthesis of **201** via the tin-lithium exchange of **203** also formed a single diastereomer of identical stereochemistry. This result suggests that either the intermediate organolithium is not configurationally stable and epimerises to > 95:5 of the favoured diastereomer (see Figure 23), or that trialkyl tin chlorides also react with our organolithiums via a retentive mechanism. Each scenario would lead to the products of **201** having identical stereochemistry.

We therefore synthesised **199** and **203**, each by the two different routes, and analysed the stereochemical outcome of each product (Scheme 72).



Scheme 72: Complimentary synthesese of **199** and **203**

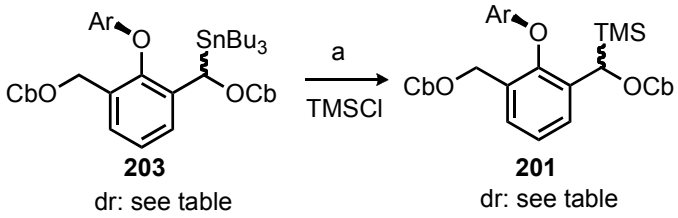
(a) *sec*BuLi, -78 °C, ether, 0.5 h, $E^+ = (CH_3)_2CO$ or $SnBu_3Cl$

(b) *n*BuLi, -78 °C, ether, 2 h, $E^+ = (CH_3)_2CO$ or $SnBu_3Cl$

Again, reaction of both **195** and **203** with BuLi and acetone led to products **199** with identical stereochemistry. Attempts to synthesise a "double inversion" product by reacting **203** with a further equivalent of $SnBu_3Cl$ after tin-lithium exchange was also made. Unfortunately, the loss of colour associated with our transmetallations after addition of *n*BuLi to the substrate indicated that the transmetallation and quench of **203** failed, and returned only starting material. In this instance, we could not rely on the stereochemical outcome of our attempts at a double stannylation although our results so far suggested that trialkyl-tin compounds, despite our initial reasoning, also react with retention.

Given Schemes 71 and 72, it was also likely that the intermediate organolithium formed after deprotonation was *not* configurationally stable, although the results from section 2.3.5.1 indicated otherwise. We therefore additionally exploited tin-lithium exchange chemistry to establish which was the case. The reaction of carbamate protected **195** with $SnBu_3Cl$ in section 2.3.5.1 had produced stannanes **203** with differing ratios of diastereomers. If we assume that tin-lithium exchange proceeds with reliable retention, the stability of the intermediate organolithium (if indeed it is configurationally stable) should reflect the original ratio of stannanes in the new product.

We therefore treated different diastereomeric ratios of stannane **203** with *n*Buli in ether at -78 ºC followed by addition of TMSCl (Scheme 73, Table 31).



203
dr: see table

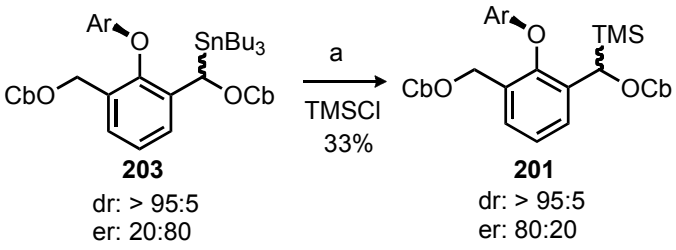
201
dr: see table

Scheme 73: Configurational stability study with Sn-Li exchange
(a) *n*BuLi, -78 °C, ether, 2 h, then quench

Entry	203 d.r. [a]	Transmetallation Conditions	Yield / %	201 dr [a]
1	5:1	-78 °C, 2 hours	22	7.6:1
2	9:1	-78 °C, 2 hours	28	94:6
3	9:1	-78 °C, 6 hours	32	94:6

Table 31: Tin-Lithium exchange of **203** followed by quench with TMSCl
[a] dr's measured as a ratio of of diastereotopic signals in ^{1}H NMR

While not delivering the exact ratio of diastereomers of starting stannane **203**, the outcome of **201** did differ depending on the ratio of starting diastereomers (compare entry 1 with entry 2) suggesting that the organolithium at least has some degree of configurational stability under these conditions. The low conversion further indicates that the observed reduction in d.r. could be a consequence of the reaction rates of each intermediate. We also treated enantioenriched stannane **203** with with *n*Buli in ether at -78 ºC followed by addition of TMS-Cl (Scheme 74).

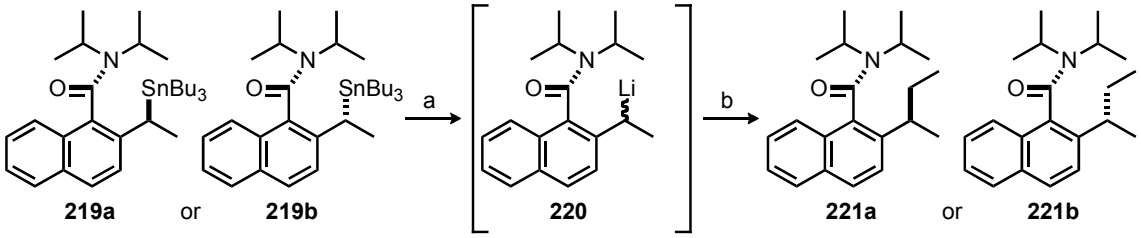


Scheme 74: Configurational stability study using Sn-Li exchange
(a) *n*BuLi, -78 °C, ether, 2 h, then quench, er = first eluted enantiomer reported first

The product **201** was enantioenriched consistent with substantial stability to O-Ar bond rotation under these reaction conditions.

2.3.6.1.1 Non stereospecificity in tin-lithium exchange

It is, however, possible that tin-lithium exchange is *not* reliably stereospecific and great care should be taken in interpreting stereochemical results which rely upon the assumption that it is.[129] Clayden reported what they believed to be the first example of a non-stereospecific tin-lithium exchange in 1997 (Scheme 75, Table 32).[122]



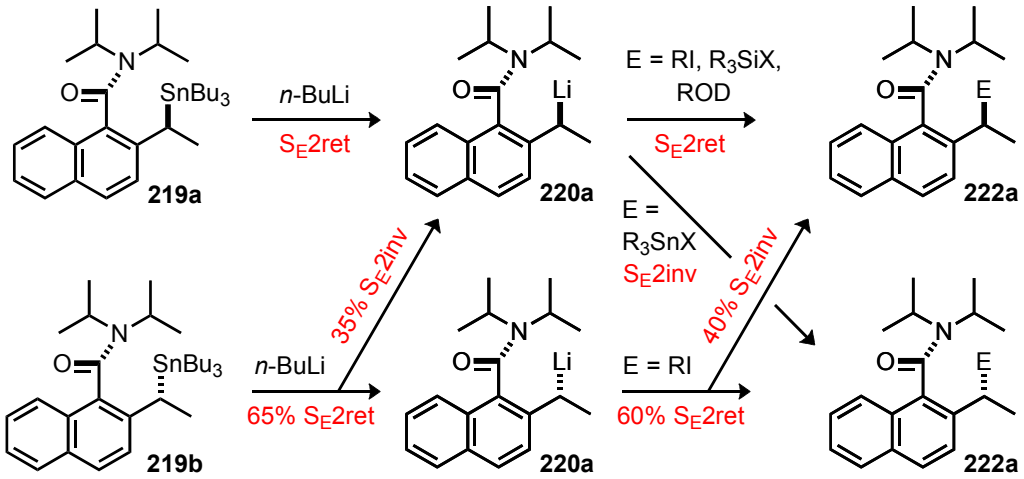
Scheme 75: Transmetallation of stannanes **219a** and **219b**
(a) *n*BuLi,
(b) excess EtI, -78 °C

Entry	219a:219b	Transmetallation Conditions	Yield / %	221a:221b
1	100:0	-78 °C, 2 hours	97	99:1
2	6:94	-78 °C, 2 hours	87	60:40
3	100:0	-40 °C, 2 hours	94	98:2
4	5:95	-40 °C, 2 hours	83	60:40
5	5:95	-78 °C, 30 min → -25 °C, 5 min → -78 °C, 100 min	83	64:36

Table 32: Stereospecificity in the transmetallation of stannanes **219a** and **219b**

Transmetallation and alkylation of each diastereomer of **219** provided evidence for lack of stereospecificity in a tin-lithium exchange. Stannane **219a** reacted entirely as

expected, giving, after transmetallation and alkylation at -78 °C or at -40 °C, essentially a single diastereomer of the product **221a** (entries 1 and 3). However, when a sample containing 95% of stannane **219b** was transmetallated and alkylated under either of these conditions, the product contained a mixture of 60:40 **219a**:**219b** (entries 2 and 4). Entries 3-5 show how the product ratios are invariant even when the intermediate organolithium is kept at -40 °C for 2 h or even warmed briefly to -25 °C. These selectivities are therefore not snapshots of a slowly equilibrating mixture of organolithiums[130] and organolithiums **220** must be configurationally stable. Given this configurational stability, the loss of stereospecificity could be occurring in either of the two seps in the sequence. NMR studies indicated that there was in fact a lack of stereospecificity in both the *formation* and *reaction* of organolithiums **220**, and their overall conclusions are summarised in Scheme 76.

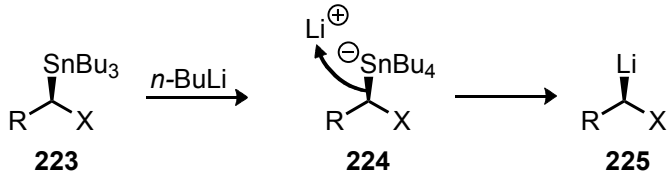


Scheme 76: Non-stereospecificity in the transmetalation of **219b** and reactions of **220b**

It might therefore be possible that our own stannanes are reacting without stereospecificity, or in fact with inversion, although this is unlikely taking into consideration the α-oxygenated structure of our compound.

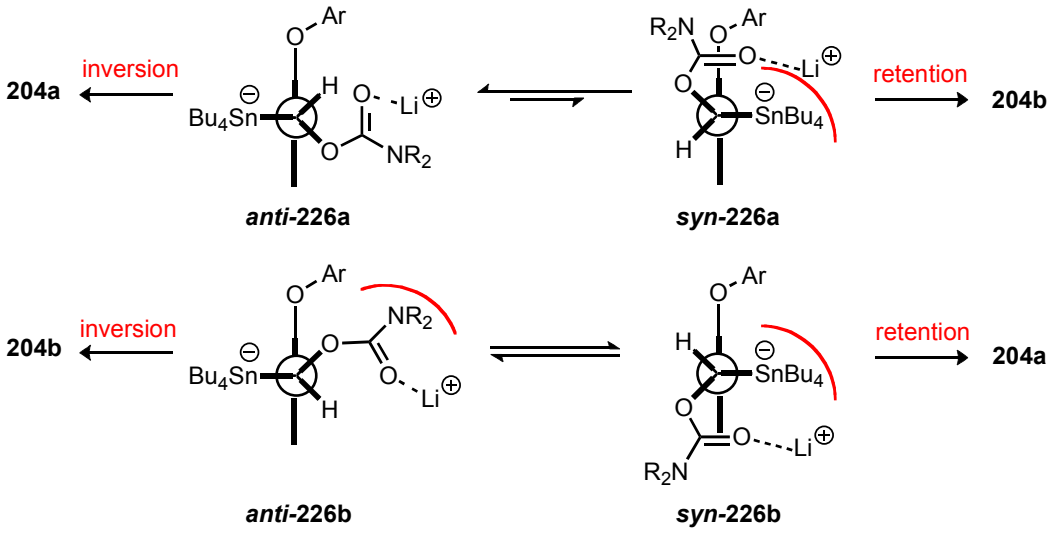
Typically, in a tin-lithium exchange, we would expect an intermediate ate complex **224** (Scheme 77). For the exchange to be retentive, **224** must collapse with retention to give **225**. Presumably the organolithium **225** must form a very short-lived ion pair, and the stereochemistry of the organolithium is dictated by the stereoselectivity of the attack of Li^+ on the carbanion. Even if an ion pair is not an intermediate, retentive and invertive electrophilic substitutions of organotin compounds are both known.[131] The reaction is so generally retentive because the exchange is only thermodynamically

favourable when the product organolithium is stabilised in some way, and there is almost always a lithium-coordinating heteroatom X involved in the ion pair collapse. The effect of the heterostom will be to anchor the lithium cation during the collapse of the ion pair, leading to overall retention. Retention might be much rarer in the formation of non-heteroatom-stabilised organolithiums.



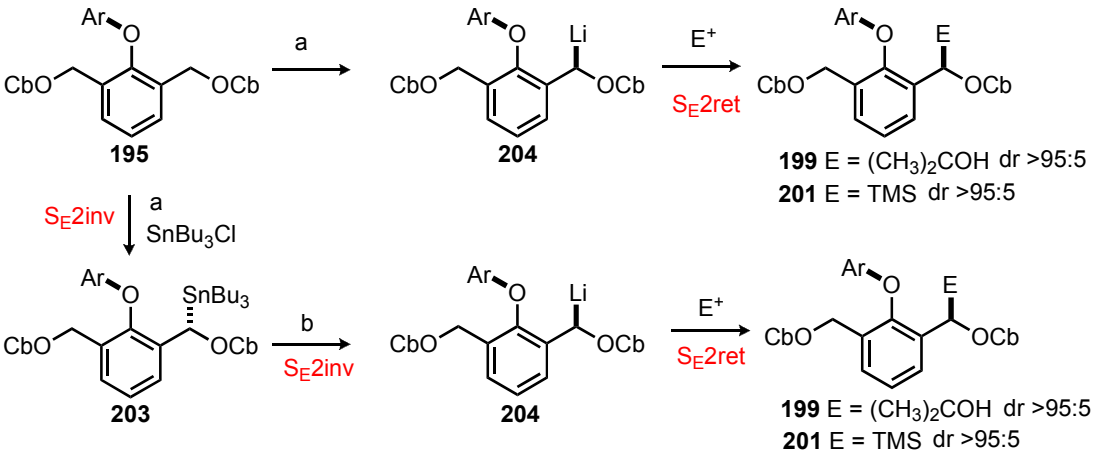
Scheme 77: Mechanism of tin-lithium exchange via ate complex **224**

If the lithium is not sufficienty anchored by the α-oxygen, the transmetallation of **203** could possibly proceed via a stannate intermediate **226**, which may collapse to give either diastereomeric organolithium depending on the direction of attack on the C-Sn bond by Li^+ (Scheme 78). The hypothetical conformation of the ate complex derived from **203** can exist as diastereomers **226a** or **226b**. In **226a**, delivery of either RLi or Li^+ (by coordination to the carbamate carbonyl) can take place in such a way that *invertive* transmetallation is preferred. The case of a diastereomer where **203** has the preferred conformation shown in stannante complex **226b** is less clear-cut. Either the tin or the carbamate substituent must lie close to the bulky Ar group on the axis, and population of either the *syn* or the *anti* conformer could lead to retentive or invertive organolithium **204**.



Scheme 78: Possible invertive and non-stereospecific tin-lithium exchange mechanisms

If in fact transmetallation is invertive then a possible mechanism to explain the identical sterechemical outcome of ether **195** and stannane **203** with acetone and silyl electrophiles to produce products with identical stereochemistry is shown below (Scheme 79).

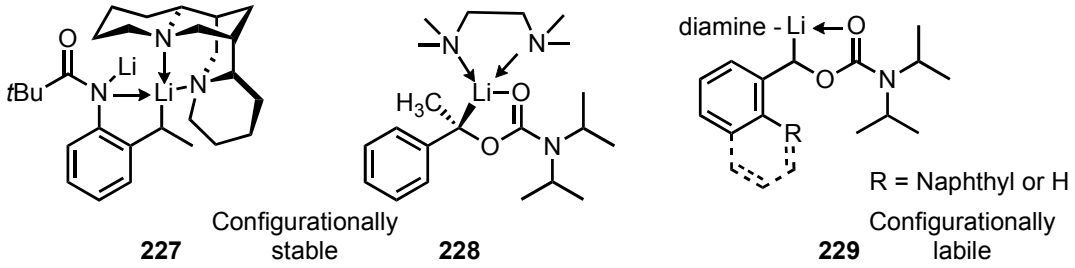


Scheme 79: Possible invertive transmetallation to explain the stereochemical outcome of **199** and **201**
(a) *s*ecBuLi, -78 °C, ether, 0.5 h
(b) *n*BuLi, -78 °C, ether, 2 h

Of course the most likely explanation is that organolithium **204** reacts retentively with trialkyl tin halides to produce products of identical stereochemistry even after transmetallation. The retention times and chemical shift properties of the supposedly "opposite" diastereomer when compared to products **199** – **202** could simply be misleading. As no X-ray crystallographic studies were possible due to the products being oils or gums, we cannot assume that **203** is the opposite diastereomer to **199**-**202**.

2.3.6.2 Reaction pathways in lithium substitution

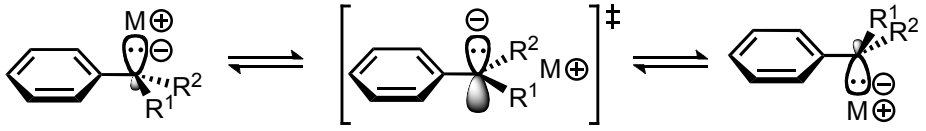
Hoppe has shown that lithiated secondary O-benzyl N,N-diisopropylcarbamate **228**[132] (Figure 25) belongs to only a small group of benzyllithium compounds that exhibit configurational stability in solution at low temperatures. His most closely related compound to ether **195**, lithiated benzyl carbamates **229**[133], although configurationally stable in the Hoffmann test,[134] exhibit configurational lability at -78 °C.



227 **228** **229**

Figure 25: Configurationally stable and configurationally labile benzyl lithium complexes

The racemisation of Hoppes chiral secondary benzyl alkali-metal derivatives **229** probably proceeds via a planar transition state (Scheme 80); therefore, the chiral information introduced during their generation is lost, and the final substitution product is formed with poor or even no enantioselectivity.[133]

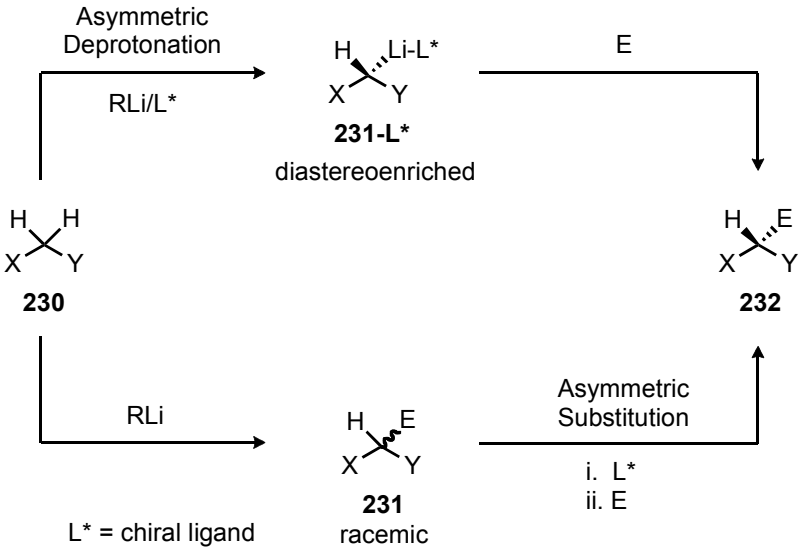


229 ***ent*-229**

Scheme 80: Possible racemisation mechanism of metallated benzylic carbanions **229**

Configurational stability plays an important role in the asymmetric organolithium reaction, and configurational stability is closely linked to the mechanism by which the reaction takes place. For an enantioselective reaction, the enantiodetermining step can be the lithiation, as an asymmetric deprotonation, or a postdeprotonation step, as an asymmetric substitution. A chiral ligand complexed to lithium can create the necessary diastereomeric environment in either step.

In an asymmetric deprotonation, the organolithium reagent complexed to the chiral ligand is a chiral base which selectively abstracts an enantiotopic proton from the prochiral substrate **230**. The enantioenriched organolithium intermediate **231** or **231-L*** is configurationally stable and reacts stereoselectively with an electrophile, providing the enantioenriched product **232** (Scheme 81).[135]

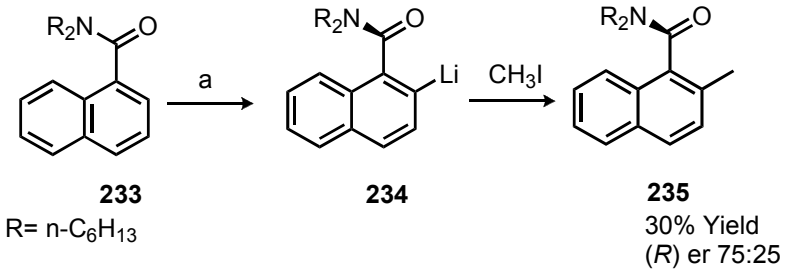


Scheme 81: Enantioselective reaction pathways

In an asymmetric substitution, the enantiodetermining step occurs after deprotonation. The racemic organolithium **231** can afford enantioenriched product **232** under the influence of the chiral ligand by different pathways depending on whether **231** is slowly or rapidly epimerising with respect to its rate of reaction with the electrophile.

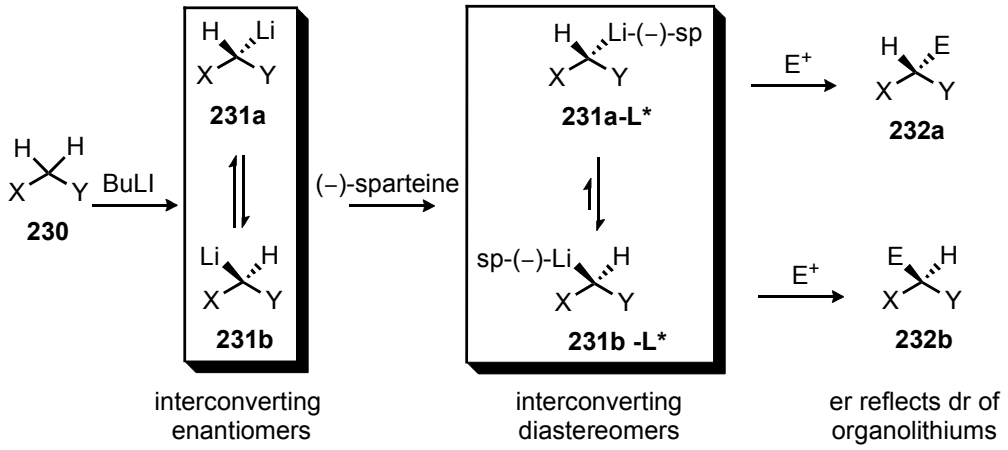
Most of Beak's work has investigated the reaction pathways of lithium substitution reactions and probed the stereochemical integrity of the organolithiums. Configurationally stable organolithiums generally promote the *formation* of an organolithium, while configurationally unstable organolithiums allow the chiral ligand to direct the course of the *reaction*.

For example, Beak concluded that the enantioselectivity in the synthesis of aromatic amide **235** was a result of a simple asymmetric deprotonation. The complex of *sec*BuLi with (–)-sparteine selectively removes the pro-*R* proton in **233**. The chiral, configurationally stable organolithium **234** then reacts with the alkylating reagent to give the product with an er of 75:25 (Scheme 82).[136]

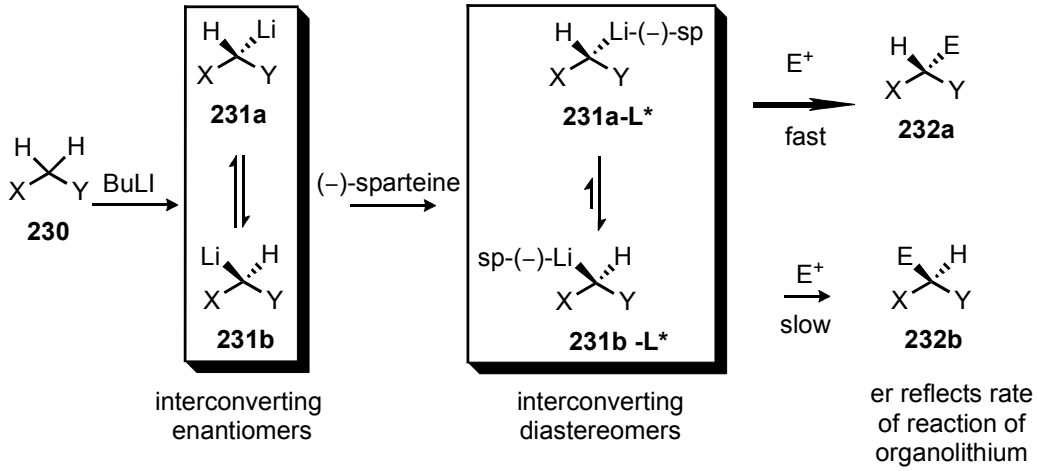


Scheme 82: Asymmetric deprotonation of aromatic amide **233**
(a) *s*-BuLi, (–)-sparteine, -78 °C, ether

For an asymmetric substitution reaction, the intermediate organolithium must usually be *configurationally unstable,* or the ligand will be unable to direct the course of the reaction (an exception might be a hypothetical reaction in which the ligand allows the two organolithium enantiomers to react with opposite stereospecificity). These diastereomeric organolithium intermediates can epimerise regardless of the stereoselectivity of the deprotonation step. If this epimerisation is slower than the rate at which the intermediate reacts with the electrophile then the product ratio reflects the ratio of the diastereomeric organolithium complexes in the reaction mixture (dynamic thermodynamic resolution) (Scheme 83). Alternatively, if the epimerisation is faster than the rate at which the intermediate reacts with the electrophile then a dynamic kinetic resolution results whereby one diastereomeric intermediate reacts more readily with the electrophile (Scheme 84). In this case the diastereoselectivity observed is determined by the difference in the transition state energies.[137]

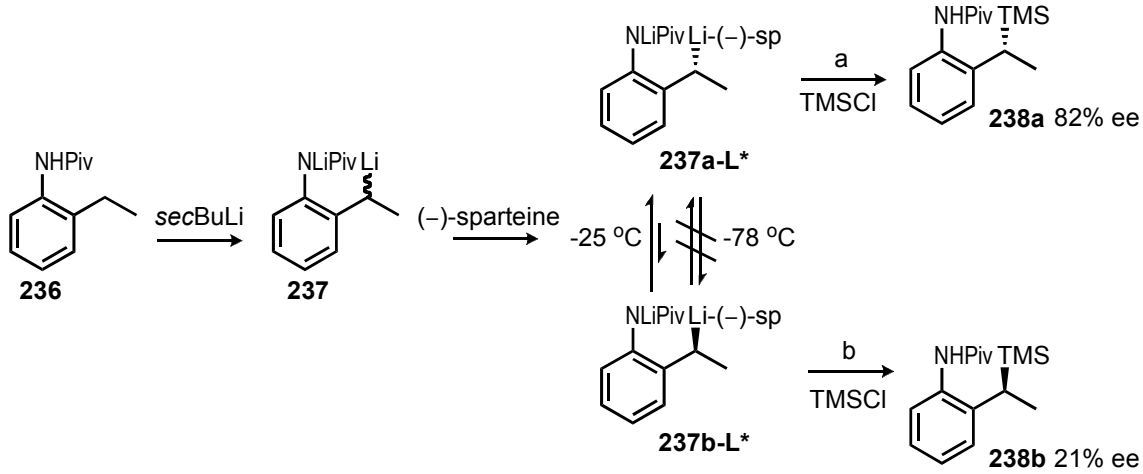


Scheme 83: Asymmetric substitution – dynamic thermodynamic resolution



Scheme 84: Asymmetric substitution by dynamic kinetic resolution

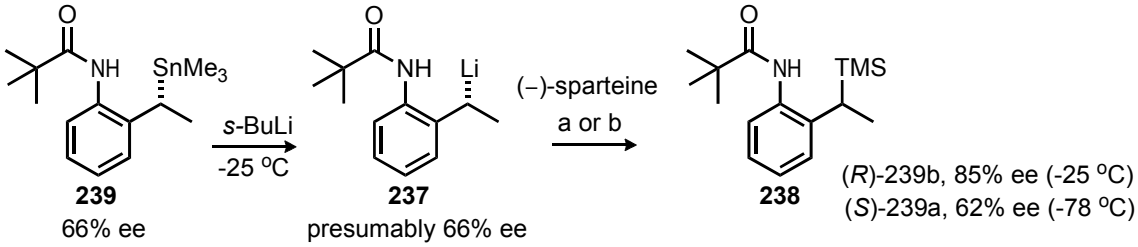
Beak studied the configurational stability of the benzylic lithiated intermediate **237** and effectively used a dynamic thermodynamic resolution to obtain enantioenriched products. He did this by modifying the temperature of the reactions. Treatment of anilide **236** with *sec*BuLi followed by a quench with TMSCl generates silane **238**. The product is formed in 82% ee if the racemic intermediate organolithium **237** is first treated with (−)-sparteine at −25 °C and then TMSCl at − 78 °C: the reaction is an asymmetric substitution, with sparteine governing the enantioselectivity of the electrophile quench step. Adding sparteine at -78 °C reduces the ee of **238** to only 21%. (–)-sparteine is able to exert its effect more efficiently at higher temperatures, exactly as would be expected if it were controlling the equilibration of a pair of organolitiums (which might be fast at −25 °C but slow at −78 °C), but in contrast to what would be expected if it were controlling the rates of reaction of two organolithiums (Scheme 85).[138]



Scheme 85: Asymmetric substitution by dynamic thermodynamic resolution
(a) -25 °C, (–)-sparteine, then -78 °C and TMSCl
(b) -78 °C, (–)-sparteine, then TMSCl

At -78 °C the diastereomeric organolithium (–)-sparteine complexes **237-L*** are configurationally stable in relation to the timescale on which they react with the electrophile and so the ratio of enantiomers **238** reflects the initial organolithium proportions. However, at -25 °C the organolithiums are configurationally unstable and therefore the diastereomers **237-L*** can interconvert. This leads to an excess of the thermodynamically more stable organolithium **237a-L*** which on reaction with TMSCl yields preferentially enantiomer **238a**.

Organolithium **237** is configurationally stable, thus transmetallation of the stannane **239** which has an ee of 66%, probably generates organolithium **237** with 66% ee. If the transmetallation is carried out at −78 °C, the product **238** of electrophilic quench has an ee close to 66% (Scheme 86).

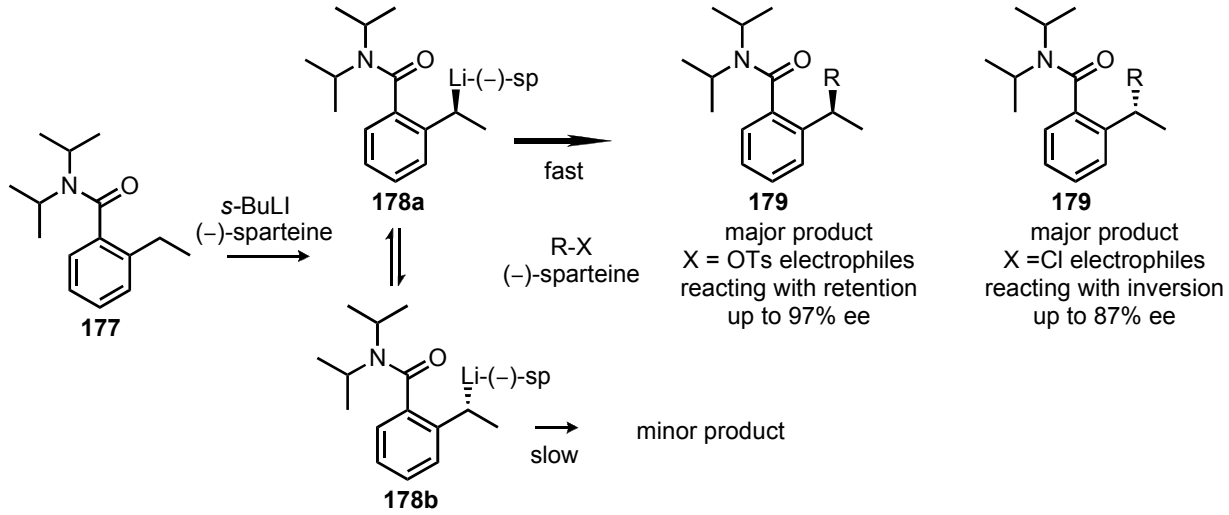


Scheme 86: Transmetallation and electrophilic quench of pivaloyl at either -25 °C or -78 °C
(a) -25 °C, (–)-sparteine, then -78 °C and TMSCl
(b) -78 °C, (–)-sparteine, then TMSCl

This suggests that at this temperature (−)-sparteine is unable to perturb the ratio of the two enantiomeric organolithiums. However, if the mixture of organolthium **237** and (−)-sparteine is warmed to −25 °C for 2 h before being cooled again to −78 °C and quenched, the other enantiomer of the product **238**b is formed in 85% ee.

The enantioselectivities arise on treatment of the non-racemising intermediate organolithium **237** with an excess of electrophile, such that both enantiomers react to completion. But since the (–)-sparteine complexes **237-L*** are diastereomeric, it should in principle be possible to separate them kinetically by using a defecit of electrophile, such that only the more reactive of the two diastereoisomeric complexes is quenched. In such a case, ee should increase, and it does. The 21% ee obtained on treatment of the unequilibrated **237-L*** with a full equivalent of TMSCl at -78 °C can be improved to 82% ee when only 0.1 equiv. TMSCl is used: in other words, the intermediate organolithium (–)-sparteine complexes are present in about a 60:40 ratio but the major diastereoisomeric complex reacts much faster than the minor, allowing the formation of one product in high enantiomeric excess. An even better result is obtained if the organolithiums **237** are first allowed to equilibrate and *then* the faster reacting one (the major one in this case) is allowed to react selectively with a defecit of electrophile: the ee improves to 98%.[128,139]

Beak also showed that a dynamic kinetic resolution was in operation in the substitution reaction of lithiated benzamide **178** (Scheme 87).[123]



Scheme 87: Asymmetric substitution by dynamic kinetic resolution

The organolithium is not configurationally stable on the timescale of the reaction, however treating **178** with electrophiles in the presence of (–)-sparteine still gives products with good enantiomeric excesses. The stereoselectivity is therefore a result of the (–)-sparteine complex reacting with the electrophile and not an initial deprotonation. The enantiomeric excess of the product does not change during the course of the reaction.

It is possible for more than one pathway to be operative with a single substrate. Schlosser has shown that *N*-Boc-*N*-methyl-*N*-benzylamine undergoes an initial asymmetric deprotonation followed by equilibration of the resultant intermediate.[140] In this case, the enantioselectivity of the product is determined in a postdeprotonation step, even though an asymmetric deprotonation occurs.

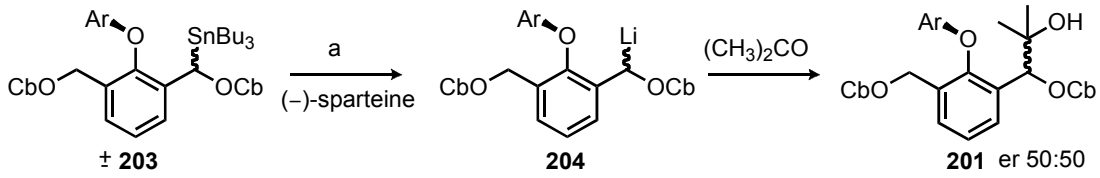
In some cases, crystallisation of the intermediate organolithium-(–)-sparteine complex complexes is necessary to force their equilibration to the major diastereomer.[141] In this type of dynamic thermodynamic resolution, the intermediate organolithium-(–)-sparteine complexes might interconvert in solution, but one diastereomer crystalises preferentially, leading to a dynamic resolution of the organolithium.

2.3.6.2.1 Investigating the reaction pathway in lithium substitution

Transmetallation studies (see section 2.3.6.1) indicated that our intermediate organolithium was probably configurationally stable under the conditions of the reaction. An enantioenriched product is formed on electrophilic quench in the presence of (–)-sparteine (section 2.3.5, Table 29), but as the axis is likely to be stable at −78 °C,

the er must be a consequence of the kinetically determined selectivity in the deprotonation. The relative stereochemistry of the product is then affected by the retentive or invertive nature of the electrophilic quench.

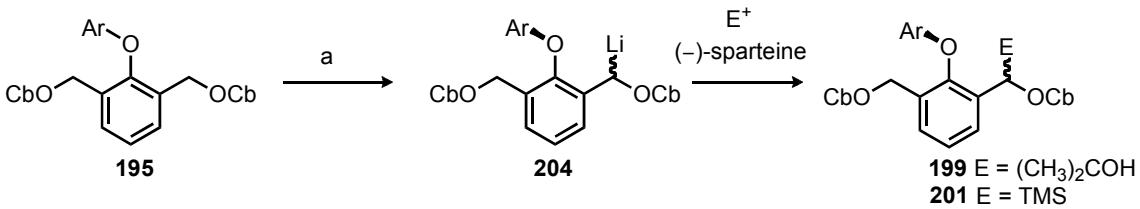
We first set out to confirm that the deprotonation determines the overall enantioselectivity of the reaction by treating racemic stannane **203** to a tin-lithium exchange followed by an electrophilic quench in the presence of (–)-sparteine (Scheme 88). As there is no proton involved in the *formation* of the organolithium, the product of the electrophilic quench can only be determined by *reaction* of the organolithium with the electrophile.



Scheme 88: Tin-lithium exchange in the presence of (–)-sparteine
(a) *n*BuLi, 2 h, -78 °C, ether, (–)-sparteine, then E^+ qunch with acetone

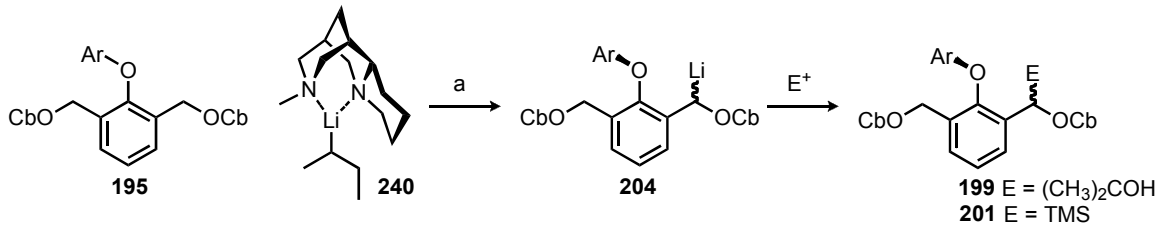
Although cude ^{1}H NMR showed minimal conversion to product, alcohol **201** was proven to be racemic by chiral phase HPLC, confirming that deprotonation determines the ee of the product.

Our method of deprotonation up until this point had been to add *sec*BuLi in the presence of a stirring suspension of (–)-sparteine. We therefore decided to carry out the deprotonation step without the presence of (–)-sparteine, only adding the chiral ligand after deprotonation was assumed to be complete. As the chiral influence of (–)-sparteine can only affect the reaction of the organolithium in this case, an ee should not be observed if an asymmetric deprotonation solely governs the stereoselectivity (Scheme 89).



Scheme 89: Reaction of racemic organolithium **204** with electrophiles in the presence of (–)-sparteine
(a) *sec*BuLi, 0.5 h, -78 °C, ether

Unfortunately, the reaction failed in the presence of both acetone and TMSCl, and thus the stereochemical outcome of the reaction was unable to be interpreted. We therefore decided to "premix" our sparteine and *sec*BuLi with the intention of increasing the enentioselectivity of the product (Scheme 90).



Scheme 90: Reaction of **195** with premixed (–)-sparteine
(a) -78 °C, ether, 0.5 h

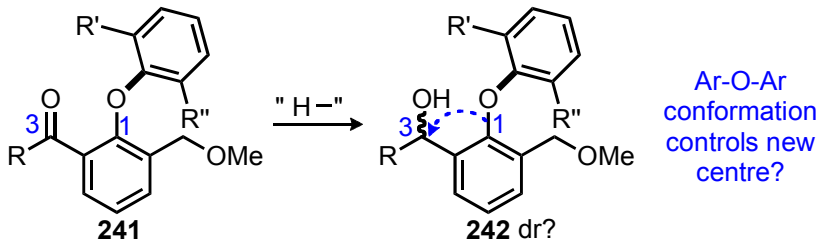
Again, the reaction returned a mixture of unidentifiable products and reprotonated starting material, however the elution times on chiral-phase HPLC in the case of **199** seemed to indicate an approximate 80:20 ratio of enantiomers where the product of **199** was usually found. This indicates that the enantioselectivity is not improved. A warm-cool sequence in the presence of (–)-sparteine, analogous to that described by Beak (section 2.3.6.2, Scheme 85), was also attempted both with a full equivalent of electrophile and with a defecit of electrophile. We aimed to determine whether more than one pathway was operative in the enantioselectivities observed for our substrate. However the reaction returned starting material and an unidentified product in minimal yield by ^{1}H NMR regardless of whether the electrophile was acetone or TMSCl, albeit in racemic form by chiral phase HPLC.

2.4 Other Stereoselective and Conformational Studies of Non-Biaryl Atropisomers

The ability for stereocentres to induce conformational control over both the diaryl ether and the diaryl sulfide axis has recently been demonstrated via their sulfoxide controlled asymmetric syntheses.[14,43] However, the ability for these axes to control the formation of new stereocentres themselves has not been investigated. Therefore, we synthesised a diaryl-ether (section 2.4.1) and a diaryl sulfide (section 2.4.2) in order to study their stereoselective reactions. A conformational analysis of what can be described as a "diaryl-amide" was also undertaken during a concurrent study into the solution behaviour of the oligo-benzanilides (section 2.4.3).

2.4.1 Stereoselective reductions of a diaryl ether

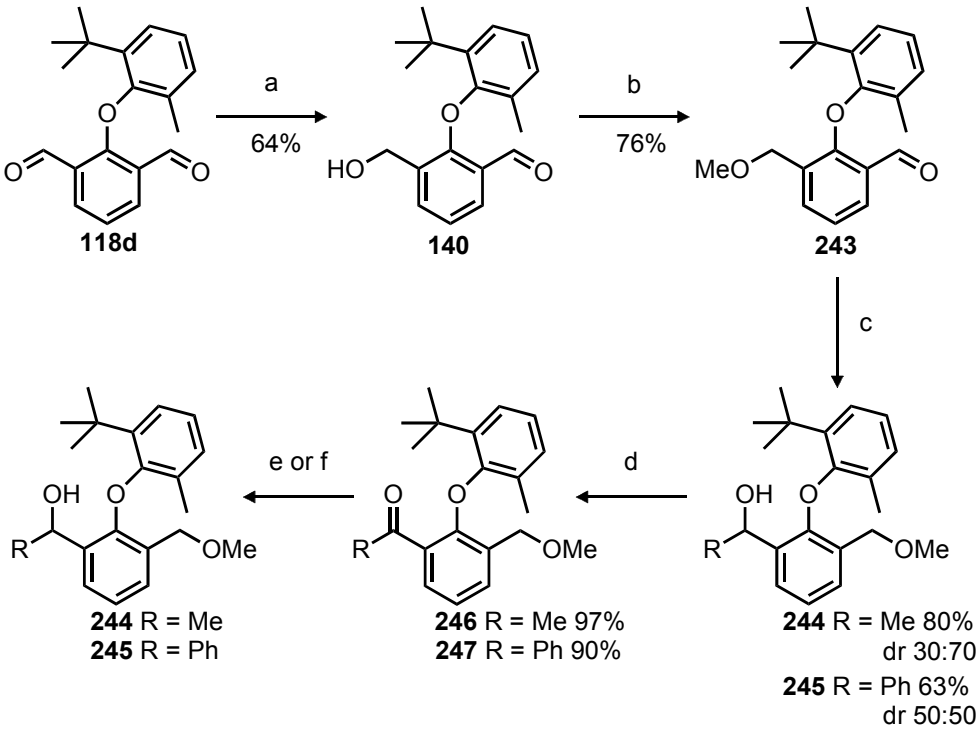
The ability of the diaryl ether axis to exert control over a new chiral centre was investigated via the reduction of a prochiral ketone **241** (capable of diastereoselective functionalisation) 1,3 remote from the axis (Scheme 91). Stereoselective reductions carried out in the group so far have provided excellent results using bulky reducing agents such as $LiBHEt_3$ "Superhydride®" (SH) and $LiBHs\text{-}Bu_3$ "L-Selectride" (LS), thus these reagents were chosen for use throughout the study.



241 **242** dr?

Scheme 91: Stereoselective reductions controlled by the diaryl ether axis

Compounds **246** and **247** were chosen as precursors for the stereoselective reductions due to the substitution pattern on the top aryl ring bestowing a large enough barrier to rotation to allow its resultant diastereomers to be separable and hence measurable by either HPLC or crude ^1H NMR. The prochiral ketone functionality allows us to determine whether the stereoselectivity observed is due to a relay of stereochemical information from the ether axis to the ketone.



Scheme 92: Synthesis and stereoselecte reduction of a prochiral ketone
(a) $NaBH_4$ 0ºC, 1 hr,
(b) i.NaH (1.2 eq); ii MeI (1.2 eq)
(c) RMgBr (1.2 eq)
(d) Dess-Martin periodinane
(e) Superhydride, THF 0 °C; (f) L-Selectride THF 0 °C

Monoaldehyde **140** was treated with a slight excess of NaH and MeI, as large excesses were found to result in nucleophilic attack at the aldehyde to yield a doubly O-methylated product. The protected alcohol **243** (76%) was then the target of Grignard addition to yield alcohols **244** (80%) and **245** (63%) as a mixture of diastereomers (R=Me, **244** = 30:70, R=Ph, **245** = 50:50). Oxidation with Dess-Martin periodinane afforded the desired prochiral ketones **246** and **247 in** yields of up to 97%. Each ketone was then treated with the reducing agent at 0^oC for 1 hour to yield back the desired alcohols, and their diastereomeric ratios were measured by crude ^1H NMR analysis (Scheme 92, Table 33).

Entry		R	Hydride Source	Yield / %	D.r.[a]
1	244	Me	Superhydride ®	98	43:57
2	244	Me	L-Selectride	98	88:12
3	245	Ph	Superhydride ®	92	>98:2
4	245	Ph	L-Selectride	98	>98:2

Table 33: Results of stereoselective reductions of diaryl ether **246** and **247**
[a] Ratios determined by crude ^{1}H crude analysis of the signals corresponding to the CH_2OMe AB system of **244** and **245**

The results of **244** and **245** upon reduction with Superhydride® and L-Selectride seem to show that the ether axis is excellent at controlling diastereoselectivity at the new chiral centre, either when a large phenyl ketone is present (entries 3 and 4) or a reducing agent at least as bulky as L-selectride is used (entry 2). The conformation of the ether axis in these cases has selectively directed attack of the hydride nucleophile to one face of the ketone. The X-ray crystal structure of the single diastereomer **245** allowed its relative configuration to be determined, and showed the hydroxyl group to be *anti* in relation to the axis (Figure 26).

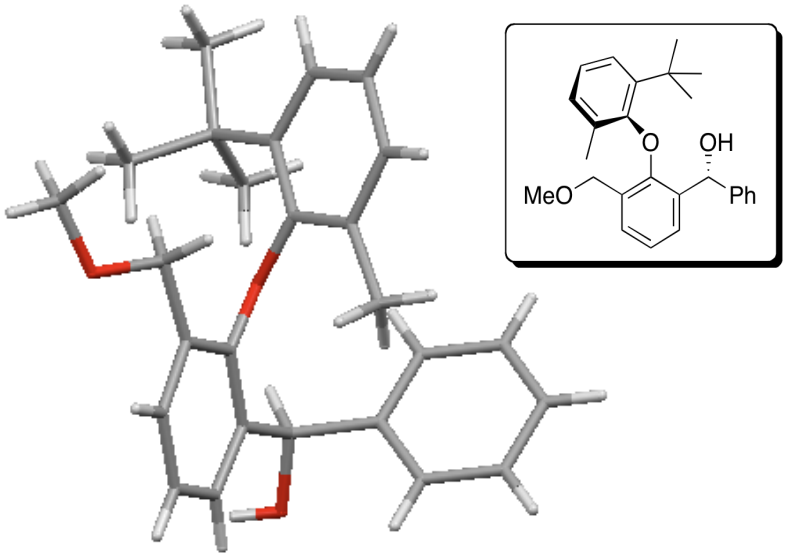
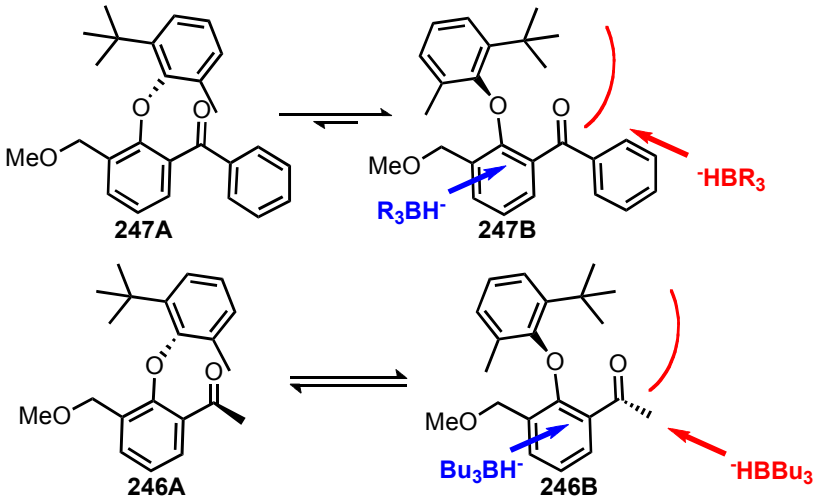


Figure 26: X-ray of relative stereochemistry of **245** showing *anti*-configuration

Heating the sample for two weeks at 50 ºC and submitting the compound to further NMR analysis suggested that **245** is the thermodynamically preferred conformation, as there was no evidence of any other diastereomer. Given our experience with the large barriers to rotation seen in these compounds (see section 2.2.2.5) it is also possible that there was no equilibration over this period.

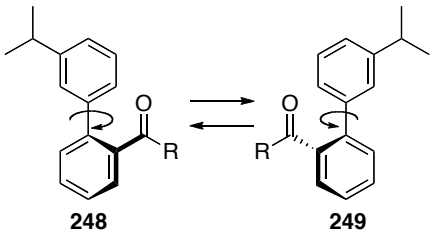
The difference in selectivity between when R=Me compared to when R=Ph (entry1 → entry 3) suggests that the conformation of the starting ketone differs in each case (Scheme 93). When R is a large, bulky phenyl group, the atropisomers could exist as conformers **247a** and **247b**, with the ketone in each case sat in the plane of the biaryl and the less sterically demanding conformation **247b** preferred. In this case hydride attack occurs away from the bulky *tert*-butyl to produces a single diastereomer (entries 3 and 4). When R is a smaller methyl group the conformations **246a** and **246b** are likely**,** with each conformation having the methyl ketone sit out of the plane of the benzene ring it is attached to in order to minimise steric interactions, and with little difference in the population of the two conformations. In this case, the trajectory of nucleophilic attack is governed by the hydride source, with increased selectivity observed only with the larger L-selectride reducing agent (compare entries 1 →2).



Scheme 93: Possible conformations of starting ketone, when R=Me and when R=Ph

Thus the difference in conformation of the methyl and phenyl ketones leads to a difference in the factors controlling the selective of attack of the hydride. Lunazzi's publication[142] on the unexpected rotation barriers in biaryls bearing *ortho*-substituted ketones also pointed to a conformational difference between methyl and phenyl ketones. Through Variable Temperature NMR experiments, he discovered that "smaller" substituents had a higher barrier to rotation than "larger" substituents (Table 34).

Entry	R	$\Delta G^{\neq}$ / kJ mol^{-1}
1	H	45.6
2	Me	34.8
3	^{i}Pr	37.3
4	^{t}Bu	30.1



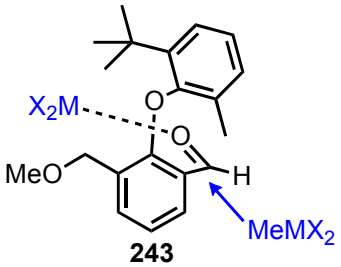
248 249

Table 34: Barriers to rotation published by Lunazzi[142]

Their proposal was that a difference in the conformation of these ketones was the origin of these unexpected observations. When R is small (H or Me, entry 1 or 2) the ketone sits essentially co-planar with the aryl ring. In this conformation the C=O moiety exerts a relatively large steric effect upon the aryl-aryl bond rotation as the aryl rings become co-planar. By contrast when R is large (entry 4) the steric effect of the R group forces the ketone out of the plane of the ring. In this *ortho*gonal conformation the steric hindrance exerted upon the axis is lower than when the ketone is co-planar leading to a lower barrier to rotation.

It is also possible that one of the conformations reacts faster than the other with the hydride reagent, and that it is interconversion between the two during the reaction that accounts for the stereoselectivity. However, the high barriers to rotation make this unlikely.

It is also worth noting that methyl Grignard addition to our formyl derivative **243** resulted in a 30:70 ratio of diastereomers, while phenyl Grigard addition gave no stereoselectivity (Scheme 92). This suggests that the conformational freedom about the C-CHO bond allows the aldehyde to present either face to the incoming nucleophile in the case of phenyl Griganrd. In the case of methyl Grignard, it is possible that the Lewis-acidic magnesium is able to coordinate to the oxygen of the carbonyl in order to present a preferred face for the organometallic reagent to attack (Figure 27).



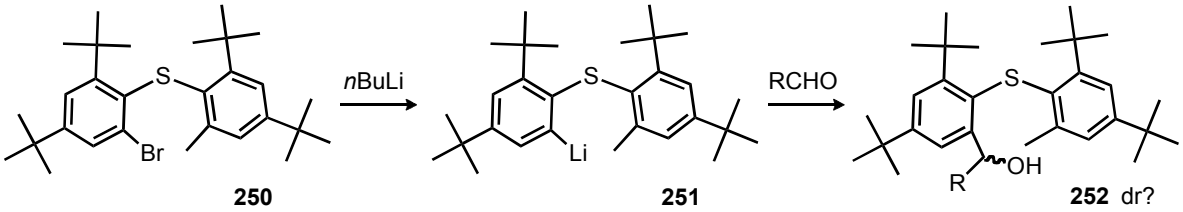
243

Figure 27: Stereoselectivity of Griganard addition to formyl **243**

2.4.2 Stereoselective additions to diaryl sulfides

The ability for diaryl-sulfides to exist as stable atropisomers was investigated by James Senior of the Clayden group on a project running concurrently with those of the diaryl ethers. It was found that the diaryl sulfides could exist as seperable atropisomers if the axis was tetra *ortho*-substituted.[14]

We decided to investigate the ability of the diaryl sulfide axis to direct diastereocontrol using *ortho*-brominated compounds **250** (Scheme 94).

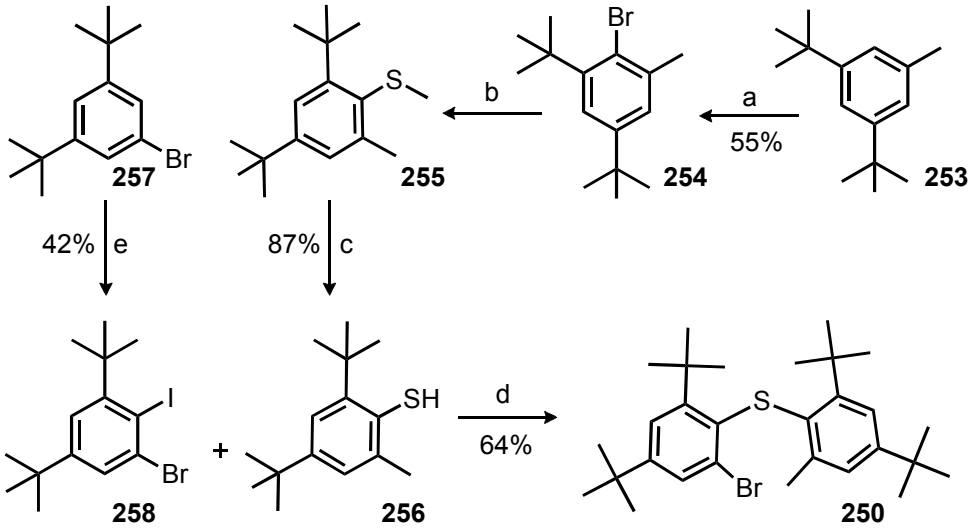


250 **251** **252** dr?

Scheme 94: Stereoselectivity of additions to a diaryl sulfide

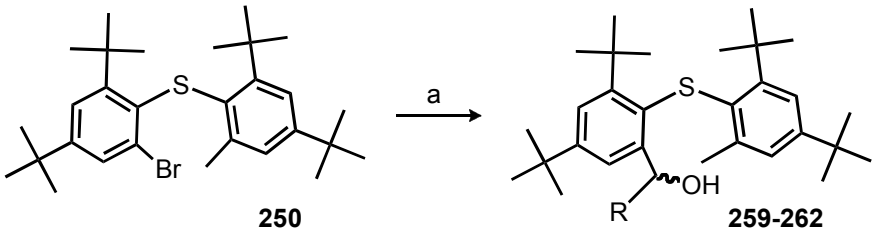
Buchwald[143] and Wang[144] have reported the coupling methodology employed in the synthesis of brominated diaryl sulfides of type **250**. They investigated the preferential coupling of iodines in the presence of bromides under copper(I) mediated cross coupling conditions, and in all cases, the considerably more reactive aryl iodide reacted preferentially with the thiophenol derivative.

A copper(I) catalysed cross coupling of aromatic iodide **258** with thiophenol **256** in the method reported by Buchwald was therefore used to afford **250** in 64% yield (Scheme 95). Thiophenol **256** was reached via bromination of commercially available 3,5-di-*tert*-butyl toluene (55%), where bromine addition occurs in the least sterically hindered position. Dimethyl disulfide then reacts cleanly with the aryl lithium derived from **254** to yield sulfide **255** which was demethylated[145] without purification to afford **256** in excellent yields (87%). Iodide **258** was reached via the conditions reported by Stavber:[146] substituted benzene **257** was heated with elemental iodine and 1-(chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octanebis(tetrafluoroborate), known under the commercial name Selectfluor™, in acetonitrile to afford **258** in 42% yield.



Scheme 95: Synthesis of *ortho*-brominated diaryl sulfide **250**
(a) Br_2, Fe powder, $CHCl_3$, 0°C, 4h
(b) i. *t*-BuLi,; ii.Me_2S_2
(c) Sodium 2-methyl-2-propanethiolate (5 eq), 16h reflux
(d) CuI (1 equiv), K_2CO_3 (2 equiv), ethylene glycol (2 equiv), *tert*-amyl alcohol, 120 °C, 24 h

The diastereoselectivity in the addition reactions of a variety of aldehydes to diaryl sulfide **250** was undertaken by subjecting the brominated compound **250** to a Br-Li exchange in THF with 1 equivalent of *n*BuLi at -78 °C for 1 minute before addition of a range of aldehyde quenches (Scheme 96, Table 35)



Scheme 96: Stereoselective synthesis of diaryl sulfides
(a) i. *n*BuLi, -78 °C, 1 min; ii. RCHO

Entry		R	Yield / %	dr[a]
1	259	Me	18	2:1
2	260	Et	23	2:1
3	261	*i*-Pr	38	6:1
4	262	Ph	68	> 95:5

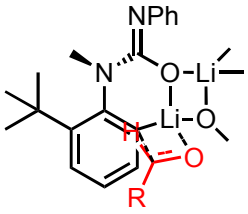
Table 35: Stereoselective addition of aldehydes to diaryl sulfide **250**
[a] dr's measured as a ratio of of diastereotopic signals in ^{1}H NMR

The reaction of diaryl sulfide **250** with acetaldehyde (entry 1), propionaldehyde (entry 2) and *i*-butryaldehyde (entry 3) occurred in low yields and gave complex reaction

mixtures, even after purification of the starting aldehydes. This is thought to be due to polymerisation of the aldehydes under the basic conditions of the reaction, as reaction with sterically encumbered lithiated **251** is slow. The diastereoselectivity increased from 2:1 → 6:1 when the size of R increased from a methyl/ethyl (entries 1 and 2) to an *iso*-propyl (entry 3). Heating the mixture of diastereomers of **260** for 16 h at 45 °C increased the presence of the less favoured diastereomer by around 14%, suggesting that that the observed selectivities must arise by kinetic control.

In an attempt to suppress aldehyde polymerisation, and increase the stereoselectivity of these reactions, benzaldehyde was employed as a quench. In this case, the reaction occurred in high yield (68%) and with complete control of stereoselectivity (entry 4). Crude ^{1}H NMR showed only one doublet peak corresponding to the C(OH)***H***Ph proton.

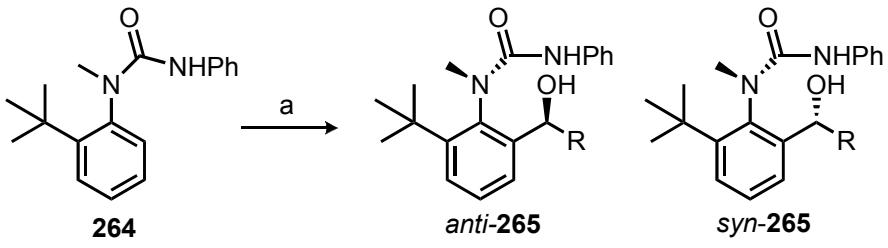
It is likely that the system seen here is analogous to that seen in the diaryl ureas[13], where the reaction proceeds through the transition state **263** (Figure 28).



263

Figure 28: Proposed transition state in the *syn* selective addition of *ortho* lithiated ureas to aldehydes[13]

Aggregation of the lithiated moiety in solution results in the aldehyde approaching *syn* to the urea methyl group. Steric hindrance between the R group and the methyl group then dictates the diastereofacial selectivity. This leads to excellent selectivity for the *syn* isomer (Scheme 97, Table 36).



264 *anti*-**265** *syn*-**265**

Scheme 97: Stereoselective addition of aldehydes to urea **264**
(a) i) *s*-BuLi (2 equiv) -78 °C, THF; ii) RCHO

R	−78 ˚C Ratio *syn*-265 : *anti*-265	−90 ˚C Ratio *syn*-265 : *anti*-265
Me	84:16	99:1
Et	83:17	97:3
i-Pr	97:3	98:2
Ph	63:37	70:30

Table 36: Stereoselective addition of aldehydes to urea **264**

2.4.3 Conformational study of a diaryl amide in solution

The amide bond structure has been studied extensively due to the amide moiety being one of the most important functions in biological systems.[147] Its usefulness in synthesis has also been previously discussed within this thesis, namely in section 1.3, where the remote stereocontrol work carried out within the Clayden group was achieved by utilising their well-defined conformation. However, the work proved difficult to extend beyond the 1,23-stereocontrol due to low yielding Suzuki couplings of more extended oligoxanthenes. This prompted the investigation of helices as potential converyors of stereochemical information, replacing the xanthene monomer with another that would be more liable to oligomerisation, such as a benzanilide.

Secondary benzanilides **266** generally adopt a ring-trans (formally *Z*) conformation (Figure 29) and their oligomers have proven to adopt a well-defined helical structure, a consequence of both the preferred geometry of the amide bonds and their hydrogen bonding ability.[148]

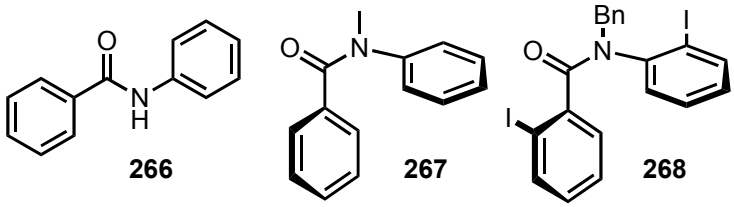
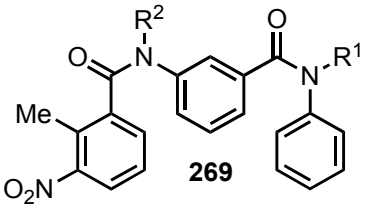


Figure 29: Conformational control in the diaryl-amides

The conformation of *N*-alkylated anilides have also been investigated in detail, and it has been shown that *N*-alkylated benzanilides favour the conformation **267**, which places the aryl rings cis (formally *E*) in the crystal and in the solution. [149] The conformational ratio of these tertiary benzamides can be altered by the size of the substituents at the aromatic *ortho* position and on the nitrogen atom.[150,151] and Clayden has shown that benzanilide **268** bearing two iodo substituents at the *ortho* position of each ring and a benzyl group on the nitrogen, exhibits high conformational control.[151]

A study investigating the conformational behaviour of this class of compound was therefore undertaken[152] in the hope that limited conformational freedom and may be the formation of helical structures would be observed. Dimeric compounds related to *meta*-linked benzanilides **269** were synthesised as part of this study and their conformational ratios in solution measured by NMR (Table 37).[153]



269

Entry	269	Substitution R^1	Substitution R^2	Ratio of conformers[a]
1	a	Me	Me	80:20
2	b	Bn	Me	80:20
				81:12 (-60 °C)
				82:18 (C_6D_6)
				87:13 (THF)
				87:13 (DMSO)
3	c	Bn	Bn	85:15

Table 37: Conformational isomerism in benzanilides **269**
[a] Ratio of conformers evident in NMR in $CDCl_3$ at 23 °C unless otherwise stated

It was seen that the tertiary diamides in entries **269a-c** existed in solution as a mixture of two major conformers in a ratio of 4:1 to 7.5:1 depending on the solvent and temperature. Although not conformationally uniform, this high level of control was still remarkable given the compounds' potential to exhibit (on the NMR timescale) four geometrical (cis/trans) amide conformers multiplied by four axial (syn/syn, syn/anti etc.) conformers.

It was somewhat unexpected that the size of the R^1 group (=Me or Bn) had virtually no influence on the conformational selectivity (compare **269a** to **269b**, entries 1 and 2). Although the selectivity slightly increased when R^2 was increased in size from Me to Bn (compare entries 2 and 3). At low temperature (-60 °C, CDCl3), the ^{1}H NMR showed an improvement of conformational ratio to 88:12, but with signals remaining broadened. Solvent effects on the conformational ratio of entry 2 were also studied at 25 °C, with marginally better conformational selectivities obtained in C_6D_6 (82:18), THF-d_8 (87:13) and DMSO-d_6 (87:13).

X-ray crystallography[154] allowed the solid-state structure of **269b** to be determined (Figure 30).

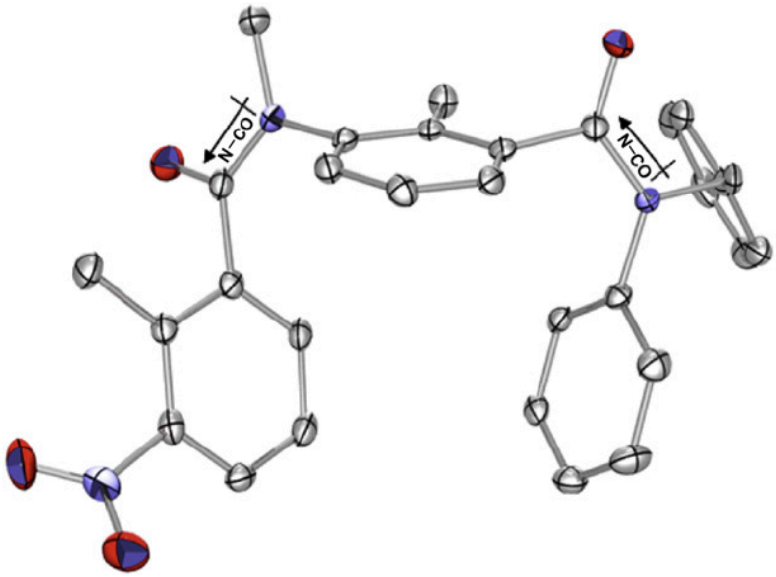
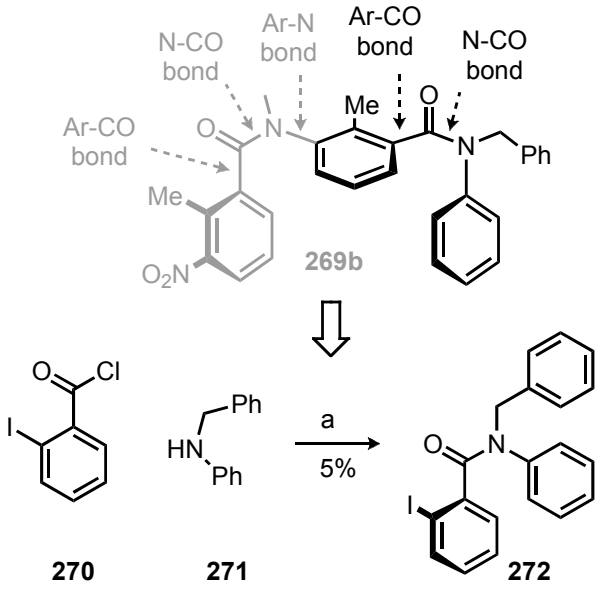


Figure 30: X-ray crystal structure of **269b**

Both amide bonds were seen to adopt a *cis* C-N conformation, in line with precedent. As has been previously observed within the group, the methyl groups on each aromatic ring flanking the benzanilide amide function align anti to avoid steric interaction.[151] The *cis* orientation of benzamides across the central aromatic ring can be explained by a dipole-dipole interaction (shown in Fig. 30) between both amide functions.[38] Unfortunately, attempts to determine whether the conformation in the solid state is the same as the major conformation in solution were unsuccessful - dissolving a crystal of **269b** at low temperature (-50°C) and acquiring a ^{1}H NMR spectrum immediately returned the same mixture of conformers as that obtained on cooling a room temperature solution. In an attempt to establish which of the conformational features of **269** are well controlled, and hence identify the second, minor, conformer, compound **272** was synthesized as part of a strategy towards studying analogues of **269b** lacking one or more of the conformationally restricted amide N-CO, Ar-CO or Ar-N bonds (Scheme 98).



Scheme 98: Synthesis of conformational analogue **272**
(a) Et_3N, DCM, 0 °C to RT

Diaryl-amide monomer **272**, analogous to the conformational features shown in bold in scheme 99, was synthesised via an amide coupling of acid chloride **270** with amine **271**.

The ^1H NMR spectrum of **272** revealed the presence of two conformers in a ratio of 90:10, which must be due to rotamers about the N-CO bond (ring cis or ring trans). The observable peaks in the spectra (those of the CH_2Ph groups of each conformer) are as the result of each conformer having a barrier to rotation about the Ar-CO bond. We therefore undertook a Variable Temperature study to find the respective barriers to rotation for each conformer.

2.4.3.1 Variable temperature NMR analysis of diaryl amide 272

The CH_2Ph group of the minor rotamer appeared as a sharp AB system (due to slow Ar-CO rotation) at ambient temperature (Figure 31). However, the CH_2Ph group of the major conformer was a broadened singlet at rt, which decoalesced to an AB system on cooling to -50 °C in $CDCl_3$.

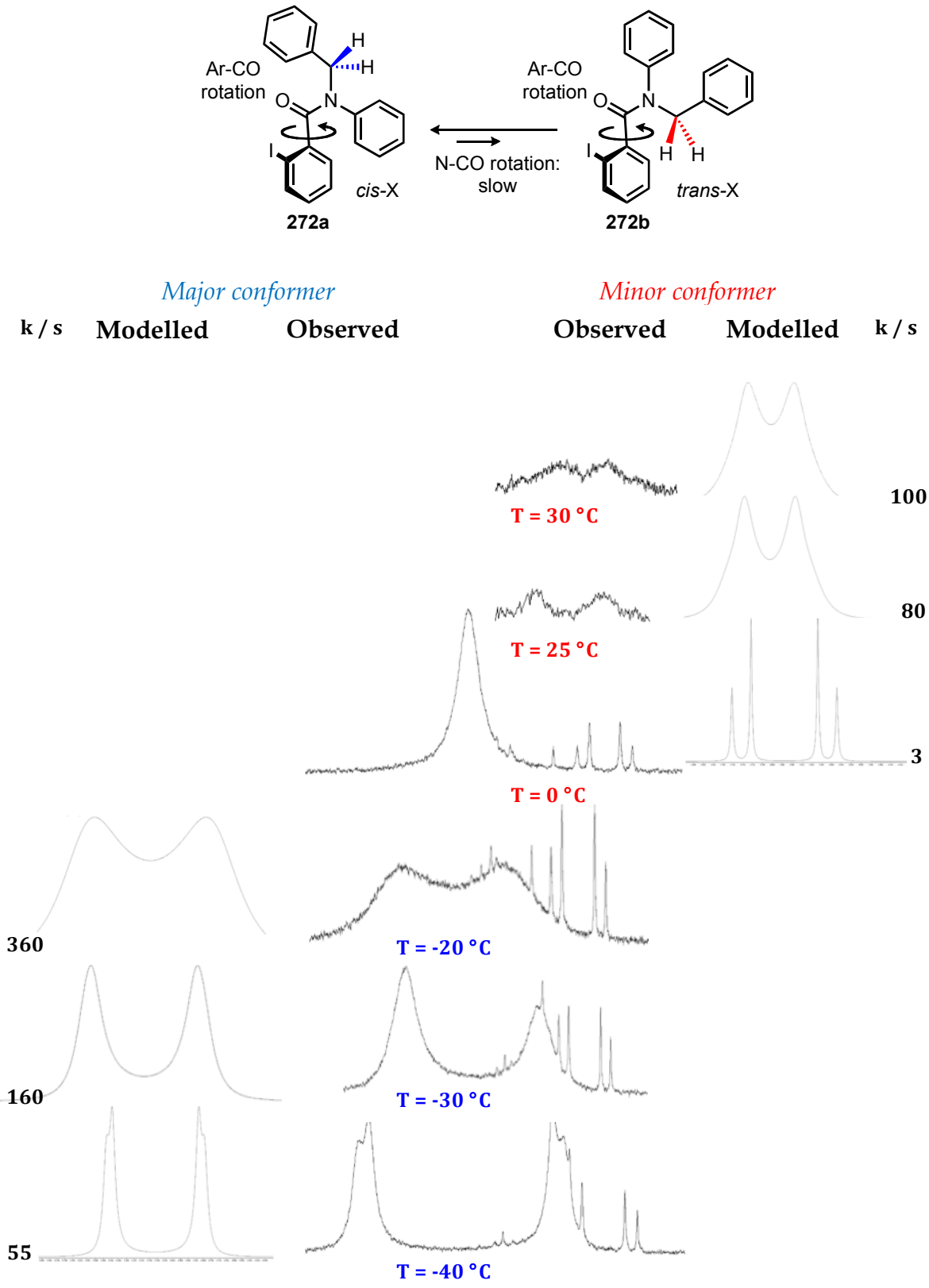


Figure 31: VT NMR and lineshape simulation using gNMR for **272**

By modeling the resultanting line-shapes, and fitting the rates obtained to the Eyring equation (see Appendix I), we obtained a barrier to rotation about the Ar-CO

bond in the major (ring-cis) conformer **272a** of 50.1 kJ mol^{-1} at 25 °C. The corresponding barrier to rotation in the minor (ring-trans) conformer **272b** was 62.6 kJ mol^{-1} at 25 °C. This higher barrier also shows that N-CO rotation must be slow, or otherwise a stepwise mechanism for Ar-CO bond rotation of the minor conformer would exist by interconversion with the major conformer.

The major conformer **272a**, which presumably has the two aryl rings *cis* about the N-CO bond as illustrated in Figure 31, has an Ar-CO barrier too low to exhibit rotamers (enantiomeric in this case) at rt, even with a large 2-iodo substituent. This presumably reflects the small size of the N-Ph group, an effect which Clayden decribed[110] during his studies of the barriers to rotation in the benzamides. Here he proposed two different transition states for the rotation about a benzamide axis, depending on the size of the substituents attached to nitrogen (Figure 32 and Figure 33).

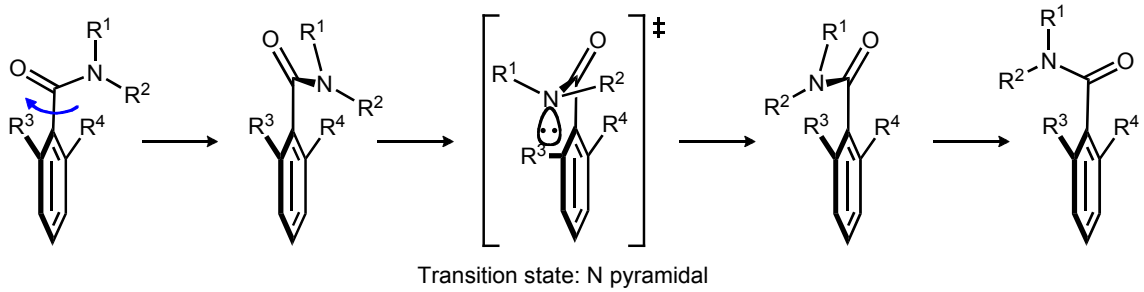


Figure 32: Transition states for rotation about a benzamide axis when R is small

Rotation about the Ar-CO bond involves the nitrogen and oxygen atoms passing through the plane of the ring. When R^1 and R^2 are small, the transition state outlined in Figure 32 is the preferred route to rotation: the lower energy pathway will be that in which NR^1R^2 passes the smaller of R^3 or R^4 thus the key interactions are between R^2 and R^3 and between the carbonyl oxygen and R^4.

When R^2 is especially large, however, and there is only one substituent at either R^3 or R^4, the group found that the sizes of R^1 and R^2 had little influence on the barrier to rotation. Thus they proposed an alternative mechanism outlined in Figure 33. R^3 is no longer small enough to allow R^2 to slip past, and instead the only way in which the NR^1R^2 group can pass R^3 is by rotating so it is no longer in the plane of the carbonyl group. The main interaction at the transition state is now between N and R^3, and they observed that changing R^2 affected the barrier to rotation less than when R^2 was small.

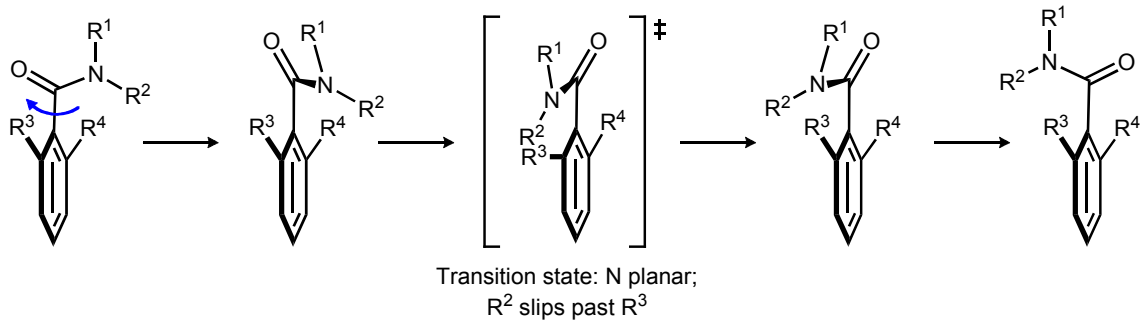
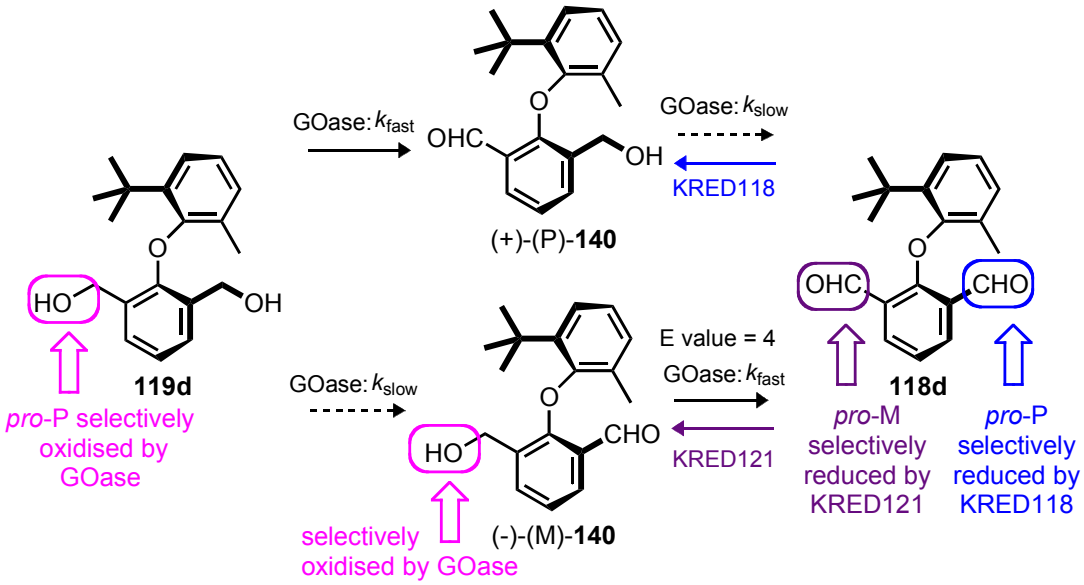


Figure 33: Transition states for rotation about a benzamide axis when R is large

It is therefore possible that the apparent conformational uniformity of dimeric **269b** could be due to a similarly fast Ar-CO bond rotation, with its Ar-CO rotomers becoming spectroscopicaly distinguishable only at low temperatures. However, the fact that little change in the ratio of conformers is seen on lowering the temperature to -60 °C suggests this is unlikely.

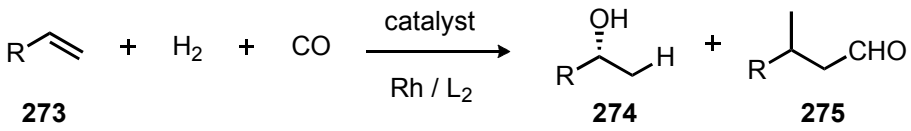
3. Conclusions and Future Work

We have established a synthesis to provide sterically encumbered atropisomeric diaryl ethers with four *ortho*-substituents. A route towards their asymmetric syntheis through desymmetrisation has also been successful. *P*-**140** was achieved through the desymmetrisation of **119d** and kinetic resolution of **140** with GAOase $M_{3\text{-}5}$ and with treatment of **118d** with KRED118 (Scheme 99). The barrier to enantiomerisation in the product is greater than 130 kJ mol^{-1} at 90 °C.



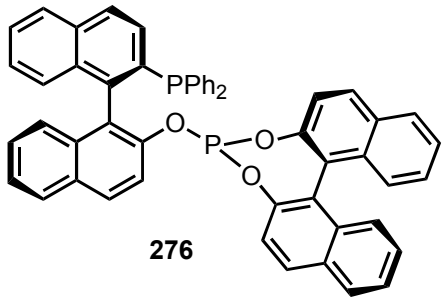
Scheme 99: Biocatalytic Desymmetrisation of an atropisomer by enantioselective oxidase and ketoreductases

A route towards synthesising a phophine containing ligand is underway, and future work will look into an applicable area of asymmetric catalysis in which to utilise it. Diaryl ether based ligands have seen success in the hydroformylation of alkenes, and an asymmetric version of this reaction would be a good starting point (Scheme 100): the asymmetric hydroformylation of olefins serves as a direct route to optically active aldehydes which are valuable precursors for various pharmaceuticals and agrochemicals.



Scheme 100: Hydroformylation of alkenes possible with bidentate ligand

The current world-record holder concerning ee for styrene is a hybrid phosphine-phosphoramidite ligand adapted from BINAPHOS **276** and was developed in 2006.[155] We could also apply our successful method of desymmetrisation to simple biaryls.

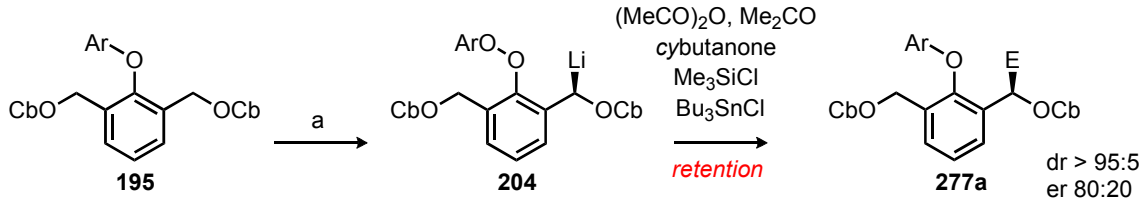


276

Figure 34: Takaya's (*R*,*S*)-BINAPHOS

Excellent d.r.'s and moderate e.r.'s are achieveable in the lateral litiation of diaryl ethers flanked by carbamate directing groups. However, our results from these investigations are limited due to the difficulties of the synthesis. We were largely unable to eliminate products of reprotonation, oxidation and other unknown side products from the reaction.

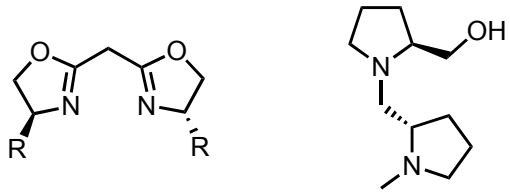
We were nevertheless able to determine that the intermediate organolithium has some degree of configurational stability and presumably that the lateral lithiation of **195** is stereoselective and yields a single diastereoisomeric atropisomer of organoithium **204.** This organolithium reacts with most electrophiles to give **277** with what we assume is retention of stereochemistry (Scheme 101).



Scheme 101: Assumed stereoselectivity in the lateral lithiation of **195**
(a): i. *sec*BuLi, (–)-sparteine; ii. Electrophile

We were also able to prove that an asymmetric deprotonation determines the overall enantioselectivity of the reaction to generate **277**. Consequently, as diethyl ether is a slightly coordinating solvent and may be competitively coordinating with the organolithium, (–)-sparteine might more strongly form a complex with lithium (and hence improve enantioselectivity) if a completely non-coordinating solvent such as

toluene is used. Other chiral bases such as the bisoxazoline ligands (BOX) **278** used by Hoppe and the β-amino-alcohol **279** reported by Coldham[156] might also establish higher enantioselectivities.



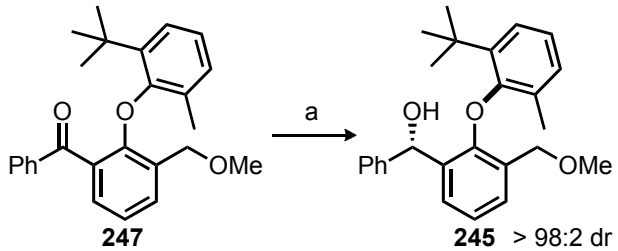
278 **279**

Figure 35: Other chiral bases for the asymmetric deprotonation of **195**

X-ray crystallographic studies of the products of lateral lithiation were not possible due to the products being oils and gums. High-level quantum chemical methods could therefore allow insight into the energetic situation of the intermediate lithiated complexes. Molecular modelling of the analogues of **277** as achieved in the assignment of configuration of **(*P*)-140** in section 2.2.2.3 could also provide useful information to help clarify the observed stereochemical results.

With regards to some of the problems experienced with the synthesis, lithiation α to the oxygen of carbamates are known in some cases to lead to products of rearrangement,[157] particularly 1,2 acyl transfer. It would be interesting to investigate the possibility of such a mechanism occurring in our own substrates. Although the isolation of side products from complicated reaction mixtures was largely unsuccesfull, conditions known to favour rearrangement (such as more concentrated reaction solutions) might force the formation of a potential rearrangement product and allow for its analysis.

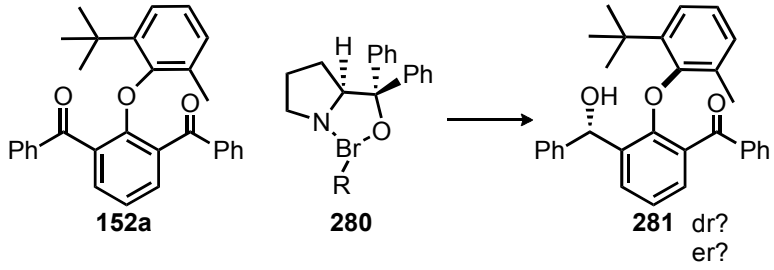
Diastereisomeric atropisomers of diaryl ethers were additionally synthesised through a stereoselective reduction to give predominantly the *anti* isomer (Scheme 102).



247 **245** > 98:2 dr

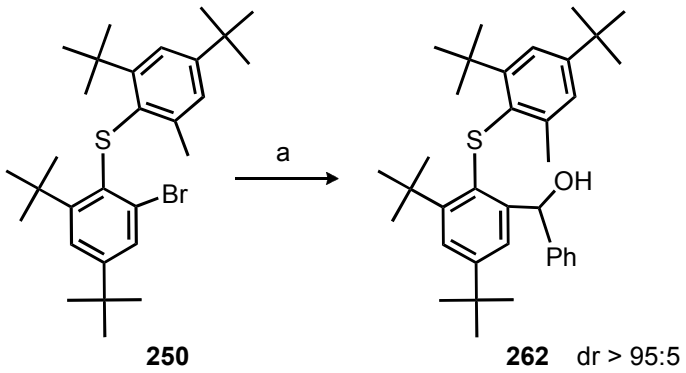
Scheme 102: Stereoselective synthesis of a diaryl ether
(a) Superhydride, THF 0 °C or L-Selectride THF 0 °C

By utilising a chiral reducing agent such as the proline derived Corey-Bakshi-Shibata catalyst[158] **280** a desymmetrising enantioselective reduction of prochiral **152a** might be possible (Scheme 103).



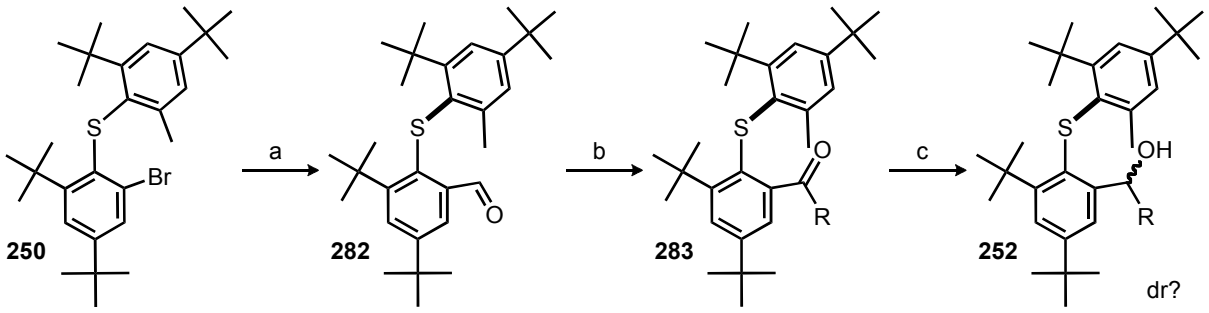
Scheme 103: Enantioselective synthesis of a diaryl ether

The diastereoselective synthesis of a diaryl sulfide was achieved by addition of benzaldehyde to the lithioderivative of **250** (Scheme 104). Smaller aldehydes led to the formation of a mixture of isomers.



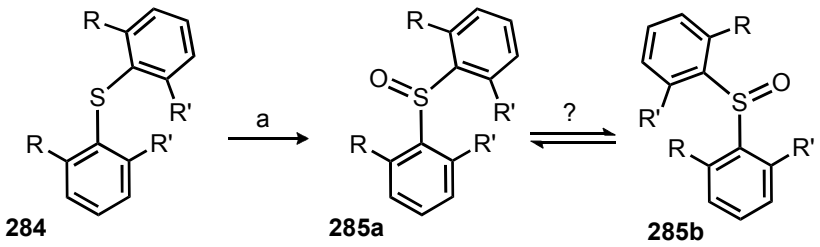
Scheme 104: Diastereoselective synthesis of a diaryl-sulfide by addition to an aldehyde
(a) i. *n*BuLi, 1 min, THF; ii. benzaldehyde

Future work in this series could look at the ability of the sulfide axis to undergo stereoselective reductions in an analogous way to that of the diaryl ethers. A precursor for the study might easily be accessible from a Br-Li exchange of **250** in the presence of DMF (Scheme 105).



Scheme 105: Stereoselective reductions of diaryl sulfides
(a) i. *n*BuLi, 1 min, THF -78 °C; ii. DMF
(b) i.RMgBr; ii dess-martin periodinane
(c) Superhydride, THF 0 °C; or L-Selectride THF 0 °C

A synthetic route towards substituted diaryl-sulfides was easily accessible through the coupling of aromatic iodides and thiophenols. Mono-oxidation will afford diaryl sulfoxides **285**, a structure also capable of displaying atropisomerism (see Appendix II). With conditions for axial chirality established for diaryl ethers, sulfides and sulfoxides, future work could establish a set of structural conditions required for **285** to display atropisomerism (Scheme 106).



Scheme 106: Atropisomerism in diaryl-sulfoxides

We studied the conformation adopted in solution of diaryl-amide **272** and found that *cis* or *trans* conformers about the N-CO bond were evident in a 90:10 ratio at room temperature (Figure 36).

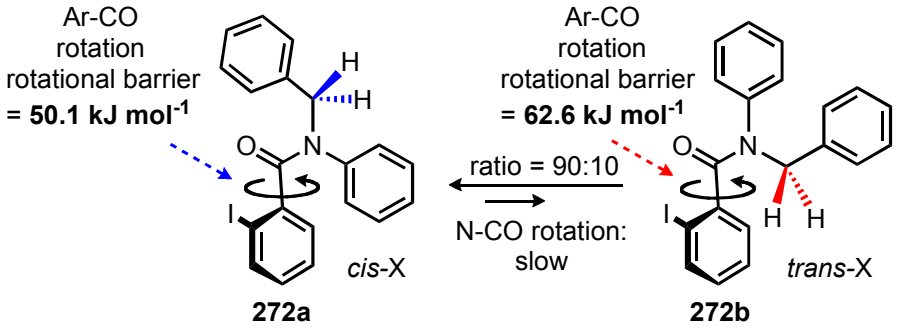


Figure 36: Conformation preferences in solution of diaryl amide **272**

The benzylic protons of the major conformer **272a** were not diastereotopic at room temperature because rotation about the Ar-N bond is fast on the NMR timescale, despite the presence of a bulky Ph. This was presumably thought to reflect the "small size" of the N-Ph group.

4. Appendices

I. Calculation of barriers to rotation using VT NMR

Variable temperature NMR studies were undertaken in order to calculate barriers, $\Delta G^{\ddagger}$, to rotation about the Ar–C(O) axis for each rotamer of benzanilide **272**. The general method for calculation of barriers to rotation in this way is described below.

As the temperature of the NMR sample increases or decreases there is an increase or decrease in the rate of interconversion; this is observed as a coalescence / decoalescence of the CH_2Ph AB system. It is possible to use the temperature of coalescence of these signals to measure the rate of, and barrier to, rotation about the axis.

The ^1H NMR spectrum is obtained at a temperature low enough for the interconverting groups to be at their slow-exchange limit. This is done to obtain the chemical shift difference $\Delta\nu$ between the interconverting signals or the coupling constant of the diastereotopic protons, J_{AB}.

The sample is gradually heated and spectra are recorded at regular temperature intervals to find the coalescence temperature T_c of the signals.

The rate of exchange, k, at the coalescence temperature T_c can be estimated using the Gutowski-Holm approximation: [159]

$k = \frac{\pi\Delta\nu}{\sqrt{2}}$ (for uncoupled signals), or

$k = \pi\sqrt{\frac{(\Delta\nu)^2 + 6(J_{AB})^2}{2}}$ (for coupled signals).

This calculation can be simplified by simulating the experimental lines shapes near the slow and fast exchange limits using commercially available gNMR software.

From the approximated value of k, $\Delta G^{\ddagger}$ can be found using the Eyring equation:

$$\Delta G^{\ddagger} = 4.575 \text{ x } 10^{-3} \times T_c \times \left[10.319 + \log_{10}\left(\frac{T_c}{k}\right)\right]$$

The VT spectra were run on a Varian 400 MHz spectrometer equipped with variable temperature probe, with a range of –90 to +120 °C.

Figure 31 (section 2 4.3.1) showed the modelled and observed line shapes at a series of temperatures and the rate constant, k, for the coalescence / decoalescence of an AB system for the CH_2Ph group for each of the major (**272a**) and minor (**272b**) conformers of benzanilide **272**. The broadening of the two benzylic AB systems were simulated and compared with the acquired spectra using difference spectra. From these simulations, the rate constant k for inversion could be determined as a function of temperature for each rotamer. The values produced for **272a** are shown in Table 38.

Temp / °C	***k* / s^{-1}**	**error**	**T / K**	**ln (*k* / T)**	**(1 / T) / K^{-1}**
–40	55	3	233.15	-1.44435	0.004289
–30	160	20	243.15	-0.41850	0.004113
–20	360	20	253.15	0.35212	0.00395

Table 38: Values produced from the Eyring equation for **272a**

Hence, from the Eyring equation, the activation parameters could be determined by plotting ln(*k* / T) versus (1 / T) (Figure 37) where:

$$\Delta H^{\ddagger} = -(\text{slope}) \times R$$

$$\Delta S^{\ddagger} = [\text{intercept} + \ln(h / K_b)] \times R$$

Where R = gas constant, h = Planck's constant and K_b = Boltzmann's constant.

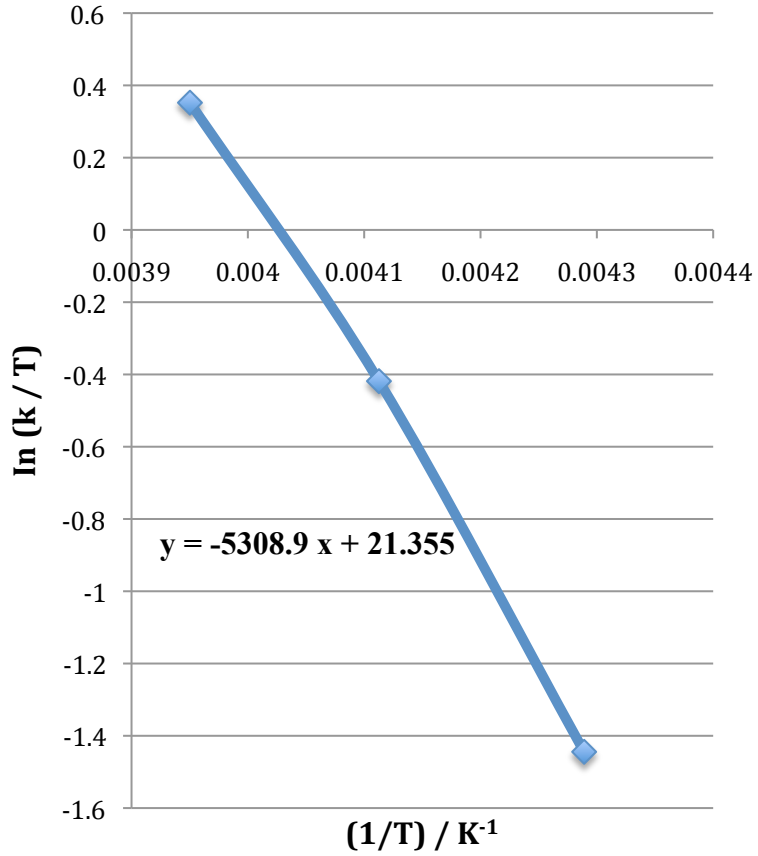


Figure 37: Plot of ln k_A vs 1/T to determine $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for rotation in **272a**

The Eyring plot of ln(k/T) vs 1/T (Figure 37) gives a straight line from which, using the equation $y = mx + c$, the gradient (m) gives the enthalpy of rotation ($\Delta H^{\ddagger}$) and the y intercept (c) gives the entropy of rotation ($\Delta S^{\ddagger}$) as described above. Inserting these values into Gibbs´ equation for free energy ($\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$) gives an estimation of the barrier to rotation ($\Delta G^{\ddagger}$) at room temperature (taken to be 25 ˚C).

Errors were calculated from the R^2 value of the line of best fit of the Eyring plot. For an analogous description of calculating activation parameters using variable temperature NMR see work by Shipman *et al.* on barriers to inversion in aziridines. [160]

m	$\Delta H^{\ddagger}$	c	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}_{298}$
–5308	+44.1 kJ mol^{-1}	21.35	–20.03 J mol^{-1}	50.1 kJ mol^{-1}

Table 39: $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ and $\Delta G^{\ddagger}$ for diaryl amide **272a**

Using this method of analysis the activation parameters for rotation about the axis for diaryl amide **272b** was also calculated (Table 40 and 41, Figure 38).

Temp / °C	k / s^{-1}	error	T / K	ln (k / T)	(1 / T) / K^{-1}
0	3	1	273.15	-4.51141	0.003661
25	80	10	298.15	-1.31557	0.003354
30	100	20	303.15	-1.10906	0.003299

Table 40: Values produced from the Eyring equation for **272b**

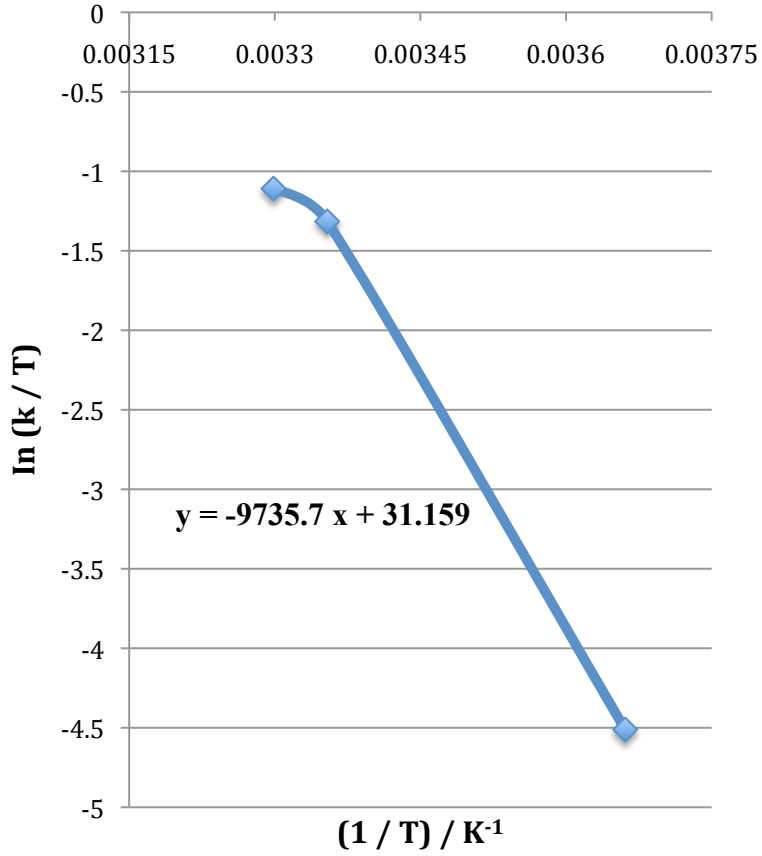


Figure 38: Plot of ln k_A vs 1/T to determine $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for rotation in **272b**

m	$\Delta H^{\ddagger}$	c	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}_{298}$
–9736	+80.9 kJ mol^{-1}	31.15	–61.44 J mol^{-1}	62.6 kJ mol^{-1}

Table 41: $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ and $\Delta G^{\ddagger}$ for diaryl amide **272b**

II. Synthesis of diaryl sulfoxides

Sulfoxides display a configurational stereogenic center (the sulfur atom) in addition to the conformational stereogenic axis. Consequently, when Ar-SO rotation is fast a pair of configurational enantiomers will be observed, whereas when this rotation is slowed a pair of atropisomers for each individual enantiomer should be detected (Figure 39).

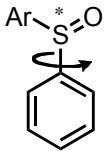
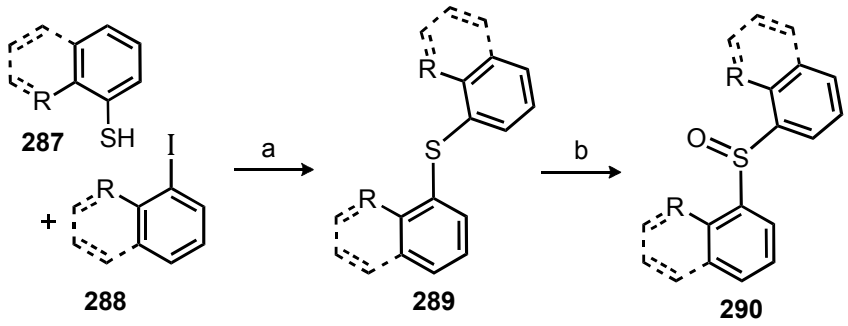


Figure 39: Atropisomerism in diaryl sulfoxides

With a direct route towards the diaryl sulfides easily accessible via the Buchwald coupling chemistry described in section 2.4.2, we synthesised diaryl sulfoxides **290a-c** via the route shown (Scheme 107, Table 42).



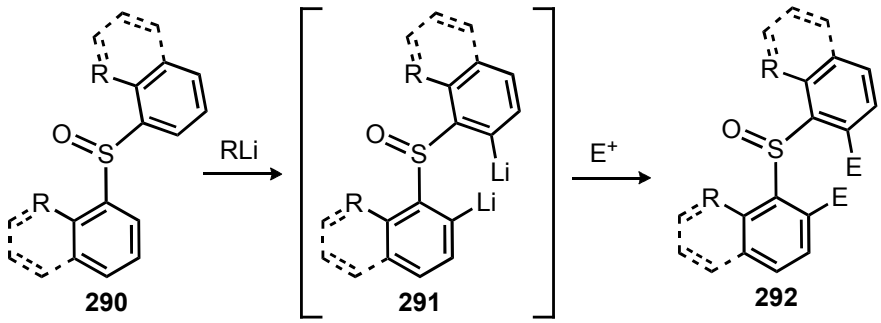
Scheme 107: Synthesis of diaryl sulfoxides **290a-c**
(a) CuI (1 eq.), K_2CO_3 (2 equiv), ethylene glycol (2 equiv), *tert*-amyl alcohol, 120 °C, 24 h
(b) *m*CPBA (1 eq), DCM, 2 h

	R	Coupling Yield 289 / %	Oxidation yield 290 / %
a	*iso*-Pr	85	95
b	*tert*-Bu	88	93
c	Naphthyl	90	90

Table 42: Yields for formation of diaryl sulfides **289a-c** and diaryl sulfoxides **290a-c**

Work undertaken in the Clayden group has already established the requirements for atropisomerism in the biaryl sulfides and sulfones and we aimed to determine a set of structural requirements to achieve atropisomerism in the diaryl sulfoxides.

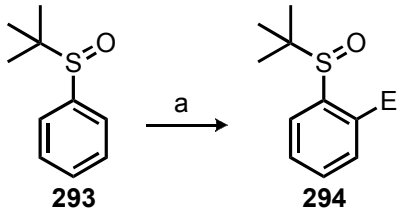
It was clear from results in previous studies that in order to observe atropisomerism, we would probably require a tetra *ortho*-substituted sulfoxide. We aimed to synthesise tetra-*ortho* substituted biaryl sulfoxides via a double *ortho*-lithiation strategy (Scheme 108) and hoped to detect line broadening or even the presence of 2 sets of NMR signals appropriate for a pair of atropisomers. VT NMR and computer line-shape simulations (as used in section 2.4.3.1) could then yield the rate constants (*k*, in s^{-1}) for the interconversion and hence corresponding free energy of activation (ΔG).



Scheme 108: Planned double *Ortho*-Ilithiation of diaryl sulfoxides

Unfortunately, initial attempts to *ortho*-lithiate with either LDA or LiTMP and TMSCl failed when R = *iso*-Propyl, and when R = Napthyl, and owing to time constraints the study was abandoned.

However, Snieckus has reported the sulfoxide functionality to direct *ortho*-lithiation in good yields.[161] When *t*-butyl aryl sulfone **293** is treated with *n*BuLi at –78 ºC in THF for one hour an *ortho* anion is generated, which can be quenched with a range of electrophiles (Scheme 109, Table 43).



293 294

Scheme 109: *Ortho*-lithiation of *tert*-butyl aryl sulfoxide **293**
(a) i. *n*BuLi, -78 °C, 30 min; ii. E^+

Entry	Electrophile (E^+)	E	Yield / %
1	MeOD	D	88
2	MeI	Me	96
3	PhCHO	Ph	82
4	$Br(CH_2)_2Br$	Br	85
5	DMF	CHO	0
6	Me_3SiCl	Me_3Si	89
7	$SnMe_3Cl$	$SnMe_3$	85

Table 43: *ortho*-lithiation of *tert*-butyl aryl sulfoxide **293**

It might therefore be possible, utilising or modifying the *ortho*-lithiation strategy above, to synthesise suitable precursors for a study into the structural requirements needed to achieve atropisomerism in diaryl sulfoxides.

III. Examples of HPLC traces used to calculate ee's in section 2.2

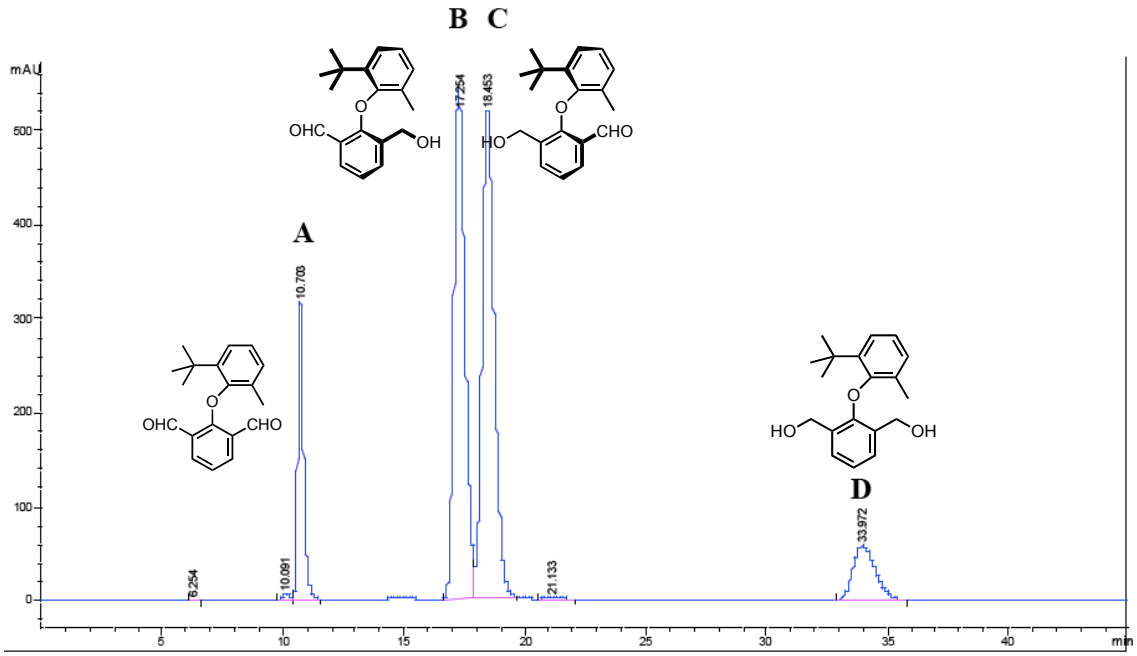


Figure 40: Normal phase HPLC for mixture of diol **119d**, monoaldehyde **140** and dialdehyde **118d**:
A = dialdehyde **118d**; **B** = monoaldehyde *M*-**140**; **C** = monoaldehyde *P*-**140**; **D** = diol **119d.**
Chiralcel® ASH, isohexane : IPA = 93:7, λ = 254 nm, flow rate = 0.5-1.0 ml/min

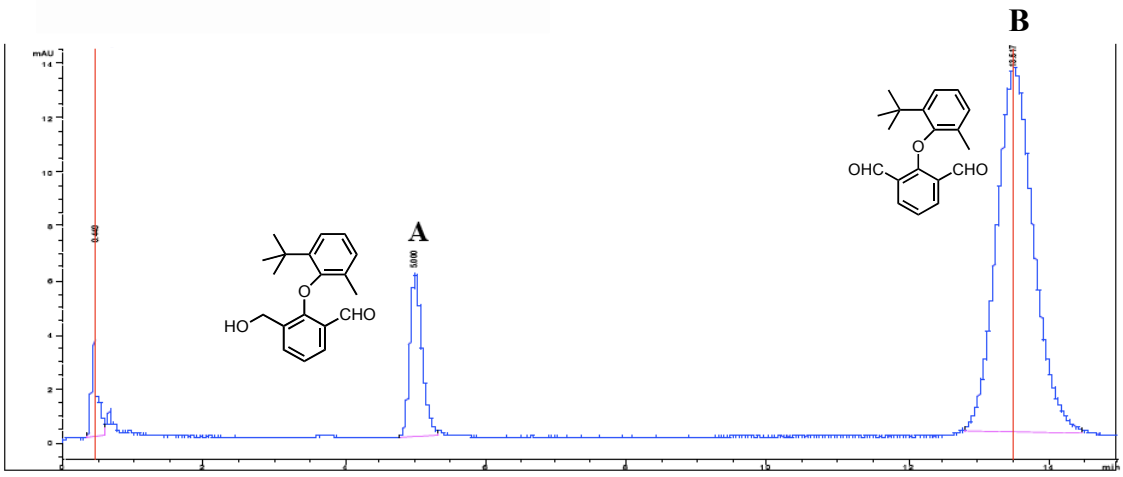


Figure 41: Reverse phase HPLC for mixture of monoaldehyde **140** and dialdehyde **118d**:
A = monoaldehyde **140**; **B** = dialdehyde **118d**
Eclipse XDB C18, acetonitrile : water = 50:50, λ = 254 nm, flow rate = 1.0 ml/min

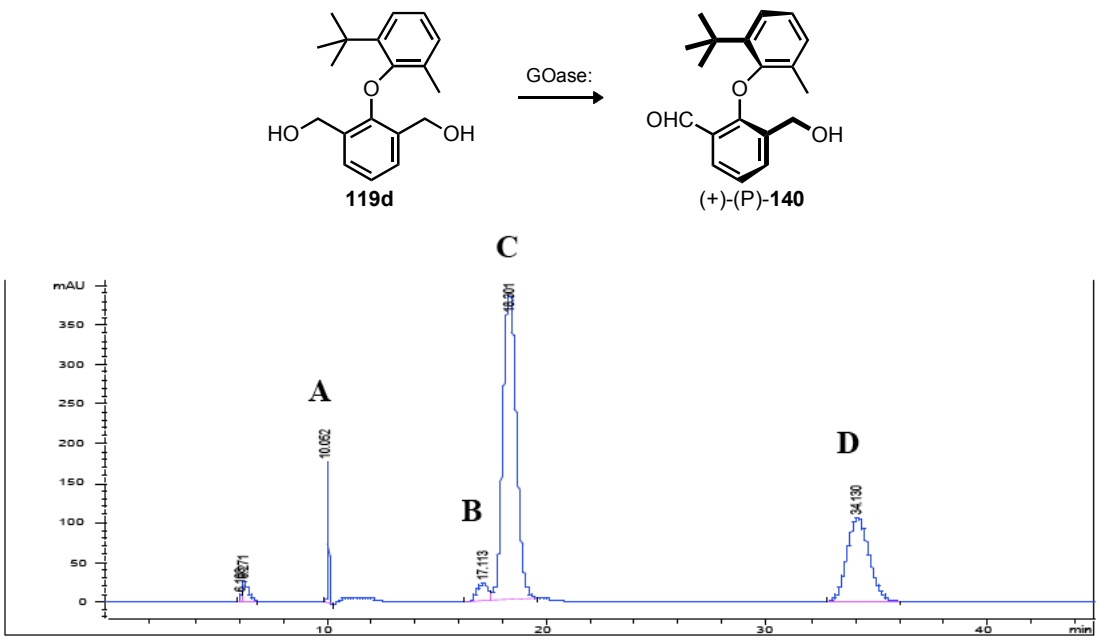


Figure 42: Desymmetrisation of **119d** using GOase (ee of **140** = 91%)
A = dialdehyde **118d**; **B** = monoaldehyde ***M*-140**; **C** = monoaldehyde ***P*-140**; **D** = diol **119d**
Chiralcel® ASH, isohexane : IPA = 93:7, λ = 254 nm, flow rate = 0.5-1.0 ml/min

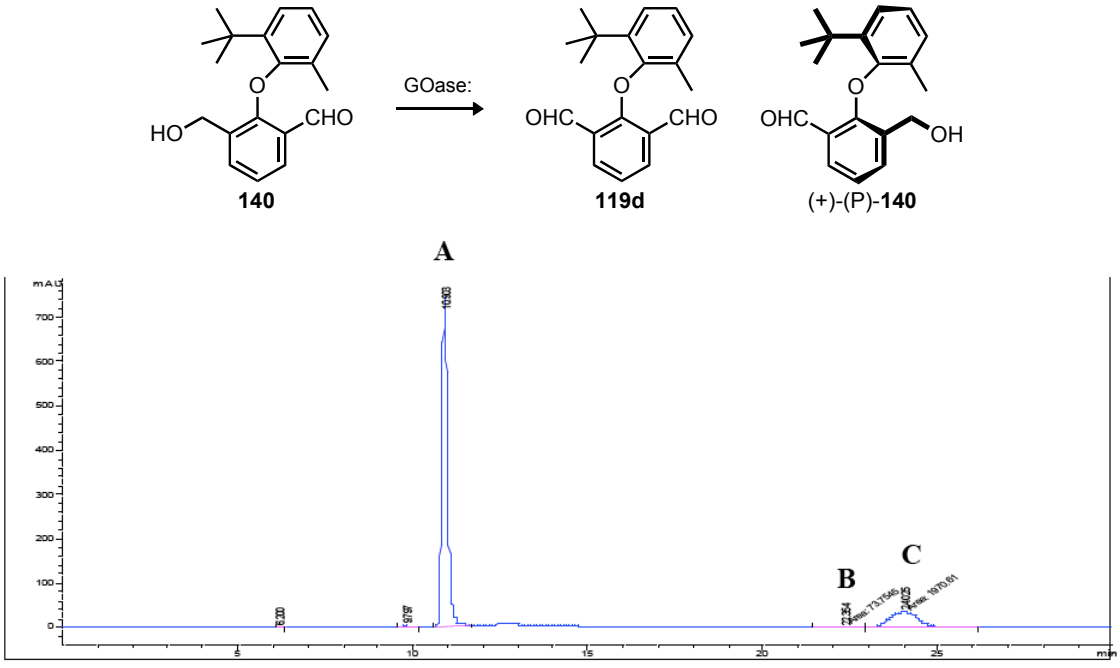


Figure 43: Kinetic Resolution of racemic **140** using GOase (ee of **140** = 94%)
A = dialdehyde **118d**; **B** = monoaldehyde ***M*-140**; **C** = monoaldehyde ***P*-140**
Chiralcel® ASH, isohexane : IPA = 93:7, λ = 254 nm, flow rate = 0.5-1.0 ml/min

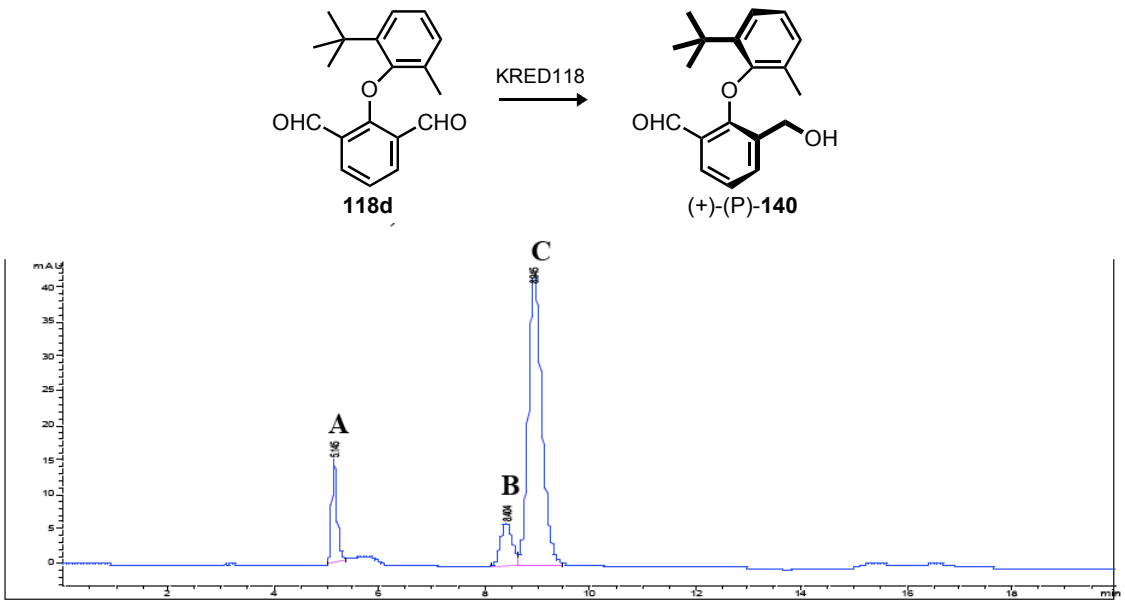


Figure 44: Reduction of dialdehyde **118d** using ketoreductase KRED 118 (P-**140**) (ee of **140** = 77%)
A = dialdehyde **118d**; **B** = monoaldehyde ***M*-140**; **C** = monoaldehyde ***P*-140**
Chiralcel® ASH, isohexane : IPA = 93:7, λ = 254 nm, flow rate = 0.5-1.0 ml/min

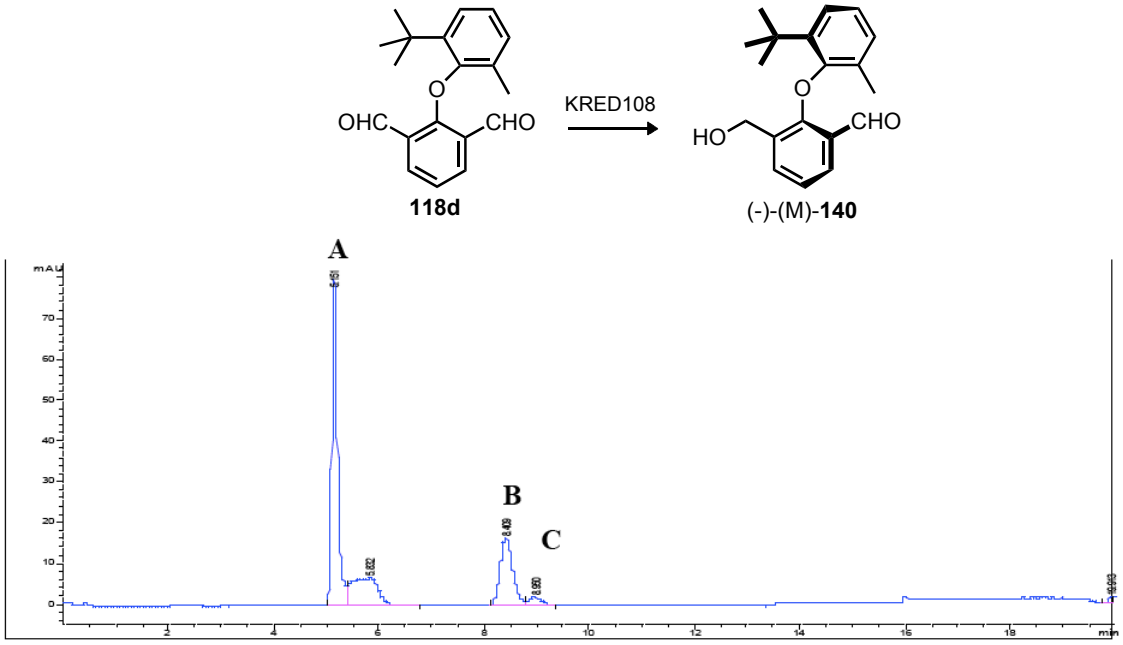
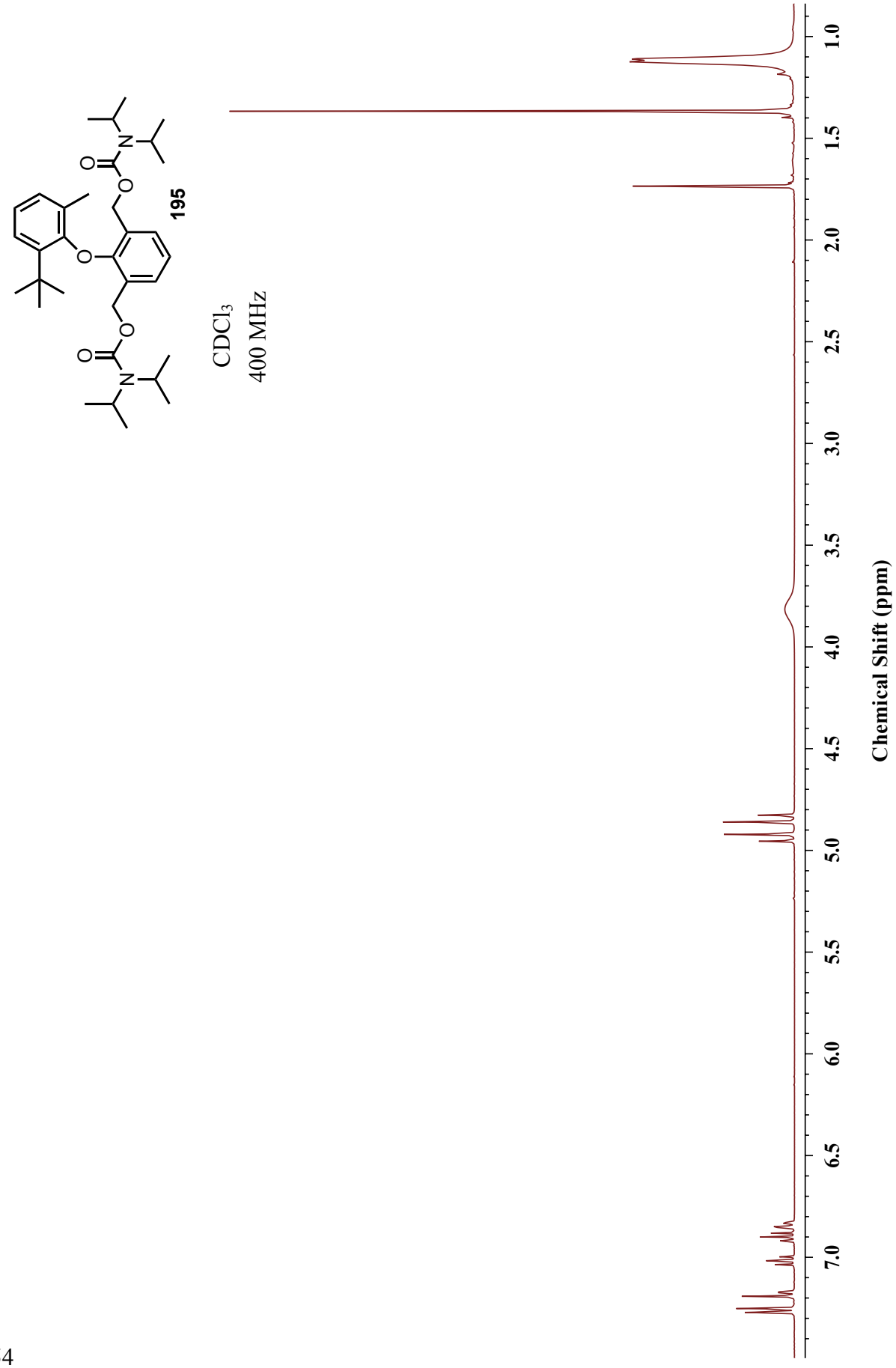
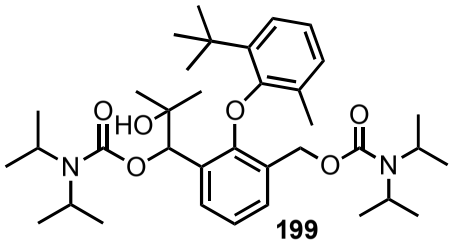


Figure 45: Reduction of dialdehyde **118d** using ketoreductase KRED108 (M-**140**) (ee of **2** = 78%)
A = dialdehyde **118d**; **B** = monoaldehyde ***M*-140**; **C** = monoaldehyde ***P*-140**
Chiralcel® ASH, isohexane : IPA = 93:7, λ = 254 nm, flow rate = 0.5-1.0 ml/min

IV. Selected NMR Spectra

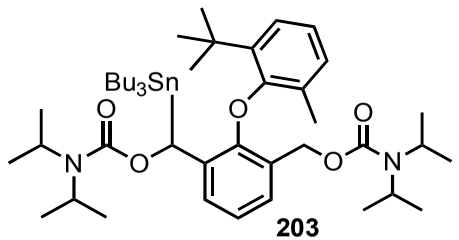




199

$CDCl_3$

400 MHz



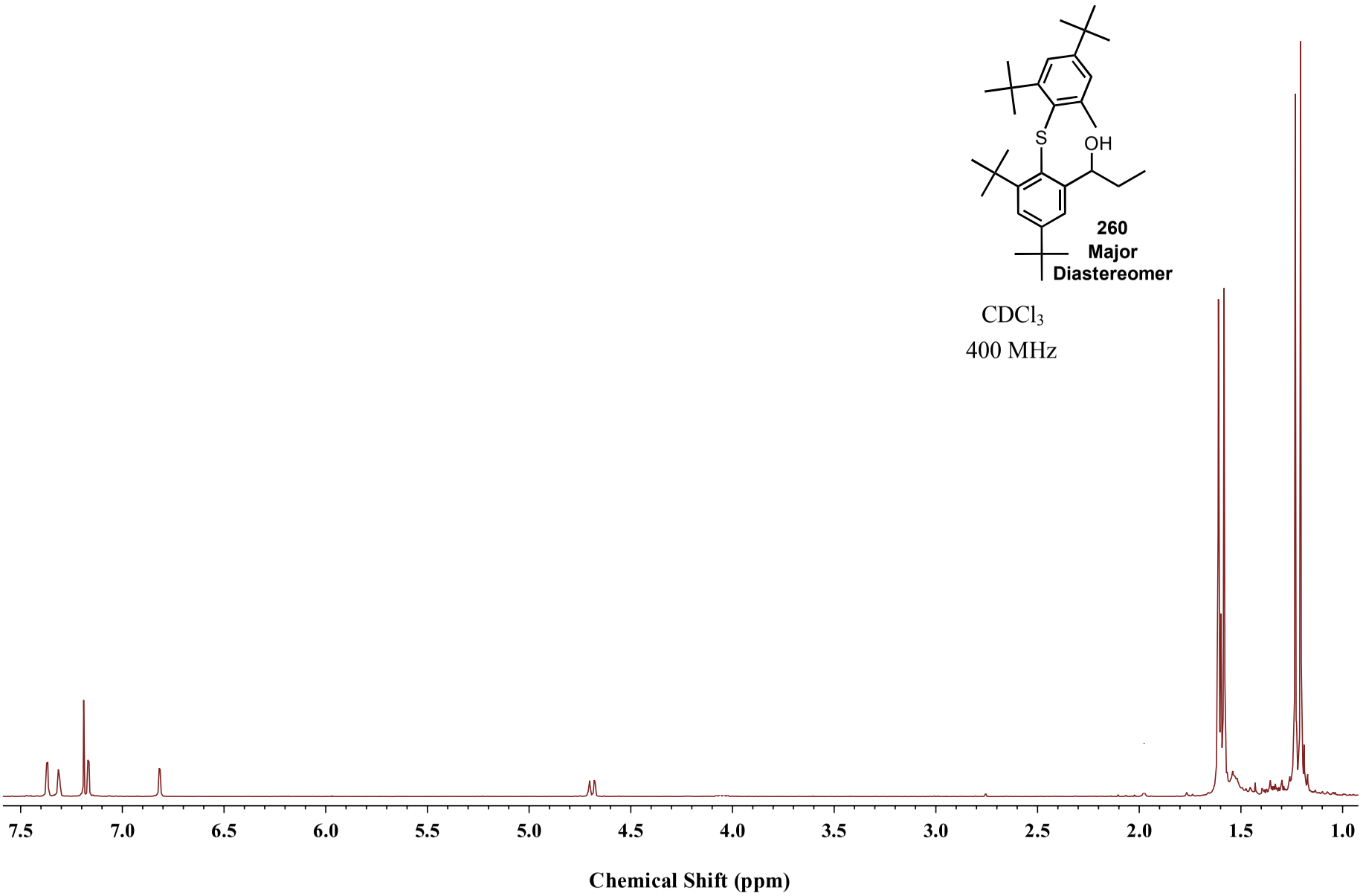
203
2:1 ratio of Diastereomers

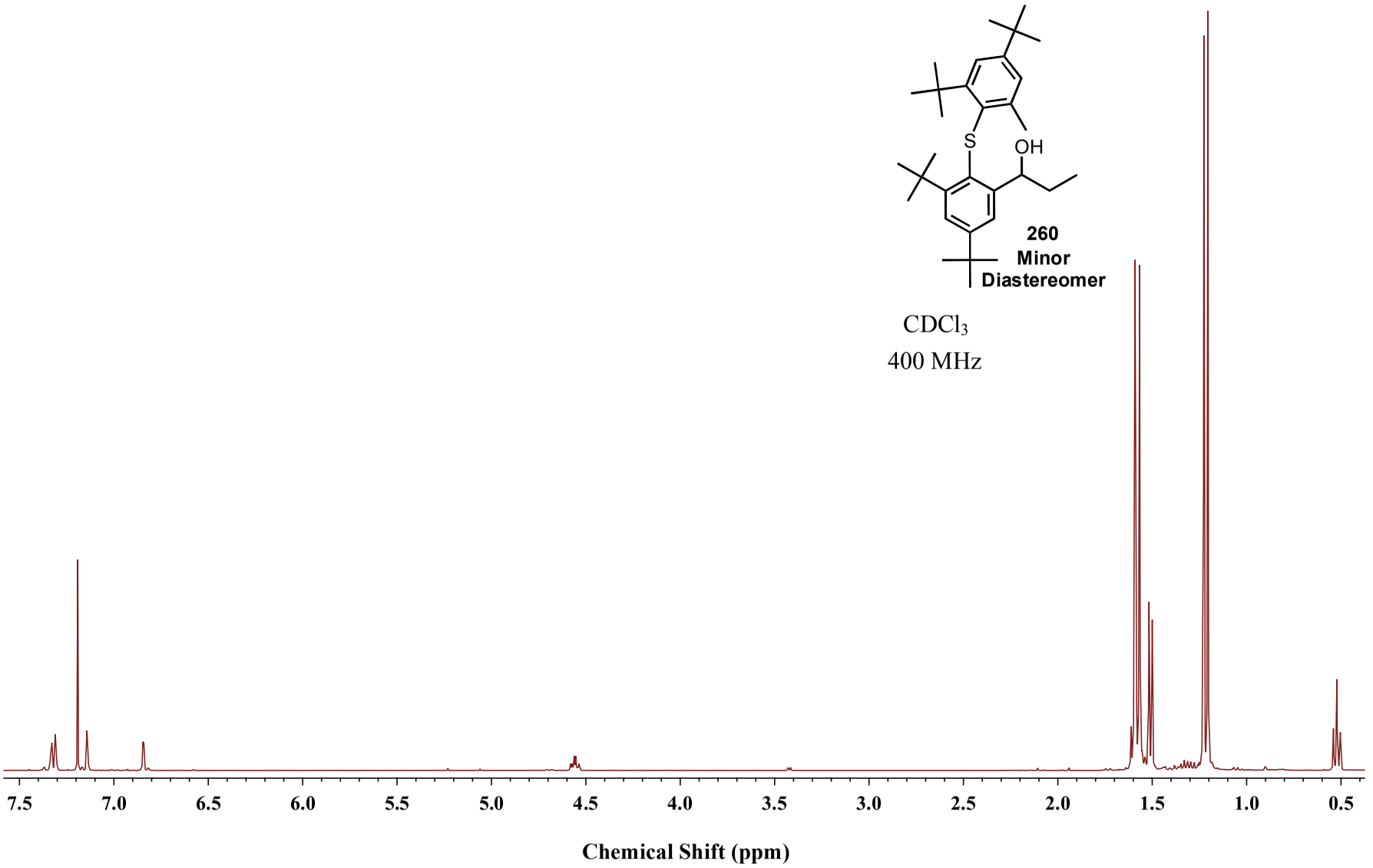
$CDCl_3$
400 MHz

2 : 1

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

Chemical Shift (ppm)


S
OH
260
Major
Diastereomer
CDCl3
400 MHz
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)


S
OH
260
Minor
Diastereomer
CDCl3
400 MHz
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

5. Experimental Section

5.1 General Procedures

All non-aqueous experiments were performed under an inert atmosphere of dry nitrogen or argon using oven dried apparatus, unless otherwise stated. The temperatures quoted are those of an external bath.

Reagents and solvents were used as received except where stated below, or in the experimental text. All solvents and reagents requiring purification were done so using standard laboratory techniques.[162] The solvents were either distilled or of Analar quality. Tetrahydrofuran and diethyl ether were freshly distilled over sodium under an atmosphere of nitrogen and using benzophenone as a radical indicator. Dichloromethane and toluene were distilled over calcium hydride under an atmosphere of nitrogen. Diisopropylamine was freshly distilled over potassium hydroxide under an atmosphere of nitrogen. Petrol refers to the fraction of light petroleum ether boiling between 40-60 °C. All other solvents and commercially obtained reagents were used as received or purified using standard procedures. *n*-Butyllithium was obtained as a solution (c. 2.5 M) in cyclohexane, *sec*- Butyllithium was obtained as a solution (c. 1.3 M) in cyclohexane and *tert*-Butyllithium was obtained as a solution (c. 1.5 M) in pentane. All organolithium solutions were titrated to use against a stirred solution of diphenylacetic acid in THF at -78 °C.

Analytical thin layer chromatography was carried out on Macher-Nagel pre-coated 0.2 mm silica plates, visualisation by UV light at 254 nm. Flash column chromatography was carried out on Fluorochem Davisil 40 – 63 μm 60 Å silica, under positive air pressure.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian XL 300 (300 MHz), Bruker Ultrashield 400 (400 MHz) or Bruker Ultrashield 500 (500 MHz) spectrometer with residual non-deuterated solvent as the internal standard (δ_H: $CDCl_3$ 7.27 ppm; δ_C: 77.0 ppm; δ_H: DMSO-d_6 2.50 ppm; δ_C: DMSO-d_6 39.4 ppm). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian XL 300 (75 MHz), Bruker Ultrashield 400 (100 MHz) or Bruker Ultrashield 500 (125 MHz)

spectrometer. Chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm), downfield of tetramethylsilane. Multiplicity is abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), septet (sept.), multiplet (m), broad (br.) or a combination of these. Coupling constants *J* are quoted in Hertz (Hz) and values rounded to nearest 0.5 Hz.

Low resolution mass spectra were recorded on Kratos MS25, Kratos Concept IS and Fisons VG Trio 2000 spectrometers using electron impact (EI), chemical ionisation (CI) and electrospray (ES). High resolution mass spectra were recorded on a Kratos Concept-IS mass spectrometer.

Infrared spectra were recorded on a Perkin-Elmer Spectrum RX I FT-IR or an ATI Matterson Genesis FT-IR spectrometer. All samples were run as an evaporated film on a sodium chloride plate. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

Melting points are uncorrected and were carried out on a 'GallenKamp Melting Point' apparatus or a Kofler microscope melting point machine.

Chiral HPLC measurements were carried out on a Hewlett Packard Series 1050 instrument with a Diode Array Detector, using Daicel Chiralcel OD-H, Daicel ChiralPak OT(+), Daicel Chiralcel AD-H, (*R,R*)-Whelk 01 or (*R,R*)-β-Gem 1 chiral stationary phases using a mixture of hexane and isopropanol (IPA) as eluent.
Chiral HPLC was also performed on an Agilent system equipped with a G1379A degasser, G1312A binary pump, a G1329A autosampler unit, a G1367A diode array detector and a G1316A temperature controlled column compartment; column Chiralcel® ASH, using a mixture of hexane and IPA as eluent, λ = 254 nm

Reverse phase chiral HPLC was performed on an Agilent system equipped with a G1379A degasser, G1312A binary pump, a G1329A autosampler unit, a G1367A diode array detector and a G1316A temperature controlled column compartment; column Eclipse XDB C18, using a mixture of acetonitrile and water as eluent, λ = 254 nm,

Optical rotations were measured on an Optical Activity AA-100 polarimeter with a 0.5 ml, 0.25 dm cell.

General Procedure A: ***Nucleophilic aromatic substitution – two step method***

Phenoxide

Phenol (1 equiv.), potassium hydroxide (1 equiv.), and toluene (100 cm^3) were charged to a flask and heated under reflux using Dean-Stark conditions for 2 hours, cooled to RT and solvent removed under reduced pressure, to yield the product that was used without further purification.

2-Phenoxy-isophthalonitrile

2-chloro-isophthalonitrile (1 equiv.), phenoxide (1 equiv.), and anhydrous DMF (100 cm^3) were charged to a flask and heated up to 156^oC under N_2. The reaction mixture was allowed to stir at this temperature for 16 hours, and the excess DMF removed by vacuum distillation. The resultant brown oil was dissolved in portions of EtOAc (x 3) and the combined organic phase washed with water (x 3), brine, dried (Na_2SO_4), and solvent removed under reduced pressure.

General Procedure B: ***Nucleophilic aromatic substitution – one step method***

Phenol (1 equiv.), base (1 equiv.), 3 Å molecular sieves (*ca.* 10 g) and anhydrous DMF (400 cm^3) were charged to a flask and stirred at RT for 30 minutes. 2-chloro-isophthalonitrile (1 equiv.) was added and the reaction mixture heated up to 156 °C under N_2. The reaction mixture was allowed to stir at this temperature for 16 hours, and the excess DMF removed by vacuum distillation. The resultant brown oil was dissolved in portions of EtOAc (x 3) and the combined organic phases washed with water (x 3), brine, dried (Na_2SO_4), and solvent removed under reduced pressure.

General Procedure C: ***DiBAl-H reduction of nitriles***

DiBAl-H (1M solution in DCM or Toluene) (2.5 equiv.) was added slowly to a stirring solution of nitrile (1 equiv.) in dry solvent (DCM or Toluene) under nitrogen at –78 °C, unless otherwise stated. The mixture was allowed warm to RT over a period of 16 hours, HCl (cooled to 5 °C) was added to the reaction mixture and allowed to stir for a further hour. A saturated solution of potassium sodium tartrate ("Rochelles salt") was added and the reaction micture stirred at rt for a minimum of 2 h. The solution was dilute diluted using EtOAc or DCM and the organic phase washed with water (x 3), brine, dried (Na_2SO_4), and the solvent removed under reduced pressure. If an insoluble precipitate remained after dilution with EtOAc or DCM, *conc.* HCl was added dropwise

to the insoluble precipitate only, until the precipitate dissolved. This was then diluted in DCM and the organic phase washed with water (x 3), brine, dried (Na_2SO_4), and the solvent removed under reduced pressure.

General Procedure D: ***Reduction of aldehydes***

The aldehyde dissolved in THF (50 cm^3) was added to a stirring suspension of sodium borohydride in THF (100 cm^3) under N_2 and stirred for 16 hours. NaOH solution (1.0 M) was added and the mixture stirred for 1 min, diluted using EtOAc and layers separated, the organic fraction was washed with water, brine, dried (Na_2SO_4), and solvent removed under reduced pressure.

General Procedure E: ***Mono-reduction of di-aldehydes***

$NaBH_4$/$LiBH_4$ (0.25 equiv.) was added to a stirring solution of dialdehyde (1 equiv.) in ethanol (50 cm^3) at 0 °C. The mixture was stirred for 1 hour at RT and quenched by addition of water. The solution was diluted using EtOAc, the organic phase washed with water, brine, dried (Na_2SO_4), and solvent removed under reduced pressure.

General Procedure F: ***Methyl protection of alcohols***

Alcohol (1 equiv.), dissolved in anhydrous THF (50 cm^3), was added to a stirring suspension of NaH (6 equiv.) in THF (50 cm^3) under N_2 and stirred for 30 mins at rt. MeI was added and the mixture stirred for 16 hours, and quenched by addition of water. The solution was diluted using EtOAc, the organic phase washed with water, brine, dried (Na_2SO_4), and solvent removed under reduced pressure.

General Procedure G: ***Lateral lithiation of diaryl ethers***

Desired ether (1 equiv.) dissolved in ether (10 cm^3) was freeze-thaw degassed under an atmosphere of argon. *sec*BuLi solution (1.6 equiv.) was added dropwise at -78 °C and the reaction mixture was stirred for 30 minutes (or the specified time if stated). The reaction was quenched with the desired electrophile and stirred at –78 °C with warming to rt over 16 h (or another specified time if stated). The reaction was quenched by addition of saturated NH_4Cl solution and diluted using EtOAc. The layers were separated and the organic phase was washed with water, brine, dried (Na_2SO_4), and solvent removed under reduced pressure.

General Procedure H: ***Lateral lithiation of diaryl ethers in the presence of (–)-sparteine***

Desired ether (1 equiv.) and freshly distilled (–)-sparteine (1.6 equiv) were dissolved in ether and freeze-thaw degassed under an atmosphere of argon. *sec*BuLi solution (1.6 equiv.) was added dropwise at -78 °C and the reaction mixture was stirred for 30 minutes (or the specified time if stated). The reaction was quenched with the desired electrophile and stirred at –78 °C with warming to rt over 16 h (or another specified time if stated). The reaction was quenched by addition of saturated NH_4Cl solution and diluted using EtOAc. The layers were separated and the organic phase was washed with water, brine, dried (Na_2SO_4), and solvent removed under reduced pressure.

General Procedure I: ***Sn → Li exchange***

A solution of stannane (1 equiv.) in ether (10 cm^3) was freeze-thaw degassed under an atmosphere of Argon. *n*BuLi solution (1.5 equiv.) was added dropwise to the solution at -78 °C and the reaction mixture was stirred for 2 hours (or the specified time if stated). The reaction was quenched with the desired electrophile and stirred at –78 °C with warming to rt over 16 h. The reaction was quenched by addition of saturated NH_4Cl solution and diluted using EtOAc. The layers were separated and the organic phase was washed with water, brine, dried (Na_2SO_4), and solvent removed under reduced pressure.

General Procedure J: ***Alkylation of mono-aldehydes***

MeMgBr (1.0 M in ether) / PhMgBr (1.0 M in THF) (1.2 equiv) was added dropwise to a stirring solution of aldehyde (1 equiv.) in THF (10 cm^3) at 0 °C under N_2, srirred for 2 hours, warmed to rt and stirred for a further 16 hours. HCl (1.0 M) was added and the mixture was stirred for 1 min. The solution was diluted using EtOAc, the organic phase was washed with water, brine, dried (Na_2SO_4), and solvent removed under reduced pressure.

General Procedure K: ***Stereoselective reduction of ketones***

L-Selectride (LS) / SuperHydride (SH) (1.0 M in THF) (1 equiv.) was added dropwise to a stirring solution of ketone (1 equiv) in THF (10 cm^3) at 0 °C under N_2 and stirred for 1 h. The mixture was quenched by addition of 2M NaOH solution in H_2O_2 60 % solution in H_2O, and then diluted using EtOAc. The organic phase was washed with water, brine, dried (Na_2SO_4), and solvent removed under reduced pressure.

General Procedure L: ***Dess-Martin oxidation***

Alcohol (1 equiv) was added to a stirring suspension of Dess-Martin periodinane in anhydrous DCM (20 cm^3) at rt under N_2, for 1 hour. 2M NaOH was added and the mixture was stirred for 0.5 h. The solution was diluted using DCM, the organic phase was washed with water, brine, dried (Na_2SO_4), and solvent removed under reduced pressure.

General procedure M: ***Br → Li exchange***

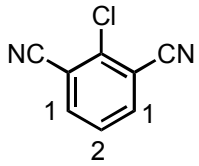
*n*BuLi solution (1 equiv.) was added dropwise to a solution of bromide (1 equiv.) in anhydrous THF (5 cm^3) at –78 °C under an atmosphere of nitrogen and stirred for 1 minute. The reaction was quenched with the desired electrophile and stirred at –78 °C with warming to rt over 16 h. The reaction was quenched by addition of saturated NH_4Cl solution and diluted using EtOAc. The layers were separated and the organics were washed with water, brine, dried (Na_2SO_4), and solvent removed under reduced pressure.

General procedure N: ***Oxidation of sulfide to sulfone***

Solid *m*CPBA (1 equiv.) was added in one portion to a solution of sulfide (1 equiv.) in DCM (0.1 M solution) at rt. The reaction was stirred at rt for a specified time and quenched by dropwise addition of saturated $Na_2S_2O_3$ solution. Organics were washed with water, NaOH solution (3.0 M) and brine, dried over $MgSO_4$ and solvent removed under reduced pressure.

5.2 Experimental Data

2-Chloro-isophthalonitrile (116)

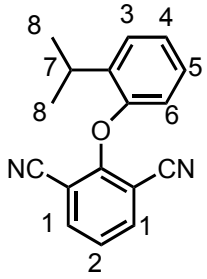


Using a modification of the method described by Krizan[87] a solution of isophthalonitrile (5 g, 39.02 mmol, 1 equiv.) in anhydrous THF (100 cm^3) was added dropwise to a stirring solution of LDA (46.82 mmol, 1.2 equiv.) in anhydrous THF (150 cm^3) at –95°C and allowed to stir for approximately 1 hr. Hexachloroethane (14.8 g, 62.44 mmol, 1.6 equiv.) dissolved in anhydrous THF (150 cm^3) was added to the reaction mixture at this temperature and the mixture allowed to stir for 1 hr and warmed to RT over a period of 16 hrs. The mixture was quenched by addition of saturated ammonium chloride solution and organics diluted using EtOAc. The organic phase was washed with water, brine, dried (Na_2SO_4) and solvent removed under reduced pressure. The product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a light yellow solid (5.69 g, 89 %).

δ_H (300 MHz, $CDCl_3$) 7.94 (2H, d, *J* 8, H-1), and 7.57 (1H, t, *J* 8, H-2).; δ_C (100 MHz; $CDCl_3$) 139.8, 137.6, 127.9, 115.5, and 114.3, Analyses matched the reported data.[87]

LDA: *n*BuLi (2.5M in Hexanes) (23 cm^3, 28.09 mmol, 1 equiv.) was added dropwise to a stirred solution of anhydrous diisopropylamine (6.6 cm^3, 28.09 mmol, 1 equiv.) dissolved in anhydrous THF (100 cm^3) at 0°C under N_2 and allowed to stir for 30 mins at this temperature.

2-(2-Isopropylphenoxy)isophthalonitrile (117a)



2-Isopropylphenoxide

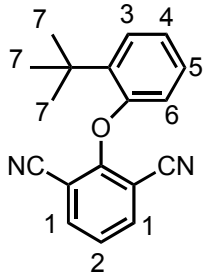
2-*Iso*propylphenol (3.31 cm^3, 24.6 mmol, 1 equiv.), potassium hydroxide (1.38 g, 24.6 mmol, 1 equiv.), and toluene (100 cm^3) were treated as described in general procedure A.

2-(2-Isopropylphenoxy)isophthalonitrile

2-Chloro-isophthalonitrile (4 g, 24.6 mmol, 1 equiv.), 2-isopropyl-phenoxide (4.31 g, 24.6 mmol, 1 equiv.), and anhydrous DMF (100 cm^3) were treated as described in General Procedure A. The crude product was purified by flash column chromatography (4:1 petrol : EtOAc) to yield the desired product as a light yellow powder (5.55 g, 86 %).

m.p. 92 – 94 °C; R_f = 0.35 (5:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 2238 (CN); δ_H (300 MHz; $CDCl_3$) 7.93 (2H, d, *J* 8, H-1), 7.44 (1H, dd, *J* 8 and 2, H-3), 7.40 (1H, t, *J* 8, H-2), 7.24 (1H, td, *J* 8 and 2, H-4), 7.17 (1H, td, *J* 8 and 2, H-5), 6.60 (1H, dd, *J* 8 and 1.5, H-6), 3.48 (1H, sept, *J* 7, H-7) and 1.39 (6H, d, *J* 7, H-8).; δ_C (75 MHz; $CDCl_3$) 160.0, 154.3, 139.1, 138.9, 127.9, 127.2, 125.7, 124.9, 115.9, 113.9, 108.0, 27.7 and 22.9.; EI *m/z* 262 (M); CI *m/z* 280 (M + NH_4^+); HRMS found M 262.1100, $C_{17}H_{14}N_2O$ requires 262.1101.

2-(2-tert-Butyl-phenoxy)-isophthalonitrile (117b)



2-t-Butylphenoxide

2-*t*-Butylphenol (3.76 cm^3, 24.6 mmol, 1 equiv.), potassium hydroxide (1.38 g, 24.6 mmol, 1 equiv.) and toluene (100 cm^3) were treated as described in general procedure A.

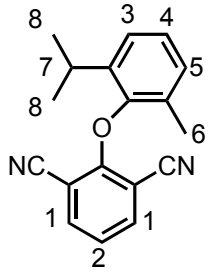
2-(2-tert-Butyl-phenoxy)-isophthalonitrile

2-Chloro-isophthalonitrile (4.0 g, 24.6 mmol, 1 equiv.), 2-*t*-butyl-phenoxide (4.64 g, 24.6 mmol, 1 equiv.), and anhydrous DMF (150 cm^3) were treated as described in general procedure A. The crude product was purified by flash column chromatography (4:1 petrol : EtOAc) to yield the desired product as a light brown powder (5.69 g, 83 %).

Also synthesised by treatment of 2-*t*-Butylphenol (15 cm^3, 98.4 mmol, 1.0 equiv.), NaH (60% dispersion in mineral oil) (1.97 g, 98.4 mmol, 1 equiv.), 2-Chloro-isophthalonitrile (16.0 g, 98.4 mmol, 1 equiv.), 3 Å molecular sieves (*ca*. 10 g) and anhydrous DMF (400 cm^3) as described in general procedure B. The crude product was purified by flash column chromatography (4:1 petrol : EtOAc) to yield the desired product as a light brown powder (22.27 g, 82 %).

m.p. 117 – 119 °C; R_f = 0.31 (5:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 2238 (CN); δ_H (300 MHz; $CDCl_3$) 7.94 (2H, d, *J* 8, H-1), 7.52-7.50 (1H, m, H-3), 7.40 (1H, t, *J* 8, H-2), 7.21-7.18 (2H, CH m, H-4 and H-5), 6.60-6.58 (1H, m, H-6) and 1.54 (9H, s, H-7).; δ_C (75 MHz; $CDCl_3$) 159.6, 155.7, 140.1, 139.0, 128.3, 127.6, 125.3, 124.8, 116.7, 114.1, 107.8, 35.2 and 30.4.; EI *m/z* 276 (M); CI *m/z* 294 (M + NH_4^+); HRMS found M 276.1247, $C_{18}H_{16}N_2O$ requires 276.1257.

2-(2-isopropyl-6-methylphenoxy)benzene-1,3-dicarbonitrile (117c)



2-Isopropyl-6-methylphenoxide

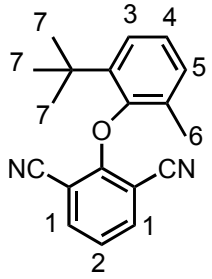
2-*Iso*propyl-6-methylphenol **123** (0.88 g, 5.83 mmol, 1 equiv.), potassium hydroxide (0.33 g, 5.83 mmol, 1 equiv.) and toluene (50 cm^3) were treated as described in general procedure A.

2-(2-Isopropyl-6-methylphenoxy)benzene-1,3-dinitrile

2-Chloro-isophthalonitrile (0.95 g, 5.83 mmol, 1 equiv.), 2-isopropyl-6-methylphenoxide (1.1 g, 5.83 mmol, 1 equiv.), and anhydrous DMF (100 cm^3) were treated as described in general procedure A. The crude product was purified by flash column chromatography (10:1 petrol : EtOAc) to yield the product as a light yellow solid (0.81 g, 50 %).

m.p. 79 – 81 °C; R_f = 0.44 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 2236 (CN); δ_H (300 MHz; $CDCl_3$) 7.84 (2H, d, *J* 8, H-1), 7.30-7.28 (2H, m, H-3 and H-4), 7.22 (1H, t, J 8, H-2), 7.15 (1H, ddd, *J* 7.5, 2 and 0.5 H-5), 3.06 (1H, sept, *J* 7, H-7), 2.18 (3H, s, H-6) and 1.28 (6H, d, *J* 7, H-8).; δ_C (75 MHz; $CDCl_3$) 160.6, 149.6, 141.8, 139.7, 130.9, 129.1, 128.1, 125.0, 122.5, 113.9, 102.9, 28.0, 23.2 and 16.8.; EI *m/z* 276 (M); CI *m/z* 294 (M + NH_4^+); HRMS found M + NH_4^+ 294.1599, $C_{18}H_{20}N_3O$ requires 294.1601.

2-(2-tert-Butyl-6-methylphenoxy)benzene-1,3-dinitrile (117d)



2-tert-Butyl-6-methylphenoxide

2-*tert*-Butyl-6-methylphenol (5.25 g, 32.03 mmol, 1 equiv.), potassium hydroxide (1.79 g, 32.03 mmol, 1 equiv.) and toluene (50 cm^3) were treated as described in general procedure A.

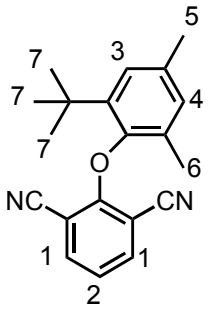
2-(2-tert-Butyl-6-methylphenoxy)benzene-1,3-dinitrile

2-Chloro-isophthalonitrile (5.2 g, 32.03 mmol, 1 equiv.), 2-*tert*-butyl-6-methylphenoxide (6.48 g, 32.03 mmol, 1.1 equiv.), and anhydrous DMF (150 cm^3) were treated as described in general procedure A. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a yellow solid (4.58 g, 49 %).

Also synthesised by treatment of 2-*tert*-Butyl-6-methylphenol (10.5 cm^3, 64.06 mmol, 1.0 equiv.), K_2CO_3 (8.86 g, 64.06 mmol, 1 equiv.), 2-Chloro-isophthalonitrile (10.4 g, 64.06 mmol, 1 equiv.), 3 Å molecular sieves (*ca*. 10 g) and anhydrous DMF (300 cm^3) as described in general procedure B. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the desired product as a yellow solid (10.03 g, 54 %).

m.p. 65 – 68 °C; R_f = 0.36 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 2253 (CN); δ_H (300 MHz; $CDCl_3$) 7.85 (2H, d, *J* 8, H-1), 7.38 (1H, dd, *J* 8 and 1.5, H-3), 7.30 (1H, t, *J* 8, H-4), 7.22 (1H, t, *J* 8, H-2), 7.15 (1H, ddd, *J* 8, 2 and 1, H-5), 2.05 (3H, s, H-6) and 1.44 (9H, s, H-7).; δ_C (75 MHz; $CDCl_3$) 160.7, 151.1, 143.3, 139.6, 130.8, 129.8, 127.6, 126.0, 122.4, 114.0, 103.2, 35.3, 30.8 and 17.2.; EI *m/z* 290 (M); CI *m/z* 308 (M + NH_4^+); HRMS found M + NH_4^+ 308.1765, $C_{19}H_{22}N_3O$ requires 308.1757.; EA found C, 77.71; H, 6.09; N; 10.15, $C_{19}H_{18}N_2O$ requires C 78.59; H, 6.25; N, 9.65%.

2-(2-tert-Butyl-4,6-dimethylphenoxy)benzene-1,3-dinitrile (117e)



2-tert-Butyl-4,6--dimethylphenoxide

2-*tert*-Butyl-4,6-xylenol (4.28 cm^3, 23.07 mmol, 1 equiv.), potassium hydroxide (1.29 g, 23.07 mmol, 1 equiv.) and toluene (100 cm^3) were treated as described in general procedure A.

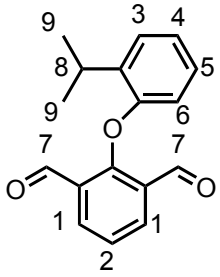
2-(2-tert-Butyl-4,6-dimethylphenoxy)benzene-1,3-dinitrile

2-Chloro-isophthalonitrile (3.75 g, 23.07 mmol, 1 equiv.), 2-*tert*-butyl-4,6-xylenoxide (4.99 g, 23.07 mmol, 1 equiv.) and anhydrous DMF (150 cm^3) were treated as described in general procedure A. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a yellow solid (4.35 g, 62 %).

Also synthesised by treatment of 2-*tert*-Butyl-4,6-xylenol (2.85 cm^3, 15.38 mmol, 1.0 equiv.), K_2CO_3 (0.86 g, 15.38 mmol, 1 equiv.), 2-Chloro-isophthalonitrile (2.5 g, 15.38 mmol, 1 equiv.), 3 Å molecular sieves (*ca*. 10 g) and anhydrous DMF (100 cm^3) as described in general procedure B. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the desired product as a yellow solid (2.53 g, 54 %).

m.p. 63 – 66 °C; R_f = 0.37 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 2235 (CN); δ_H (300 MHz; $CDCl_3$) 7.85 (2H, dd, *J* 8 and 0.5, H-1), 7.21 (1H, td, *J* 8 and 0.5, H-2), 7.16 (1H, d, *J* 0.5, H-3), 6.96 (1H, br s, H-4), 2.41 (3H, s, H-5) 2.01 (3H, s, H-6) and 1.43 (9H, s, H-7).; δ_C (75 MHz; $CDCl_3$) 161.0, 149.0, 142.7, 139.6, 137.1, 130.4, 130.1, 126.7, 122.2, 114.1, 103.2, 35.2, 30.8, 21.6 and 17.2.; EI *m/z* 322 (M + NH_4^+), 304 (M); CI *m/z* 322 (M + NH_4^+); HRMS found M 304.1568, $C_{20}H_{20}N_2O$ requires 304.1570.

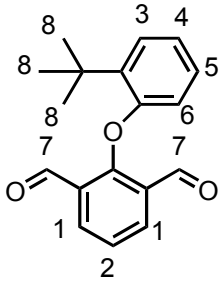
2-(2-Isopropylphenoxy)benzene-1,2-dicarbaldehyde (118a)



DiBAl-H (1.0 M solution in toluene) (22.9 cm^3, 22.8 mmol, 3 equiv.), dicyano **117a** (2 g, 7.6 mmol, 1 equiv.) and toluene (200 cm^3) were treated as described in general procedure C. The crude product was purified by flash column chromatography (5:1 Petrol : EtOAc) to yield the product as a yellow solid (1.28 g, 63 %).

m.p. 63 – 65 °C; R_f = 0.69 (5:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 1708 and 1684 (CHO); δ_H (300 MHz; $CDCl_3$) 10.22 (2H, s, H-7), 8.30 (2H, d, *J* 7.5, H-1), 7.57 (1H, tt, *J* 7.5 and 0.5, H-2), 7.42-7.40 (1H, m, H-3), 7.09-7.04 (2H, m, H-4 and H-5), 6.37-6.35 (1H, m, H-6), 3.64 (1H, sept, *J* 7, H-8) and 1.41 (6H, d, *J* 7, H-9).; δ_C (75MHZ; $CDCl_3$) 187.9, 159.8, 158.5, 136.4, 135.1, 130.4, 127.9, 127.5, 126.3, 123.7, 113.7, 27.6 and 23.0.; EI *m/z* 268 (M); CI *m/z* 286 (M + NH_4^+); HRMS found M + NH_4^+ 286.1445, $C_{17}H_{16}O_3$ requires 286.1438.

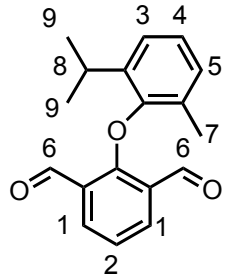
2-(2-tert-Butylphenoxy)benzene-1,2-dicarbaldehyde (118b)



DiBAl-H (1.0 M solution in toluene) (61.4 cm^3, 61.37 mmol, 3 equiv.), dinitrile **117b** (5.69 g, 20.46 mmol, 1 equiv.) and anhydrous toluene (200 cm^3) were treated as described in general procedure C. The crude was purified by flash column chromatography (15:1 Petrol : EtOAc) to the product as a light yellow solid (3.0 g, 54 %).

m.p. 81 – 84 °C; R_f = 0.41 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 1708 and 1684 (CHO); δ_H (300 MHz; $CDCl_3$) 10.21 (2H, s, H-7), 8.31 (2H, d, *J* 8, H-1), 7.57 (1H, tt, *J* 8 and 0.5, H-2), 7.49-7.47 (1H, m, H-3), 7.09 (2H, CH m, H-4 and H-5), 6.38-6.35 (1H, m, H-6) and 2.62 (9H, s, H-8).; δ_C (75 MHz; $CDCl_3$) 188.0, 160.1, 159.3, 137.3, 135.2, 130.5, 128.3, 128.1, 136.3, 123.5, 114.6, 35.3 and 30.0.; EI *m/z* 282 (M); CI *m/z* 300 (M + NH_4^+); HRMS found M 282.1245, $C_{18}H_{18}O_3$ requires 282.1250.

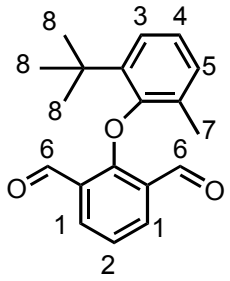
2-(2-isopropyl-6-methylphenoxy)benzene-1,3-dicarbaldehyde (118c)



DiBAl-H (1M solution in toluene) (7 cm^3, 7 mmol, 2.5 euiv.), dinitrile **117c** (0.77 g, 2.8 mmol, 1 equiv.) and anhydrous toluene (40 cm^3) were treated as described in general procedure C. The crude product was purified by flash column chromatography (15:1 Petrol : EtOAc) to yield the product as a yellow oil (0.59 g, 75 %).

R_f = 0.65 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 1679 (CHO); δ_H (300 MHz; $CDCl_3$) 10.08 (2H, s, H-6), 8.10 (2H, d, *J* 7.5, H-1), 7.30–7.25 (2H, m, H-3 and H-4), 7.21 (1H, t, *J* 7.5, H-2), 7.10 (1H, ddd, *J* 7.5, 2 and 0.5, H-5), 3.29 (1H, sept, *J* 7, H-8), 2.10 (3H, s, H-7) and 1.26 (6H, d, *J* 7, H-9).; δ_C (75MHz; $CDCl_3$) 188.1, 161.8, 154.6, 139.7, 135.3, 130.6, 128.3, 127.5, 126.7, 126.0, 123.0, 28.0, 23.2 and 17.6.; EI *m/z* 282 (M); CI *m/z* 300 (M + NH_4^+), 283 (M + H); HRMS found M 282.1252, $C_{18}H_{18}O_3$ requires 282.1250.

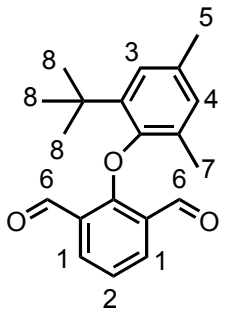
2-(2-tert-butyl-6-methylphenoxy)benzene-1,3-dialdehyde (118d)



DiBAl-H (1.0 M solution in toluene) (40.6 cm^3, 40.6 mmol, 2.5 equiv.), dinitrile **117d** (3.93 g, 13.5 mmol, 1 equiv.) and anhydrous toluene (200 cm^3) were treated as described in general procedure C. The crude product was dissolved in a further portion of EtOAC and 6.0 M HCL added (30 cm^3) until the solid dissolved. The organic phase was then washed with water, brine, dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (20:1 Petrol:EtOAc) to yield the product as a yellow solid (2.99 g, 74 %).

m.p. 75 – 79 °C; R_f = 0.78 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 1679 (CHO); δ_H (400 MHz; $CDCl_3$) 9.98 (2H, s, H-6), 8.10 (2H, d, *J* 7.5, H-1), 7.36 (1H, d, *J* 7.5, H-3), 7.25-7.22-7.20 (1H, m, H-4), 7.15 (1H, t, *J* 7.5, H-2), 7.08 (1H, d, *J* 7.5, H-5), 1.93 (3H, s, H-7) and 1.46 (9H, s, H-8).; δC (100MHz; $CDCl_3$) 187.9, 161.1, 155.7, 140.9, 135.4, 131.5, 127.6, 127.0, 126.5, 126.1, 122.7, 35.3, 30.4 and 17.8.; EI *m/z* 296 (M); CI *m/z* 314 (M + NH_4^+), 297 (M + H); HRMS found M + NH_4^+ 314.1752, $C_{15}H_{24}NO_3$ requires 314.1751.

2-(2-tert-Butyl-4,6-dimethylphenoxy)benzene-1,3-dialdehyde (118e)

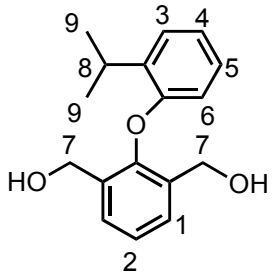


DiBAl-H (1.0 M solution in toluene) (33.6 cm^3, 33.6 mmol, 3 equiv.), dinitrile **117e** (3.41 g, 11.2 mmol, 1 equiv.) and anhydrous toluene (200 cm^3) were treated as described

in general procedure C, at -40 °C. The crude product was purified by flash column chromatography (20:1 Petrol : EtOAc) to yield the product as a cream coloured solid (2.15 g, 62 %).

m.p. 118 – 121 °C; R_f = 0.81 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 1683 (CHO); δ_H (300 MHz; $CDCl_3$) 10.06 (2H, s, H-6), 8.16 (2H, d, *J* 7.5, H-1), 7.29 (1H, t, *J* 7.5, H-2), 7.21 (1H, s, H-3), 6.95 (1H, s, H-4), 2.40 (3H, s, H-5), 1.976 (3H, s, H-7) and 1.51 (9H, s, H-8).; δ_C (75MHz; $CDCl_3$) 188.4, 162.0, 153.8, 140.7, 135.8, 135.6, 132.0, 127.5, 127.4, 127.3, 122.7, 35.4, 30.6, 21.4 and 17.9.; EI *m/z* 328 (M + NH_4^+), 310 (M); CI *m/z* 328 (M + NH_4^+), 310 (M); HRMS found M 310.1563, $C_{20}H_{22}O_3$ requires 310.1563.

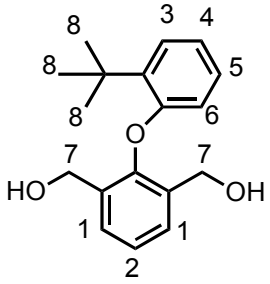
[3-Hydroxymethyl-2-(2-isopropyl-phenoxy)-phenyl]-methanol (119a)



Dialdehyde **118a** (2.6 g, 9.69 mmol, 1 equiv.), sodium borohydride (3.67 g, 97 mmol, 10 equiv.) and anhydrous THF (150 cm^3) were treated as described in general procedure D, to yield the product, with no purification, as a white powder (2.13 g, 81 %).

m.p. 106 – 108 °C; R_f = 0.12 (5:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3258 (OH).; δ_H (300 MHz; $CDCl_3$) 7.55 (2H, d, *J* 7.5, H-1), 7.36-7.32 (2H, m, H-2 and H-3), 7.02-6.97 (2H, m, H-4 and H-5), 6.29-6.27 (1H, m, H-6), 4.68 – 4.52 (4H, CH AB m, H-7), 3.56 (1H, sept, *J* 7, H-8) and 1.39 (6H, d, *J* 7, H-9).; δ_C (75 MHz; d_6-DMSO) 155.2, 147.7, 135.9, 135.7, 127.5, 127.3, 127.0, 125.9, 122.3, 112.0, 58.2, 27.4 and 23.3.; CI *m/z* 290 (M + NH_4^+); HRMS found: M + NH_4^+ 290.1742, $C_{17}H_{24}NO_3$ requires 290.1751.

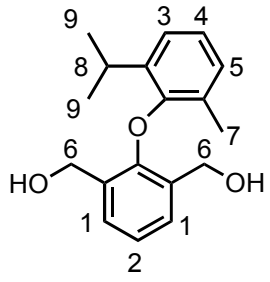
[2-(2-tert-Butyl-phenoxy)-3-hydroxymethyl-phenyl]-methanol (119b)



2-*tert*-Butyl-dialdehyde **118b** (1.44 g, 5.25 mmol, 1 equiv.), sodium borohydride (1.99 g, 52.5 mmol, 10 equiv.) and anhydrous THF (150 cm^3) were treated as described in general procedure D. The crude product was purified by flash column chromatography (5:1 petrol : EtOAc) to yield the product as a white solid (1.34 g, 92 %).

m.p. 102 – 105 °C; R_f = 0.08 (7:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3305 (OH).; δ_H (300 MHz; $CDCl_3$) 7.58 (2H, d, *J* 8, H-1), 7.43 (1H, dd, *J* 7.5 and 2, H-3), 7.38 (1H, t, *J* 8, H-2), 7.01-6.97 (2H, CH m, H-4 and H-5), 6.31 (1H, dd, *J* 7.5 and 2, H6), 4.68 – 4.56 (4H, CH AB m, H-7) and 1.57 (9H, s, H-8).; δ_C (75 MHz; d_6-DMSO) 156.5, 147.1, 136.8, 135.6, 128.0, 127.8, 127.1, 126.0, 122.1, 112.3, 58.4, 35.3 and 30.3.; EI *m/z* 286 (M); CI *m/z* 304 ($M + NH_4^+$); HRMS found M 286.1558, $C_{18}H_{22}O_3$ requires 286.1563.

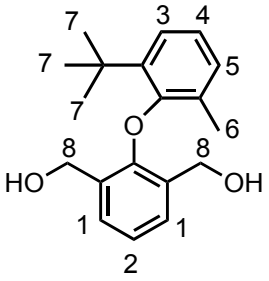
(2-(2-isopropyl-6-methylphenoxy)-1,3-phenylene)dimethanol (119c)



Dialdehyde **118c** (1.24 g, 4 mmol, 1 equiv.), sodium borohydride (1.51 g, 40 mmol, 10 equiv.) and anhydrous THF (150 cm^3) were treated as described in general procedure D. The crude product was purified by flash column chromatography (4:1 petrol : EtOAc) to yield the product as a white solid (920 mg, 73 %).

m.p. 107 – 110 °C; R_f = 0.14 (4:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3311 (OH).; δ_H (500 MHz; $CDCl_3$) 7.4 (2H, d, *J* 7.5, H-1), 7.13-7.10 (2H, m, H-3 and H-4), 7.1 (1H, t, *J* 7.5, H-2), 6.78 (1H, ddd, *J* 7.5, 2 and 0.5, H-5), 4.53-4.43 (4H, CH AB m, H-6), 3.40 (1H, sept, *J* 7, H-8), 2.3 (3H, s, H-7), 1.40 (6H, d, *J* 7, H-9).; ES+ *m/z* 309.2 (M + Na); HRMS found M + Na 309.1466, $C_{18}H_{22}O_3Na$ requires 309.1467.

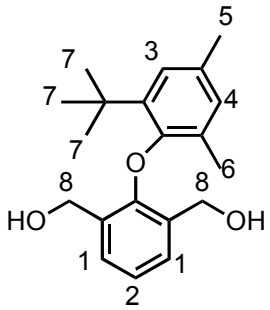
[2-(2-tert-Butyl-6-methyl-phenoxy)-3-hydroxymethyl-phenyl]-methanol (119d)



Dialdehyde **118d** (2.59 g, 8.74 mmol, 1 equiv.), sodium borohydride (3.3 g, 87.4 mmol, 10 equiv.) and anhydrous THF (150 cm^3) were treated as described in general procedure D. The crude product was purified by flash column chromatography (7:1 petrol : EtOAc) to yield the product as a white solid (2.5 g, 95 %).

m.p. 103 – 108 °C; R_f = 0.32 (4:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3323 (OH).; δ_H (300 MHz; $CDCl_3$) 7.45 (2H, d, *J* 8, H-1), 7.32 (1H, dd, *J* 7.5 and 2, H-3), 7.16 (1H, t, *J* 7.5, H-4), 7.07 (1H, t, *J* 8, H-2), 7.00 (1H, ddd, *J* 7.5, 2 and 0.5, H-5), 4.57 – 4.44 (4H, CH AB m, H-8), 1.84 (3H, s, H-6) and 1.48 (9H, s, H-7).; δ_C (75 MHz; $CDCl_3$) 155.0, 151.8, 140.4, 130.6, 130.1, 129.0, 128.1, 125.9, 124.3, 123.3, 61.1, 35.6, 30.7 and 18.1.; EI *m/z* 300 (M); CI *m/z* 318 (M + NH_4^+), 300 (M), 283 (M – OH); HRMS found M + Na, 318.2066, $C_{19}H_{24}O_3Na$ requires 318.2064.

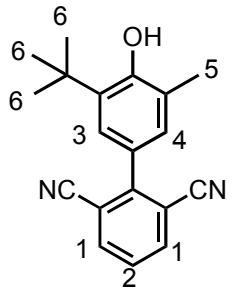
[2-(2-tert-butyl-4,6-dimethylphenoxy)-1,3-phenylene]-dimethanol (119e)



Dialdehyde **118e** (1.24 g, 4 mmol, 1 equiv.), sodium borohydride (1.51 g, 40 mmol, 10 equiv.) and anhydrous THF (150 cm^3) were treated as described in General Procedure D. The crude product was purified by flash column chromatography (4:1 petrol : EtOAc) to yield the product as a white solid (0.92 g, 73 %).

m.p. 128 - 130 °C; R_f = 0.14 (4:1 petrol:EtOAc); δ_H (500 MHz; $CDCl_3$) 7.4 (2H, d, *J* 7.5, H-1), 7.10 (1H, t, *J* 7.5, H-2), 7.06 (1H, s, H-3), 6.78 (1H, s, H-4), 4.53-4.43 (4H, CH AB m, H-8), 2.3 (3H, s, H-5), 1.8 (3H, s, H-6), 1.4 (9H, s, H-7).; δ_C (75 MHz; $CDCl_3$) 152.6, 151.8, 139.8, 133.3, 130.6, 129.8, 128.9, 127.5, 126.5, 122.9, 64.3, 43.8, 30.5, 21 and 17.7.; ES+ *m/z* 337 (M + Na); HRMS found M + Na 337.1771, $C_{20}H_{26}O_3Na$ requires 337.1775.; EA found C, 75.81; H, 8.89, $C_{20}H_{26}O_3$ requires C 76.40; H, 8.33%.

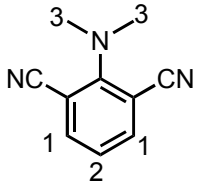
3'-tert-butyl-4'-hydroxy-5'-methylbiphenyl-2,6-dicarbonitrile (120)



2-Chloro-isophthalonitrile **116** (0.49 g, 3.04 mmol, 1 equiv.), 2-*tert*-butyl-6-methylphenol (0.5 g, 3.04 mmol, 1 equiv.), NaH (60% dispersion in mineral oil) (0.22 g, 9.13 mmol, 3 equiv.) and anhydrous DMF (50 cm^3) were treated as described in general procedure B. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as an orange solid (0.11 g, 13 %).

m.p. 207 – 210 °C; R_f = 0.13 (9:1 petrol:EtOAc); δ_H (400 MHz; $CDCl_3$) 7.94 (2H, d, *J* 7.9, H-1), 7.51 (1H, t, *J* 7.9, H-2), 7.33 (1H br s, H-3 or H-4), 7.21 (1H, br s, H-3 or H-4), 2.32 (3H, s, H-5), 1.46 (9H, s, H-6).; δ_C (125 MHz; $CDCl_3$) 154.6, 149.41, 137.25, 136.1, 129.36, 127.51, 126.95, 125.47, 123.73, 117.2, 114.2, 34.9, 29.6 and 16.13.; ES-*m/z* 289.2 ($M - H^+$); HRMS found $M - H^+$ 289.1332, $C_{19}H_{18}N_2O$ requires 289.1341.

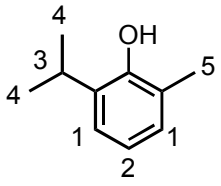
2-(dimethylamino)benzene-1,3-dicarbonitrile (121)[150]



2-Chloro-isophthalonitrile **116** (0.49 g, 3.04 mmol, 1 equiv.), 2-*tert*-butyl-6-methylphenol (0.5 g, 3.04 mmol, 1 equiv.), NaH (60% dispersion in mineral oil) (0.22 g, 9.13 mmol, 3 equiv.) and anhydrous DMF (50 cm^3) were treated as described in general procedure B. The crude product was purified by flash column chromatography to yield the product as a light brown solid (0.03 g, 3%).

m.p. 138 – 141 °C; R_f = 0.25 (9:1 petrol EtOAc); δ_H (400 MHz; $CDCl_3$) 7.65 (2H, d, *J* 7.8, H-1), 6.93 (1H, t, *J* 7.8, H-2), 3.25 (6H, s, H-3). Analyses matched the reported data.[163]

2-Isopropyl-6-methylphenol (123)[164]



By the method of Jones;[88] 2-*iso*-propyl-6-methylaniline (2 cm^3, 12.87 mmol, 1 equiv.) was dissolved in conc HCl (4 cm^3, 2 vol'), water (4 cm^3, 2 vol') and dioxane (10 cm^3)

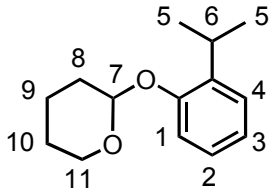
and treated with sodium nitrite (0.977 g, 14.16 mmol, 1.1 equiv.) dissolved in water (20 cm^3) at rt for 4 h to yield the diazonium salt.

By the method of Shine;[89] the mixture containing the diazonium salt was added to a stirred solution of conc H_2SO_4 (6 cm^3, 3 vol') in water (12 cm^3) and heated to 50 °C. The mixture was stirred at this temperature for 16 h, cooled to RT and extracted using EtOAc (3 x 30 cm^3). The combined organic phases were washed with water (x 3), brine, dried (Na_2SO_4) and solvent removed under reduced pressure. The crude product was purified by flash column chromatography (10:1 petrol : EtOAc) to yield the product as a light yello oil (1.53 g, 79 %).

b.p 225 – 226 °C (1 mmHg); R_f = 0.80 (4:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3466 (OH); δ_H (300 MHz; $CDCl_3$) 7.15 (1H, t, *J* 5.5, H-2), 7.05 (2H, d, *J* 5.5, H-1), 3.43 (1H, sept, *J* 7, H-3), 2.35 (3H, s, H-5) and 1.26 (6H, d, *J* 7, H-4).; EI *m/z* 150 (M). Analysis matched the published data.[151]

Also synthesised by slow (40 min) addition at between 0-10°C under N_2 of **136** (1g, 4.53 mmol, 1 equiv.) to a solution of tetramethylethylenediamine (1.21 cm^3 8.16 mmol) which had been added to a 2.4 N solution of *n*-butyllithium in *n*-hexane (3.4 cm^3, 8.16 mmol) and ether (20 cm^3 at 25°C with stirring and under N_2. After 20 mins, MeI (0.5cm^3, 8.16 mmol, 1 equiv.) was added, and the solution stirred for 16 hours. The mixture was quenched by addition of saturated ammonium chloride solution and organics diluted using EtOAc. The organic phase was washed with water, brine, dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was then added to a solution of THF (20 cm^3, 1 vol'), AcOH (80 cm^3, 4 vol') and water (40 cm^3, 2 vol') and heated at 45°C for 16 hours, cooled to rt and diluted using EtOAc (3 x 30 cm^3). The combined organic phases were washed with water (x 3), brine, dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (19:1 petrol : EtOAc) to yield the product as a light yellow oil (2.06 g, 56 %).

2-(2-isopropylphenoxy)-tetrahydro-2H-pyran (136)



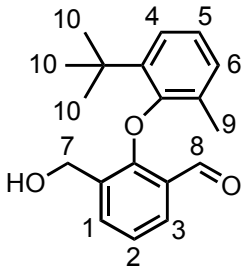
A solution of 2-isopropyl phenol (20 cm^3, 149 mmol, 1 equiv.) in 3,4-dihydro-2H-pyran (27 cm^3, 297 mmol) in DCM (150 cm^3) was stirred at room temperature in the presence of acidic silica gel (0.02 g, catalytic) for 1 hour. The catalyst was removed by filtration and 1-2 drops triethylamine added. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel (15:1 Petrol : EtOAc) to yield the product as a colourless oil (29.7 g, 90 %).

R_f = 0.82 (9:1 petrol:EtOAc); δ_H (500 MHz; $CDCl_3$) 7.14 (1H, d, *J* 8, H-3), 7.08-7.00 (2H, m, H-1 and H-4), 6.88 (1H, t, *J* 7, H-2), 5.36 (1H, t, *J* 3, H-7), 3.83 (1H, td, *J* 8 and 3, H-11), 3.55 (1H, dt, *J* 11 and 3 H-11), 3.28 (1H, sept, *J* 7, H-6) 2.02-1.90 (1H, m, H-8), 1.84-1.79 (2H, m, H-9 and H-10), 1.69-1.48 (3H, m, H-9, H-10 and H-8) and 1.17 (6H, dd, *J* 15 and 8, H-5).; δ_C (75 MHz; $CDCl_3$) 151.2, 135.5, 126.8, 126.4, 121.7, 114.4, 96.5, 63.8, 30.9, 27.6, 25.6, 23.1 and 19.1; not visible by MS.

Adsorption of Sulfuric Acid on Silica Gel:

A solution of concentrated sulphuric acid (2 cm^3) in acetone (18 cm^3) was added to a suspension of silica gel (100g, Fluorochem Davisil 40-63 μm 60 A) in acetone (200 cm^3) at room temperature with vigorous stirring. After 1 h, the solvent was removed in a rotary evaporator under reduced pressure at 50°C for 4 hours.

2-(2-tert-butyl-6-methylphenoxy)-3-(hydroxymethyl)benzaldehyde (140)



Dialdehyde **118d** (2.25 g, 7.59 mmol, 1 equiv.), lithium borohydride (72 mg, 1.90 mmol, 0.25 equiv.) and ethanol (20 cm^3) were treated as described in general procedure E. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a light yellow oil (1.46 g, 64 %).

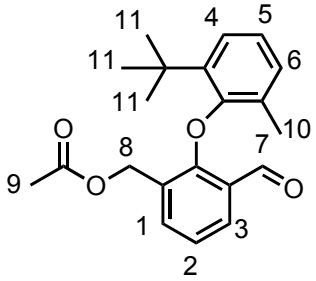
Also synthesised by kinetic resolution of **140** and desymmetrisation of **119d** (see section 4.3) to afford ***(P)-140***

HPLC: (R,R-Whelk-O1), eluting with hexane:IPA 97:3 at 0.5 ml/min; retention times 34.18 (minor) and 35.68 min (major).

R_f = 0.10 (9:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3406 (OH), 1675 (CHO).; δ_H (500 MHz; $CDCl_3$) 9.45 (1H, s, H-8), 7.63 (2H, dd, *J* 7.5 H-1 and H-3), 7.18 (1H, d, *J* 8.0, H-4), 7.03 (1H, t, *J* 8.0, H-5), 6.95 (1H, t, *J* 7.5, H-2), 6.89 (1H, d, *J* 8.0, H-6), 4.69 – 4.60 (2H, CH AB m, H-7), 1.72 (3H, s, H-9) and 1.32 (9H, s, H-10).; δ_C (125 MHz; $CDCl_3$) 188.6, 156.7, 155.8, 140.5, 134.6, 131.1, 129.8, 128.6, 127.7, 126.1, 126.0, 125.2, 122.6, 60.81, 35.3, 30.4, and 17.6; ES+ *m/z* 321.2; (M + Na); ES- *m/z* 296.9 (M) ; HRMS found M + Na, 321.1467, $C_{15}H_{21}O_3Na$ requires 321.1467.

Material of 42% ee derived from kinetic resolution had $[\alpha]_D^{26}$ = +2.4 (c = 0.166, heptane.

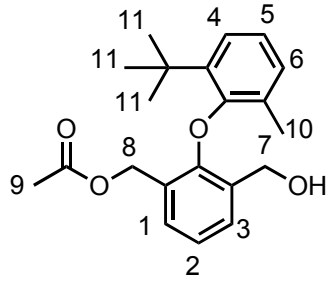
2-(2-tert-butyl-6-methylphenoxy)-3-formylbenzyl ethanoate (141)



Monoaldehyde **140 (**0.1 g, 0.35 mmol, 1 equiv.), sodium hydride (0.025 g, 0.62 mmol, 1.8 equiv.) and ether (15 cm^3) were charged to a flask at RT and stirred under an atmosphere of nitrogen for 30 minutes. Acetic anhydride (0.13 cm^3, 1.38 mmol, 4 equiv.) was then added and the reaction mixture heated to 40 °C for 12 hours. The reaction mixture was quenched with water, and the organic phase washed with water, brine, dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (9:1 petrol:EtOAc) to yield the product as a cream coloured solid (0.08 g, 74 %).

m.p. 107 – 109 °C; R_f = 0.60 (4:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3434 (OH), 1728 ($MeCOOCH_2Benz$).; δ_H (400 MHz; $CDCl_3$) 9.46 (1H, s, H-7), 7.80 (1H, dd, *J* 7.5 and 2, H-1), 7.65 (1H, dd, *J* 7.5 and 2, H-3), 7.32 (1H, dd, *J* 8, H-4), 7.14 (1H, t, *J* 8, H-5), 7.09 (1H, t, *J* 7.5, H-2), 7.03 (1H, dd, *J* 8 and 2, H-6), 5.23 (2H, CH AB m, H-8), 2.11 (3H, s, H-9), 1.86 (3H, s, H-10) and 1.45 (9H, s, H-11).; δ_C (100 MHz; $CDCl_3$) 188.27, 170.7, 157.5, 155.9, 140.5, 136.26, 131.14, 129.8, 127.6, 126.6, 126.2, 126.1, 125.3, 122.4, 61.9, 35.3, 30.28, 21.0 and 17.5.; ES+ *m/z* 363 (M + Na); HRMS found M + Na 363.1555, $C_{21}H_{24}O_4Na$ requires 363.1567.

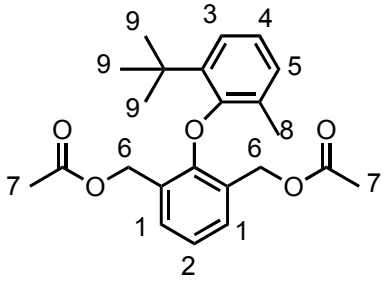
2-(2-tert-butyl-6-methylphenoxy)-3-(hydroxymethyl)benzyl ethanoate (142)



Monoaldehyde **141 (**0.08 g, 0.25 mmol, 1 equiv.), sodium borohydride (0.028 g, 1.0 mmol, 4 equiv.) and THF (2 cm^3) were charged to a flask at RT and stirred under an atmosphere of nitrogen at RT for 16 hours. The reaction mixture was quenched with water, and the organics washed with water, brine, dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a colourless oil (0.08 g, 97 %).

R_f = 0.47 (4:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3430 (OH), 1739 ($MeCOOCH_2Benz$).; δ_H (300 MHz; $CDCl_3$) 7.50 (1H, dd, *J* 7.5 and 2, H-3), 7.34 (1H, dd, *J* 7.5 and 2, H-1), 7.31 (1H, dd, *J* 8 and 2, H-4), 7.14 (1H, t, *J* 7.5, H-2), 7.06 (1H, t, *J* 8, H-5), 6.96 (1H, ddd, *J* 8, 2 and 0.5, H-6), 5.02 (2H, s, H-8), 4.43 (2H, CH AB m, H-7), 2.07 (3H, s, H-9), 1.86 (3H, s, H-10) and 1.47 (9H, s, H-11).; δ_C (75 MHz; $CDCl_3$) 170.9, 154.7, 152.5, 140.4, 130.4, 130.4, 130.3, 130.1, 128.3, 125.9, 125.4, 124.3, 123.0, 62.4, 60.8, 35.6, 30.6, 21.2 and 18.0.; EI *m/z* 360 (M + NH_4^+), 342 (M); CI *m/z* 360 (M + NH_4^+), 342 (M); HRMS found M + NH_4^+ 360.2176, $C_{21}H_{30}NO_4$ requires 360.2169.

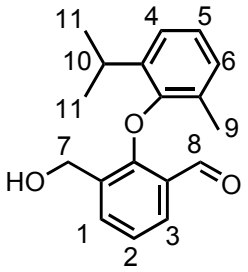
Acetic acid-3-acetoxymethyl-2-(2'-tert-butyl-6'-methyl-phenoxy)-benzyl ester (143)



Monoaldehyde **140 (**0.1 g, 0.35 mmol, 1 equiv.), sodium hydride (0.056 g, 1.38 mmol, 4 equiv.) and ether (15 cm^3) were charged to a flask at RT and stirred under an atmosphere of nitrogen for 30 minutes. Acetic anhydride (0.26 cm^3, 2.76 mmol, 8 equiv.) was then added and the reaction mixture heated to 40 °C for 12 hours. The reaction mixture was quenched with water, and the organics washed with water, brine, dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a white solid (0.093 g, 69 %).

m.p. 102 – 105 ^oC; R_f = 0.55 (4:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 1730 ($MeCOOCH_2Benz$).; δ_H (300 MHz; $CDCl_3$) 7.35 (2H, d, *J* 7.5, H-1), 7.27 (1H, dd, *J* 7.5 and 2, H-3), 7.10 (1H, t, *J* 7.5, H-2), 7.03 (1H, t, *J* 8, H-4), 6.96 (1H, ddd, *J* 7.5, 2 and 0.5, H-5), 4.92 (4H, s, H-6), 2.04 (6H, s, H-7), 1.86 (3H, s, H-8) and 1.45 (9H, s, H-9).; δ_C (75 MHz; $CDCl_3$) 170.8, 154.3, 153.3, 140.4, 131.4, 130.3, 128.5, 125.8, 125.5, 124.4, 122.8, 62.2, 35.6, 30.6, 21.1 and 18.0.; CI *m/z* 402 ($M + NH_4^+$); HRMS found $M + NH_4^+$ 402.2276, $C_{23}H_{32}NO_5$ requires 402.2275.

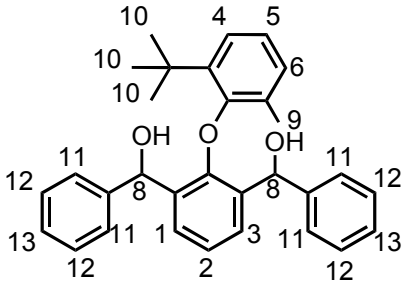
3-(hydroxymethyl)-2-(2-isopropyl-6-methylphenoxy)benzaldehyde (149)



Dialdehyde **118c** (0.24 g, 0.86 mmol, 1 equiv.), lithium borohydride (0.005 g, 0.22 mmol, 0.25 equiv.) and anhydrous THF (20 cm^3) were treated as described in general procedure E. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a light yellow oil (0.12 g, 50 %).

R_f = 0.11 (9:1 petrol:EtOAc); 3386 (OH), 1672 (CHO).; δ_H (500 MHz; $CDCl_3$) 9.79 (1H, s, H-8), 7.69 (1H, d, *J* 7.5 H-1), 7.62 (1H, d, *J* 7.5, H-3), 7.13 (1H, d, *J* 8, H-4), 7.09 (1H, t, *J* 7.5, H-2), 7.04 (1H, t, *J* 8, H-5), 6.94 (1H, d, *J* 8, H-6), 4.61 – 4.51 (2H, CH AB, m, H-7), 3.18 (1H, sept, *J* 7, H-10), 1.93 (3H, s H-9), 1.16 (3H, d, *J* 7 H-11) and 1.11 (3H, d, *J,* H-11).; δ_C (125 MHz; $CDCl_3$) 188.8, 157.6, 154.0, 139.4, 135.0, 131.3, 129.9, 128.5, 128.0, 126.5, 125.6, 125.3, 122.8, 60.9, 27.5, 23.3, 23.1, and 17.5.; ES+ *m/z* 307.3 (M + Na); HRMS found M + Na 307.1310, $C_{18}H_{20}O_3Na$ requires 307.1310. HPLC: (R,R-Whelk-O1), eluting with hexane:IPA 97:3 at 0.5 ml/min; retention times 41.28 min and 42.51 min.

(2-(2-*tert*-butyl-6-methylphenoxy)-1,3-phenylene)bis(phenylmethanol) (150b)

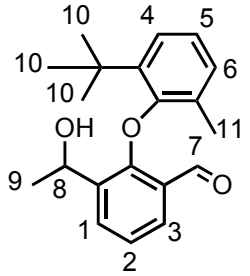


PhMgBr (1.4 M in THF) (3.26 cm^3, 4.56 mmol, 4 equiv.) was added dropwise to a stirring solution of dialdehyde **118d** (0.2 g, 0.76 mmol, 1 equiv.) in anhydrous ether at -

78 °C under N_2, The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a light yellow gum (0.01 g, 62 %).

R_f = 0.13 (9:1 petrol:EtOAc); δ_H (400 MHz; $CDCl_3$) 7.56 (1H, dd, *J* 7.5, H-1 or H-3), 7.31-7.20 (9H, m, H-11 or H-12 or H-13 or H-1 or H-3 or H-4 or H-5), 7.14-7.10 (2H, m, H-11 or H-12 or H-13 or H-4 or H-5), 6.94 (1H, t, *J* 7.5, H-2), 6.79 (1H, dd, *J* 8 and 2, H-6), 6.18 (1H, d, *J* 4, H-8), 5.87 (1H, d, *J* 5, H-8), 1.57 (3H, s, H-9), and 1.41 (9H, s, H-10).; δ_C (100 MHz; $CDCl_3$) 155.4, 152.2, 143.4, 142.1, 140, 133.4, 133.3, 130.2,130.1, 128.3, 128.0, 127.7, 127.7, 71.1, 69, 35.4, 30.5, and 17.8.; ES- *m/z* 451.4 (M); ES+ *m/z* 475.6 (M + Na); HRMS found M + Na 475.2247, $C_{31}H_{32}O_3Na$ requires 475.2249.

2-(2-t-Butyl-6-methylphenoxy)-3-(1-hydroxyethyl)benzaldehyde (151a)



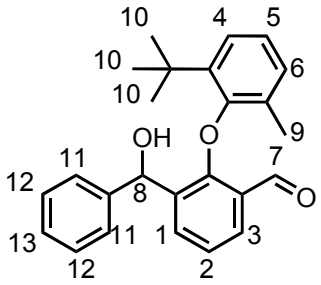
MeMgBr (1.4 M in THF) (2.17 cm^3, 3.04 mmol, 4 equiv.) was added dropwise to a stirring solution of dialdehyde **118d** (0.20 g, 0.76 mmol, 1 equiv.) in anhydrous THF at 0 °C under N_2, The crude product was purified by flash column chromatography (15:1 petrol : EtOAc) to yield the product as a light yellow oil (0.10 g, 52 %).

R_f = 0.71 (5:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3424 (OH), 1678 (CHO); δ_H (300 MHz; $CDCl_3$) 9.52 (1H, s, H-7), 7.85 (1H, ddd, *J* 7.5, 2 and 0.5, H-3), 7.74 (1H, dd, *J* 8 and 2, H-1), 7.35 (1H, dd, *J* 8 and 2, H-4), 7.20 (1H, t, *J* 8, H-2), 7.12 (1H, t, *J* 7.5, H-5), 7.05 (1H, ddd, J 7.5, 2 and 0.5, H-6), 5.38 (1H, q, *J* 6.5, H-8), 1.87 (3H, s, H-11), 1.56 (3H, d, *J* 6.5, H-9) and 1.50 (9H, s, H-10); δ_C (75 MHz; $CDCl_3$) 188.8, 156.3, 156.2, 140.7, 136.2, 133.1, 131.6, 128.8, 127.5, 126.4, 125.4, 123.1, 65.0, 35.5, 30.7, 23.6 and 18.1.; ES- *m/z* 311.2 (M - H); ES+ *m/z* 330 (M + NH_4^+), 312 (M), 295 (M – OH); HRMS found M + NH_4^+ 330.2069, $C_{20}H_{28}NO_3$ requires 330.2064.

Also obtained was a second diastereoisomer as a white solid (0.06 g, 28 %).

m.p. 45 – 48 °C; R_f = 0.58 (5:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3424 (OH), 1679 (CHO); δ_H (300 MHz; $CDCl_3$) 9.45 (1H, s, H-7), 7.90 (1H, ddt, *J* 8, 2 and 0.5, H-3), 7.75 (1H, dd, *J* 8 and 2, H-1), 7.34 (1H, dd, *J* 7.5 and 2, H-4), 7.21 (1H, td, *J* 8 and 0.5, H-2), 7.10 (1H, t, *J* 7.5, H-5), 7.03-7.00 (1H, m, H-6), 5.51 (1H, q, *J* 6.5, H-8), 1.85 (3H, s, H-11), 1.63 (3H, d, *J* 6.5, H-9) and 1.49 (9H, s, H-10).; δ_C (75 MHz; $CDCl_3$) 188.7, 156.8, 156.0, 140.4, 137.2, 132.6, 131.7, 128.6, 127.4, 126.4, 126.3, 125.2, 123.2, 64.7, 35.5, 30.4, 24.9 and 18.1.; ES- *m/z* 311.2 (M-H); ES+ *m/z* 335.1 (M + Na); CI *m/z* 330 (M + NH_4^+), 312 (M), 295 (M – OH); HRMS found M + NH_4^+ 330.2070, $C_{20}H_{28}NO_3$ requires 330.2064.

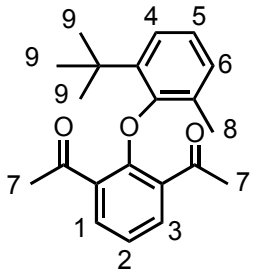
2-(2-tert-butyl-6-methylphenoxy)-3-(hydroxy(phenyl)methyl)benzaldehyde (151b)



PhMgBr (1.4 M in THF) (2.17 cm^3, 3.04 mmol, 4 equiv.) was added dropwise to a stirring solution of dialdehyde **118d** (0.20 g, 0.76 mmol, 1 equiv.) in anhydrous THF at 0 °C under N_2, The crude product was purified by flash column chromatography (15:1 petrol : EtOAc) to yield the product as a light yellow gum (0.08 g, 31 %).

R_f = 0.53 (4:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3425 (OH), 1675 (CHO); δ_H (300 MHz; $CDCl_3$) 9.17 (1H, s, H-7), 8.03 (1H, dd, *J* 7.5 and 2, H-3), 7.70 (1H, dd, *J* 8 and 2, H-1), 7.41 (2H, dd, *J* 8 and 2, H-11), 7.33-7.26 (4H, m, H-4, H-12 and H-13), 7.20 (1H, t, *J* 8, H-2), 7.03 (1H, t, *J* 8, H-5), 6.88 (1H, dd, *J* 7.5 and 1, H-6), 6.34 (1H, s, H-8), 1.49 (9H, s, H-10) and 1.13 (3H, s, H-9).; δ_C (75 MHz; $CDCl_3$) 188.5, 156.3, 156.1, 142.5, 140.8, 134.2, 132.9, 131.5, 129.0, 128.9, 128.3, 128.1, 127.6, 126.2, 126.0, 125.5, 122.6, 72.1, 35.4, 30.8 and 16.7.; EI *m/z* 374 (M); CI *m/z* 392 (M + NH_4^+), 375 (M + H); HRMS found M + Na^+ 397.1778, $C_{25}H_{26}O_3Na$ requires 397.1774.

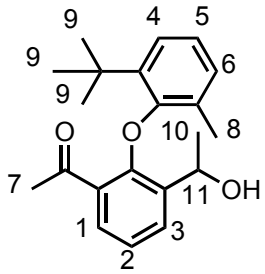
1,1'-(2-(2-tert-butyl-6-methylphenoxy)-1,3-phenylene)diethanone (152a)



MeLi (1.2 M solution in hexanes) (3.8 cm^3, 4.5 mmol, 6 equiv.) was added dropwise to a stirring solution of dinitrile **117d** (0.20 g, 0.76 mmol, 1 equiv.) in ether at -78 °C under N_2, stirred for 90 minutes and warmed to RT. 1.0 M HCl was added (1 cm^3) and the mixture stirred for a further 20 minutes. The reaction mixture was diluted using EtOAc, the organic phase was washed with water, brine, dried ($MgSO_4$), and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a light yellow solid (0.16 g, 72 %).

m.p 148 – 150 °C; R_f = 0.71 (4:1 petrol:EtOAc); δ_H (400 MHz; $CDCl_3$) 7.96 (1H, dd, *J* 7.6 and 2, H-1 or H-3), 7.81 (1H, dd, *J* 7.6 H-1 or H-3), 7.35 (1H, d, *J* 8, H-4), 7.15 (1H, d, *J* 8, H-6), 7.08 (1H, t, *J* 7.6, H-2), 6.93 (1H, t, *J* 8, H-5), 2.76 (3H, s, H-7), 2.20 (3H, s, H-7), 2.03 (3H, s, H-8), and 1.32 (9H, s H-9).; δ_C (100 MHz; $CDCl_3$) 199.9, 172.5, 163.6, 144.1, 140.3, 134.5, 133.7, 128.7, 128.0, 124.8, 117.4, 35.2, 30.5, 18.8 and 18.4.; ES+ *m/z* 347.3 (M + Na); HRMS found M + Na 347.1617, $C_{21}H_{24}O_3Na$ requires 347.1623.

1-(2-(2-tert-butyl-6-methylphenoxy)-3-(1-hydroxyethyl)phenyl)ethanone (154)

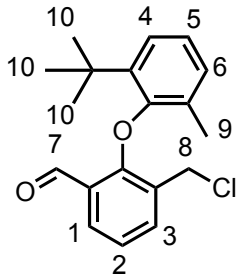


Diketone **152a** (0.1 g, 0.29 mmol, 1 equiv.), lithium borohydride (0.0016 g, 0.07 mmol, 0.25 equiv.) and anhydrous THF (10 cm^3) were treated as described in general procedure E. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a light yellow oil, and as a mixture of diastereomers (0.07 g, 68 %).

R_f = 0.28 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3412 (OH); δ_H (400 MHz; $CDCl_3$) 7.56 (1H, dd, *J* 8 and 2, H-1), 7.44 (1H, dd, *J* 8 and 2, H-3), 7.33 (1H, dd, *J* 8 and 2, H-4), 7.13-7.11 (1H, m, H-6), 7.06 (1H, t, *J* 8, H-2), 6.90 (1H, t, *J* 8, H-5), 5.19 (1H, q, *J* 6, H-11), 2.98 (3H, s, H-7), 2.02 (3H, s, H-8), 1.61 (3H, d, *J* 7, H-10), and 1.30 (9H, s, H-9).; ES+ *m/z* 349.4 (M + Na); HRMS found M + Na 349.1780, $C_{21}H_{26}O_3Na$ requires 349.1780.

Also obtained was a 2nd diastereomer as a light yellow oil. Rf = 0.27 (9:1 petrol:EtOAc).

2-(2-tert-butyl-6-methylphenoxy)-3-(chloromethyl)benzaldehyde (161)

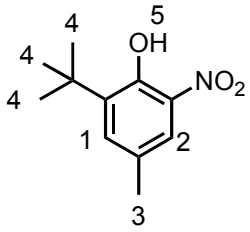


A mixture of Monoaldehde **140** (0.066 g, 0.21 mmol, 1 equiv.) and $SOCl_2$ (1 cm^3) was refluxed for 1 h. $SOCl_2$ was then evaporatd off with nitrogen and the residue was treated with aq. 10% K_2CO_3 and diluted using $CHCl_3$. The organic phase was washed with

water, brine, dried ($MgSO_4$), and solvent removed under reduced pressure. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a light yellow oil (0.046 g, 73 %).

R_f = 0.32 (9:1 petrol:EtOAc); δ_H (400 MHz; $CDCl_3$) 9.43 (1H, s, H-7), 7.78 (1H, dd, *J* 8 and 2, H-1), 7.71 (1H, dd, *J* 8 and 2, H-3), 7.32 (1H, dd, *J* 7.6 and 2, H-4), 7.15 (1H, t, *J* 7.6, H-2), 7.10 (1H, t, *J* 7.6, H-5), 7.04 (1H, dd, *J* 7.6 and 1.5, H-6), 4.76 (2H, CH AB m, H-8), 1.88 (3H, s, H-9), and 1.47 (9H, s, H-10).;).; δ_C (100 MHz; $CDCl_3$) 188.1, 157.1, 155.9, 140.6, 137.0, 133.4, 130.7, 128.1, 127.7, 126.1, 125.79, 125.4, 122.6, 41.2 (*C*-Cl), 35.3, 30.3, and 17.7.; ES+ *m/z* 339 (M + Na); HRMS found M + Na 339.1122, $C_{19}H_{24}O_2ClNa$ requires 339.1128.

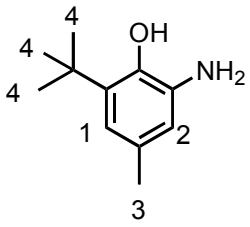
2-tert-butyl-4-methyl-6-nitrophenol (169)[115]



A suspension of 2-*tert*-butyl-4-methyl phenol (1 g, 6.0 mmol, 1 equiv.), silica sulphuric acid (1.35 g, equiv. = 0.225 g $mmol^{-1}$), wet SiO_2 (1.2 g, equiv. = 50% *w/w*) and $Al(NO_3)_3.9H_2O$ (1.6 g, 4.3 mmol, 0.7 equiv.) in DCM (50 cm^3) was stirred at rt for 7 h and then filtered. The organic phase was dried ($MgSO_4$), and solvent removed under reduced pressure. The crude product was purified by flash column chromatography (100% DCM) to yield the product as a yellow solid (0.68 g, 53%).

m.p. = 89 – 90 °C; R_f = 0.58 (4:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3089 (OH), 1537 and 1487 (NO); δ_H (400 MHz; $CDCl_3$) 11.43 (1H, s, H-5), 7.79 (1H, s, H-1), 7.39 (1H, s, H-2), 2.33 (3H, s, H-3) and 1.44 (9H, s, H-4).; δ_C (100 MHz; $CDCl_3$) 153.1, 140.2, 136.1, 133.8, 128.6, 122.2, 35.4, 29.3, and 20.7. Analyses matched the reported data.[120]

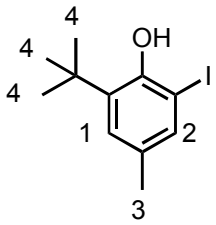
2-amino-6-tert-butyl-4-methylphenol (170)



Nitrophenol **169** (1 g, 4.8 mmol, 1 equiv.), Fe (reduced) (2.67 g, 0.05 mol, 10 equiv.), ethanol (4 cm^3), *conc.* HCl (0.05 cm^3) and H_2O (1 cm^3) were charged to a flask fitted with a reflux condenser and heted at 100 °C for 1 h. The reaction mixture was filtered over celite and solvent removed under reduced pressure. The crude product was purified by flash column chromatography (4:1 petrol: EtOAc) to yield the product as a light purple powder (0.57 g, 67%).

R_f = 0.25 (4:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3389 (OH), 3418, 3340 and 1628 (NH_2); δ_H (500 MHz; $CDCl_3$) 6.68 (1H, s, H-1), 6.61 (1H, s, H-2), 2.23 (3H, s, H-3), 1.41 (9H, s, H-4).; δ_C (100 MHz; $CDCl_3$) 143.7, 136.6, 129.2, 123.5, 120.4, 118.8, 34.6, 29.8, 21.; ES- *m/z* 178 (M - H); HRMS found M - H 178.1231, $C_{11}H_{17}NO$ requires 178.1237.

2-tert-butyl-6-iodo-4-methylphenol (171)

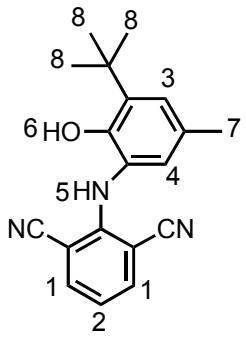


Aniline **171** (0.12 g, 0.67 mmol, 1 equiv.) in DMSO (1 cm^3) was added to a solution of *conc.* H_2SO_4 (0.15 cm^3) and H_2O (1 cm^3) at rt and the solution cooled using ice (1.5 g). $NaNO_2$ (0.05 g, 0.74 mmol, 1.1 equiv.) dissolved in H_2O (0.5 cm^3) was added slowly to the solution of aniline sulfate and the aniline was left to diazotise for 40 min. DMSO (2 cm^3) was added to the reaction mixture to redissolve the resultant precipitate. KI (0.13 g, 0.80 mmol, 1.2 equiv.) in H_2O (0.5 cm^3) was added and the reaction mixture heated to 90 °C for 1 h. The reaction mixture was cooled to rt and diluted using EtOAc. The organic phase was washed with water, brine, dried ($MgSO_4$), and solvent removed under

reduced pressure. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a brown oil (0.04 g, 23%)

R_f = 0.71 (4:1 petrol:EtOAc); δ_H (400 MHz; $CDCl_3$) 7.43-7.41 (1H, m, H-2), 7.29 (1H, s, H-1), 2.42 (3H, s, H-3), 1.45 (9 H, s, H-4).; δ_C (100 MHz; $CDCl_3$) 156.4, 135.5, 132.4, 131.4, 127.4, 117.6, 34.7, 29.3, 21.3.; not visible by MS.

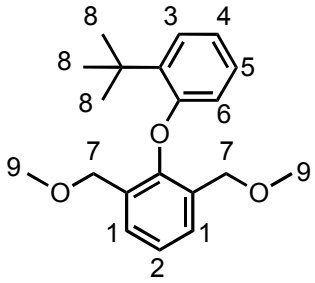
2-(3-*tert*-butyl-2-hydroxy-5-methylphenylamino)benzene-1,3-dicarbonitrile (173)



Phenol **170** (0.20 g, 1.12 mmol, 1.2 equiv.), K_2CO_3 (0.26 g, 1.86 mmol, 2 equiv.), 2-Chloro-isophthalonitrile (0.15 g, 0.93 mmol, 1 equiv.), 3 Å molecular sieves (*ca*. 1 g) and anhydrous DMF (20 cm^3) were treated as described in general procedure B. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a light brown solid (0.088 g, 31 %).

R_f = 0.59 (4:1 petrol:EtOAc). δ_H (400 MHz; $CDCl_3$) 7.62 (2H, d, *J* 7.5, H-1), 7.03 (1H, s, H-3), 6.92 (2H, t, *J* 7.5, H-2), 6.68 (1H, s, H-4), 6.06 (1H, bs, H-5), 5.78 (1H, s, H-6), 2.19 (3H, s, H-7) and 1.36 (9H, s, H-8).; δ_C (100 MHz; $CDCl_3$) 151.0, 150.0, 138.7, 137.0, 136.0, 129.2, 128.1, 125.9, 124.9, 120.1, 115.1, 101.4, 34.7, 29.4 and 20.9.; ES-*m/z* 304 (M - H).

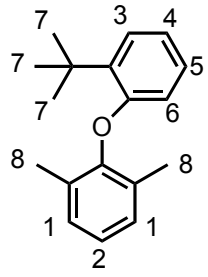
2-(2-tert-butylphenoxy)-1,3-bis(methoxymethyl)benzene (184)



Diol **119b** (0.4 g, 1.45 mmol, 1 equiv.), sodium hydride (60% dispersion in mineral oil) (0.35 g, 14.4 mmol, 6 equiv.), MeI (0.28 cm^3, 4.34 mmol, 3 equiv.) and anhydrous THF (50 cm^3) were treated as described in general procedure F. The crude product was purified by flash column chromatography (2:1 petrol:EtOAc) to yield the product as a white solid (0.39 g, 79%).

m.p 103-104 °C, R_f = 0.84 (9:1 petrol:EtOAc). δ_H (300 MHz; $CDCl_3$) 7.50 (2H, d, *J* 7.5, H-1), 7.30-7.26 (2H, m, H-2 and H-3), 7.00-6.95 (2H, m, H-4 and H-5), 6.20 (1H, dd, *J* 8 and 1.5, H-6), 4.4 – 4.2 (4H, CH AB m, H-7), 3.3 (6H, s, H-9) and 1.54 (9H, s, H-8).; δ_C (100 MHz; $CDCl_3$) 156.9, 148.8, 136.8, 132.0, 128.6, 127.2, 126.5, 125.6, 121.4, 112.6, 69.3, 58.4, 35.0 and 29.8.; ES+ *m/z* 337 (M + Na); HRMS found M + Na 337.1776, $C_{20}H_{26}O_3Na$ requires 337.1775.

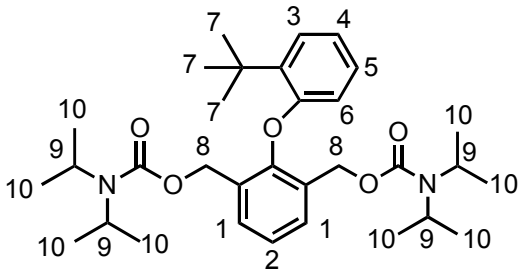
2-(2-*tert*-butylphenoxy)-1,3-dimethylbenzene (187)



Diol **119b** (0.4 g, 1.45 mmol, 1 equiv.), dissolved in ethanol (20cm^3) was placed under a hydrogen atmosphere through a continuous flow system over 10% Pd/C at a flow rate of 1ml/min. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (15:1 petrol: EtOAc) to yield the products as a clear oil (0.15 g, 68%).

R_f = 0.54 (18:1 petrol:EtOAc); δ_H (300 MHz; $CDCl_3$) 7.4 (1H, dd, *J* 7.5 and 1.5, H-3), 7.08-7.18 (3H, m, H-4 and H-5 and H-2), 7.0 (1H, td, *J* 7.8 and 1.9, H-1), 6.9 (1H, td, *J* 7.5 and 1.5, H-1), 6.3 (1H, dd, *J* 8 and 1.5, H-6), 2.16 (6H, s, H-8), 1.6 (9H, s, H-7).

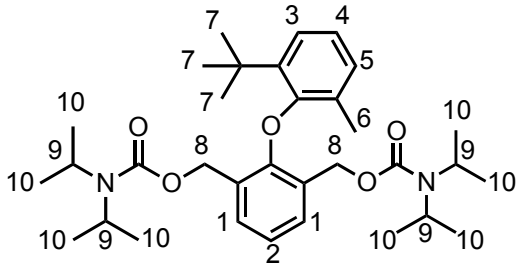
(2-(2-tert-butylphenoxy)-1,3-phenylene)bis(methylene) bis(diisopropylcarbamate) (194)



Diol **119b** (0.1 g, 0.35 mmol, 1 equiv.), NaH (60% dispersion in mineral oil) (0.08 g, 2.1 mmol, 6 equiv.), 18-crown-6 ether (0.002 g, *catalytic*), and anhydrous ether (20 cm^3) were charged to a flask at rt and stirred for 30 min. Diisopropyl carbamoyl chloride (0.24 g, 1.40 mmol, 4 equiv.). was added to the reaction mixture and the solution heated to reflux (35 °C) for 16 h. The reaction was quenched by adition of H_2O and the organic phase was washed with water, brine, dried ($MgSO_4$), and solvent removed under reduced pressure. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a colourless oil turning into a white solid on standing (0.16 g, 87 %).

m.p. 92 – 94 °C; R_f = 0.33 (9:1 petrol:EtOAc); δ_H (400 MHz; $CDCl_3$) 7.40 (2H, d, *J* 7.5, H-1), 7.26 (1H, dd, *J* 8 and 2, H-3), 7.22 (1H, t, *J* 7.5, H-2), 6.89-6.79 (2H, m, H-4 and H-5), 6.18 (1H, dd, *J* 8, and 2, H-6), 5.04 – 4.84 (4H AB m, H-8), 3.99 – 3.50 (4H br m, H-9) 1.45 (9H, s, H-7) and 1.15 – 1.00 (24H, br m, H-10); δ_C (100MHz; $CDCl_3$) 156.9, 155.1, 149.9, 137, 131.1, 129.8, 127.3, 127.1, 125.4, 121.6, 112.7, 61.6, 45.9 (br), 35, 29.9, 21.3 and 20.70 (br).; ES+ *m/z* 563.4 ($M + Na^+$); HRMS found: $M + Na^+$ 541.3633, $C_{32}H_{48}N_2O_5$ requires 541.3636.

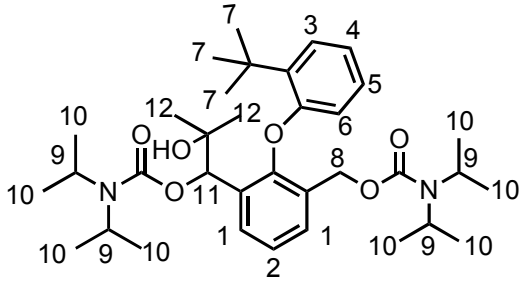
(2-(2-tert-butyl-6-methylphenoxy)-1,3-phenylene)bis(methylene) bis (diisopropylcarbamate) (195)



Diol **119d** (1.0 g, 3.73 mmol, 1 equiv.), NaH (60% dispersion in mineral oil) (0.90 g, 22.35 mmol, 6 equiv.), 18-crown-6 ether (0.02 g, *catalytic*), and anhydrous ether (200 cm^3) were charged to a flask at rt and stirred for 30 min. Diisopropyl carbamoyl chloride (1.76 g, 14.9 mmol, 4 equiv.) was added to the reaction mixture and the solution heated to reflux (35 °C) for 16 h. The reaction was quenched by adition of water and the organic phase was washed with water, brine, dried ($MgSO_4$), and solvent removed under reduced pressure. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a colourless oil turning into a white solid on standing (1.50 g g, 72 %).

m.p. 96 – 98 °C. R_f = 0.38 (9:1 petrol:EtOAc); δ_H (400 MHz; $CDCl_3$) 7.26 (2H, d, *J* 7.6, H-1), 7.17 (1H, dd, *J* 7.5 and 1.5, H-3), 7.02 (1H, t, *J* 7.5, H-2), 6.89 (1H, t, *J* 7.5, H-4), 6.84 (1H, dd, *J* 7.5 and 1.5, H-5), 4.96 – 4.82 (4H AB m, H-8), 3.95 – 3.65 (4H br m, H-9) 1.73 (3H, s, H-6), 1.37 (9H, s, H-7) and 1.15 – 1.05 (24H, bd, *J* 6, H-10); δ_C (100MHz; $CDCl_3$) 155.1, 154.5, 152.1, 139.7, 130.5, 129.5, 127.5, 126.9, 125.5, 123.7, 122.6, 61.5, 45.9 (br), 35.3, 30.4, 21.2 (br) and 18.1.; ES+ *m/z* 577 ($M + Na^+$); HRMS found M + Na 577.3618, $C_{33}H_{50}N_2O_5$ Na requires 577.3612; EA found C, 71.12; H, 9.56; N; 5.08, $C_{33}H_{50}N_2O_5$ requires C 73.57; H, 9.35; N, 5.20%.

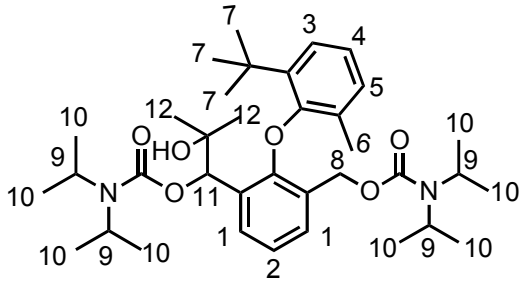
Diisopropyl-carbamicacid 1-{2-(2-*tert*-butyl-phenoxy)-3-[(diisopropylcarb amoyloxy)-methyl]-phenyl}-2-hydroxy-2-methyl-propyl ester (198)



Carbamate **194** (0.14 g, 0.25 mmol, 1.0 equiv.), *sec*-BuLi (1.3 M in hexanes) (0.31 cm^3, 0.41 mmol, 1.6 equiv.), acetone (1 cm^3, excess) and anhydrous ether (14 cm^3) were treated as described in general procedure G. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a light yellow oil (0.095 g, 63 %).

R_f = 0.10 (9:1 petrol:EtOAc); δ_H (400 MHz; $CDCl_3$) 7.55 (1H, dd, *J* 8 and 1.5, H-1), 7.40 (1H, dd, *J* 8 and 1.5, H-1), 7.30-7.20 (2H, m, H-2 and H-3), 6.81 (2H, dd, *J* 6 and 1.5 H-4 and H-5), 6.13 (1H, dd, *J* 6, and 1.5, H-6), 5.80 (1H, br s, H-11), 4.99–4.75 (2H AB m, H-8), 4.00-3.45 (4H, br m, H-9) 1.49 (9H, s, H-7), 1.18 (6H, br s, H-12) and 1.12–1.00 (24H, bm, H-10); δ_C (100MHz; $CDCl_3$) 157.0, 155.4, 155.1, 150.1, 136.8, 132.5, 130.7, 130.0, 128.9, 127.4, 126.9, 125.1, 121.9, 114.0, 76.5, 73.6, 61.9, 45.4 (br), 34.9, 30.1, 27.1, 25.4, and 20.5 (br).; ES+ *m/z* 621.5 ($M + Na^+$); HRMS found $M + H^+$ 599.4048, $C_{35}H_{55}N_2O_6$ requires 599.4055.

Di-isopropyl-carbamic acid 1-{2-(2-*tert*-butyl-6-methyl-phenoxy)-3-[(diisopropyl carbamoyloxy)-methyl]-phenyl}-2-hydroxy-2-methyl-propyl ester (199)



Carbamate **195** (0.13 g, 0.23 mmol, 1.0 equiv.), *sec*-BuLi (1.3 M in hexanes) (0.28 cm^3, 0.37 mmol, 1.6 equiv.), acetone (1 cm^3, excess) and anhydrous ether (13 cm^3) were

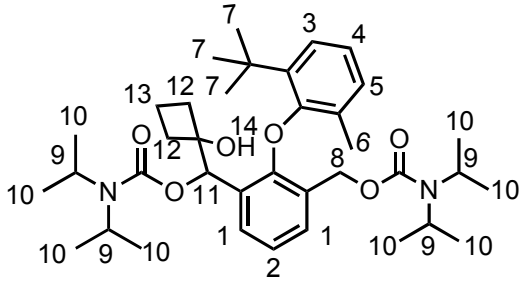
treated as described in general procedure G. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a light yellow oil (0.1 g, 75 %).

Also synthesised by treatment of carbamate **195** (0.1 g, 0.18 mmol, 1.0 equiv.), *sec*-BuLi (0.22 cm^3, 0.29 mmol, 1.6 equiv.), (–)-sparteine (0.07 cm^3, 0. 29mmol, 1.6 equiv), acetone (1 cm^3, excess) and anhydrous ether (10 cm^3) as described in general procedure G. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a light yellow oil (0.12 g, 86 %).
HPLC: (R,R-Whelk-O1), eluting with hexane:IPA 97:3 at 1.0 ml/min; retention times 14.04 min (major) and 15.85 min (minor).
Material of 50% ee had $[\alpha]_D^{22} = +28$ (c = 1.000, chloroform).

Also synthesised by treatment of stannane **203** (0.05 g, 0.09 mmol, 1.0 equiv.), *n*-BuLi (2.4 M in hexanes) (0.06 cm^3, 0.14 mmol, 1.5 equiv.), acetone (0.5 cm^3, excess) and anhydrous ether (5 cm^3) as described in general procedure I. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a light yellow oil (0.02 g, 27 %).

R_f = 0.13 (9:1 petrol:EtOAc); δ_H (400 MHz; $CDCl_3$) 7.49 (1H, dd, *J* 8 and 1.5, H-1), 7.21-7.15 (2H, m, H-1 and H-3), 7.05 (1H, t, *J* 8, H-4), 6.86 (1H, t, *J* 7.5, H-2), 6.78 (1H, dd, *J* 7.5, and 1, H-5), 6.51 (1H, s, H-11) 4.62 – 4.32 (2H AB m, H-8), 3.93–3.50 (4H br m, H-9), 1.6 (3H, s, H-6), 1.41 (9H, s, H-7), 1.24 (6H, d, *J* 4, H-12), and 1.10 (24H, dd, *J* 21 and 7, H-10); δ_C (100MHz; $CDCl_3$) 155.2, 155.0, 152.4, 139.3, 130.9, 130.2, 129.7, 129.1, 127.8, 126.4, 125.4, 123.6, 122.5, 75.5, 73.8, 60.8, 46.0 (br), 35.4, 30.3, 26.9, 26.0, 21.4 (br) and 18.2.; ES+ *m/z* 635 ($M + Na^+$), HRMS found $M + H^+$ 613.4229, $C_{36}H_{57}N_2O_6$ requires 613.4212.

Diisopropyl-carbamic acid {2-(2-*tert*-butyl-6-methyl-phenoxy)-3-[(diisopro pylcarbamoyloxy)-methyl]-phenyl}-(1-hydroxy-cyclobutyl)-methyl ester (200)

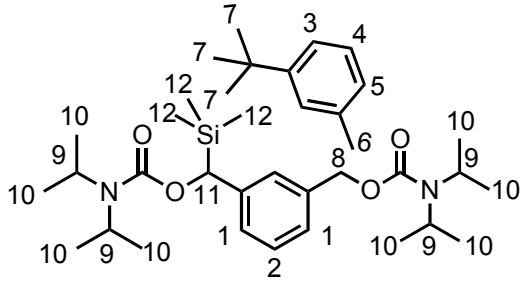


Carbamate **195** (0.1 g, 0.18 mmol, 1.0 equiv.), *sec*-BuLi (1.3 M in hexanes) (0.22 cm^3, 0.29 mmol, 1.6 equiv.), cyclobutanone (1 cm^3, excess) and anhydrous ether (10 cm^3) were treated as described in general procedure G. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a clear gum (0.06 g, 56 %).

Also synthesised by treatment of carbamate **195** (0.1 g, 0.18 mmol, 1.0 equiv.), *sec*-BuLi (0.22 cm^3, 0.29 mmol, 1.6 equiv.), (–)-sparteine (0.07 cm^3, 0. 29mmol, 1.6 equiv), cyclobutanone (1 cm^3, excess) and anhydrous ether (10 cm^3) as described in general procedure G. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a clear gum (0.028 g, 26 %).
HPLC: (R,R-Whelk-O1), eluting with hexane:IPA 97:3 at 1.0 ml/min; retention times 14.79 min (major) and 16.89 min (minor).
Material of 46% ee had $[\alpha]_D^{22} = +9$ (c = 0.100, chloroform).

R_f = 0.10 (9:1 petrol:EtOAc); δ_H (500 MHz; $CDCl_3$) 7.66 (1H dd, *J* 7.5 and 1.5, H-1), 7.30 (1H, dd, *J* 8 and 1, H-1), 7.24 (1H, br d, *J* 7, H-3), 7.15 (1H, t, *J* 7.5, H-2), 6.94 (1H, t, *J* 7.5, H-4), 6.87 (1H, br d, *J* 7, H-5), 6.67 (1H, br s, H-11), 4.73-4.45 (2H, AB m, H-8), 4.05-3.60 (4H, br m, H-9), 3.22 (1H, s, H-14), 2.55-2.50 (1H, br m, H-12), 2.35-2.28 (1H, br m, H-12), 2.17-1.95 (4H, br m, H-12 and H-13), 1.70 (3H, s, H-6), 1.26 (9H, s, H-7), 1.22-1.15 (24 H, br m, H-10).; δ_C (100MHz; $CDCl_3$) 155.1, 155.0, 152.2, 139.3, 130.95, 130.0, 129.0, 127.8, 126.5, 125.4, 123.6, 122.6, 78.0, 73.9, 60.8, 45.9 (br), 35.4, 33.4, 320, 30.4, 21.1 (br), 18.3 and 12.5.; ES+ *m/z* 647 ($M + Na^+$); HRMS found M + Na 647.4028, $C_{37}H_{56}N_2O_6$ Na requires 647.4036.

Diisopropyl-carbamic acid {2-(2-*tert*-butyl-6-methyl-phenoxy)-3-[(diisopro pylcarbamoyloxy)-methyl]-phenyl}-trimethylsilanyl-methyl ester (201)



Carbamate **195** (0.1 g, 0.18 mmol, 1.0 equiv.), *sec*-BuLi (1.3 M in hexanes) (0.22 cm^3, 0.29 mmol, 1.6 equiv.), TMSCl (1 cm^3, excess) and anhydrous ether (10 cm^3) were treated as described in general procedure G. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a light yellow oil (0.079 g, 70 %).

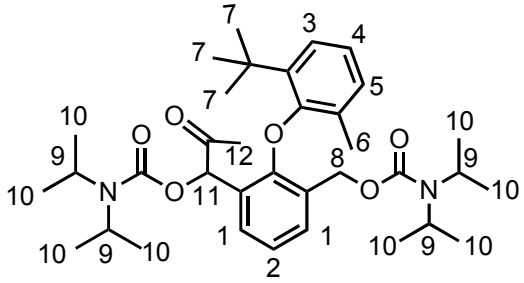
Also synthesised by treatment of carbamate **195** (0.1 g, 0.18 mmol, 1.0 equiv.), *sec*-BuLi (0.22 cm^3, 0.29 mmol, 1.6 equiv.), (–)-sparteine (0.07 cm^3, 0. 29mmol, 1.6 equiv), TMSCl (1 cm^3, excess) and anhydrous ether (10 cm^3) as described in general procedure G. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a light yellow oil (0.08 g, 72 %).
HPLC: (R,R-Whelk-O1), eluting with hexane:IPA 97:3 at 1.0 ml/min; retention times 9.54 min (major) and 10.81 min (minor).
Material of 56% ee had $[\alpha]_D^{22} = +52$ (c = 1.000, chloroform).

Also synthesised by treatment of stannane **203** (0.05 g, 0.09 mmol, 1.0 equiv.), *n*-BuLi (2.4 M in hexanes) (0.06 cm^3, 0.14 mmol, 1.5 equiv.), TMSCl (0.5 cm^3, excess) and anhydrous ether (5 cm^3) as described in general procedure I. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a light yellow oil (0.037 g, 33 %).

R_f = 0.60 (9:1 petrol:EtOAc); δ_H (400 MHz; $CDCl_3$) 7.31 (1H, dd, *J* 8 and 2, H-1), 7.20 (1H, dd, *J* 8 and 2, H-1), 7.16 (1H, dd, *J* 8 and 2, H-3), 7.08 (1H, t, *J* 8, H-2 or H-4), 6.90 (1H, t, *J* 8, H-2 or H-4), 6.84 (1H, br dd, *J* 7.5 and 1, H-5), 6.28 (1H, s, H-11), 4.63-4.35 (2H, AB m, H-8), 3.90-3.76 (4H, br m, H-9), 1.64 (3H, s, H-6), 1.36 (9H, s, H-7) 1.11 (12H, br d, *J* 4, H-10), 1.04 (12H, br d, *J* 4, H-10) and 0.00 (9H, s, H-12).; δ_C (100MHz; $CDCl_3$) 153.7, 153.5, 149.1, 137.3, 131.5, 129.6, 126.7, 126.3, 125.0, 123.6,

121.6, 121.2, 64.3, 59.5, 44.6 (br), 33.9, 28.8, 19.7 (br), 16.8 and -4.2.; ES+ *m/z* 649 (M + Na^+), HMRS Found M + Na 649.3996 $C_{36}H_{58}N_2O_5Si$ Na requires 649.4008.

Diisopropyl-carbamic acid 1-{2-(2-#tert!-butyl-6-methyl-phenoxy)-3-[(diisop= ropylcarbamoyloxy)-methyl]-phenyl}-2-oxo-propyl ester (202)



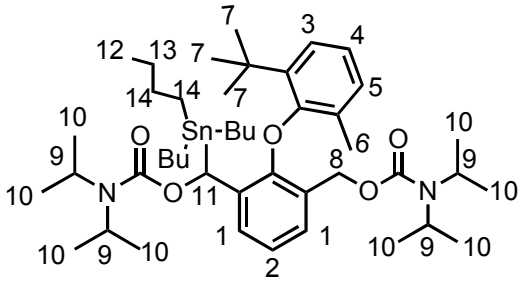
Carbamate **195** (0.1 g, 0.18 mmol, 1.0 equiv.), *sec*-BuLi (1.3 M in hexanes) (0.22 cm^3, 0.29 mmol, 1.6 equiv.), acetic anhydride (1 cm^3, excess) and anhydrous ether (10 cm^3) were treated as described in general procedure G. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a light yellow oil (0.11 g, 69 %).

Also synthesised by treatment of carbamate **195** (0.1 g, 0.18 mmol, 1.0 equiv.), *sec*-BuLi (0.22 cm^3, 0.29 mmol, 1.6 equiv.), (–)-sparteine (0.07 cm^3, 0. 29mmol, 1.6 equiv), TMSCl (1 cm^3, excess) and acetic anhydride (10 cm^3) as described in general procedure G. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a light yellow oil (0.10 g, 66 %).
HPLC: (R,R-Whelk-O1), eluting with hexane:IPA 97:3 at 1.0 ml/min; retention times 11.89 min (major) and 16.11 min (minor).
Material of 60% ee had $[\alpha]_D^{22} = +102$ (c = 0.9, chloroform).

R_f = 0.29 (9:1 petrol:EtOAc); δ_H (400 MHz; $CDCl_3$) 7.38 (1H, dd, *J* 7.5 and 2, H-1), 7.33-7.29 (2H, m, H-1 and H-3), 7.13 (1H, t, *J* 7.5, H-2), 6.98 (1H, t, *J* 8, H-4), 6.88 (1H, dd, *J* 7.5 and 1, H-5), 6.54 (1H, s, H-11), 4.92-4.70 (2H, AB m, H-8), 4.05-3.75 (4H, br m, H-9), 2.14 (3H, s, H-12), 1.74 (3H, s, H-6), 1.52 (9H, s, H-7), 1.35-1.15 (24H, br m, H-10).; δ_C (100MHz; $CDCl_3$) 202.8, 154.5, 154.3, 152.7, 139.4, 131.2, 130.7, 129.6, 127.6, 127.4, 125.7, 124.0, 123.3, 74.1, 61.1, 45.6 (br), 35.4, 30.5, 26.8,

20.9 (br), and 18.3.; ES+ *m/z* 619 (M + Na^+), HMRS Found M + H 597.3889, $C_{35}H_{53}N_2O_6$ requires 597.3899.

Diisopropyl-carbamic acid {2-(2-*tert*-butyl-6-methyl-phenoxy)-3-[(diisopro pylcarbamoyloxy)-methyl]-phenyl}-tributylstannanyl-methyl ester (203)



Carbamate **195** (0.1 g, 0.18 mmol, 1.0 equiv.), *sec*-BuLi (1.3 M in hexanes) (0.22 cm^3, 0.29 mmol, 1.6 equiv.), $SnBu_3Cl$ (0.5 cm^3, excess) and anhydrous ether (10 cm^3) were treated as described in general procedure G. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a light yellow oil (0.088 g, 58 %) and as a mixture of diastereomers in the ratio 9:1

HPLC: minor diastereomer elutes first, (R,R-Whelk-O1), eluting with hexane:IPA 97:3 at 1.0 ml/min; retention times 3.13 min and 6.29 min; major diastereomer elutes second, (R,R-Whelk-O1), eluting with hexane:IPA 97:3 at 1.0 ml/min; retention times 5.84 min and 6.63 min;

Also synthesised by treatment of carbamate **195** (0.1 g, 0.18 mmol, 1.0 equiv.), *sec*-BuLi (0.22 cm^3, 0.29 mmol, 1.6 equiv.), (–)-sparteine (0.07 cm^3, 0. 29mmol, 1.6 equiv), TMSCl (1 cm^3, excess) and anhydrous ether (10 cm^3) as described in general procedure G. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a light yellow oil (0.094 g, 62 %).

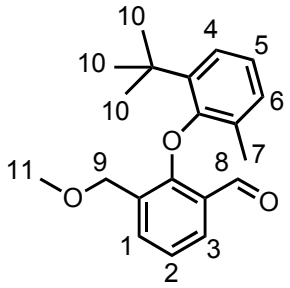
HPLC: (R,R-Whelk-O1), eluting with hexane:IPA 97:3 at 1.0 ml/min; retention times 5.84 min (minor) and 6.63 min (minor).

Material of 50% ee had $[\alpha]_D^{22} = -21$ (c = 1.000, chloroform).

R_f = 0.29 (9:1 petrol:EtOAc); δ_H (400 MHz; $CDCl_3$) 7.27-7.16 (3H, m, H-1 and H-3), 7.07 (1H, t, *J* 7.5, H-2 or H-4), 6.97 (1H, t, *J* 7.5, H-2 or H-4), 6.91 (1H, dd, *J* 7.5 and

1.5, H-5), 5.92 (1H, s, H-11^{MINOR}), 5.50 (1H, s, H-11^{MAJOR}), 5.10-4.98 (2H, AB m, H-8^{MAJOR}), 4.75-4.55 (2H, s, H-8^{MINOR}), 4.10-3.85 (3H, br m, H-9), 3.70 – 3.60 (1H, br m, H-9), 1.80 (3H, s, H-6), 1.41 (9H, s, H-7), 1.40-1.27 (9H, m, H-14), 1.22-1.14 (24H, br m, H-10), 1.02 (3H, br m, H-12), 0.84 (9H, t, *J* 7.5, H-12), 0.72 (6H, q, *J* 8, H-13).; δ_C (100MHz; $CDCl_3$) 155.4, 155.2, 151.2, 139.4, 130.6, 130.5, 127.3, 126.8, 125.7, 123.6, 122.5, 123.3, 74.1, 62.0, 58.08, 46.1 (br), 35.4, 30.4, 29.1, 27.6, 21.5 (br), 20.5, 18.6, 13.7 and 10.7.; ES+ *m/z* 867 (M + Na^+).

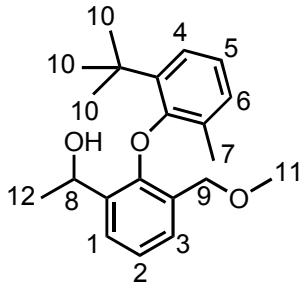
2-(2-tert-butyl-6-methylphenoxy)-3-(methoxymethyl)benzaldehyde (243)



Monoaldehyde **140** (1.46 g, 4.9 mmol, 1 equiv.), NaH (60% dispersion in mineral oil) (0.29 g, 5.88 mmol, 1.2 equiv.), MeI (0.37 cm^3, 5.22 mmol, 1.2 equiv) and anhydrous THF (200 cm^3) were treated as described in general procedure F. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a light yellow solid (1.17 g, 76 %).

m.p. 79 – 81 °C. R_f = 0.56 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 1679 (CHO); δ_H (500 MHz; $CDCl_3$) 9.53 (1H, s, H-8), 7.68 (1H, dd, *J* 7.5 and 2, H-3), 7.64 (1H, dt, *J* 7.5 and 1, H-1), 7.23 (1H, dd, *J* 8 and 1.5, 1, H-4), 7.07 (1H, t, *J* 7.5, H-2), 7.00 (1H, t, *J* 8, H-5), 6.94 (1H, ddd, *J* 8, 2 and 0.5, H-6), 4.46-4.39 (2H, AB m, H-9), 3.33 (3H, s, H-11), 1.77 (3H, s, H-7) and 1.38 (9H, s, H-10).; δC (100MHz; $CDCl_3$) 188.7, 156.8, 155.8, 140.4, 135.0, 131.0, 129.1, 128.6, 127.7, 126.1, 125.9, 124.9, 122.4, 58.7, 35.3, 30.4, and 17.6.; ES+ *m/z* 335 (M + Na); HRMS found: M + Na 335.1629, $C_{20}H_{24}O_3$ Na requires 335.1618.

1-(2-(2-tert-butyl-6-methylphenoxy)-3-(methoxymethyl)phenyl)ethanol (244)



MeMgBr (1.4 M solution in THF) (0.82 cm^3, 1.15 mmol, 1.2 equiv.), aldehyde **243** (0.30 g, 1.15 mmol, 1 equiv.) and anhydrous THF (10 cm^3) were treated as described in general procedure J. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a light yellow gum (0.25 g, 80 %) and as a mixture of diastereomers (29:71) by ^{1}H NMR.

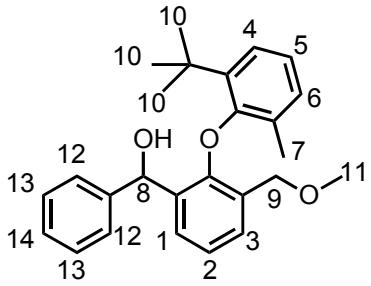
R_f = 0.2 (9:1 petrol:EtOAc); δ_H (500 MHz; $CDCl_3$) Mixture of diastereoisomers in the ratio of 29:71. 7.44 (1H, dd, *J* 7.5 and 1.5 H-1^{major} or H-3^{major}), 7.39 (1H, dd, *J* 7.5 and 1.5, H-1^{minor} or H-3^{minor}) 7.29 (1H, td, *J* 8 and 1.5, H-1^{m} or H-3), 7.21-7.18 (1H, m, H-2), 7.10-7.03 (1H, m, H-4), 6.92 (1H, t, *J* 7.5 H-5), 6.87 (1H, br d, *J* 7.5 H-6), 5.16 (2H, q, H-8^{major}), 4.96 (2H, q, H-8^{minor}), 4.15-3.86 (2H, AB m, H-9), 3.14 (3H, s, H-11^{minor}), 3.06 (3H, s, H-11^{major}), 1.72 (3H, s, H-7^{major}), 1.69 (3H, s, H-7^{minor}), 1.41 (3H, d, *J* 6.5, H-12^{major}), 1.39 (9H, s, H-10^{minor}), 1.38 (9H, s, H-10^{major}) and 1.26 (3H, d, *J* 6.5, H-12^{minor}).; δ_C (100 MHz; $CDCl_3$) 155.0, 154.8, 151.1, 150.8, 139.8, 139.7, 135.9, 135.7, 135.0, 134.9, 130.6, 129.9, 128.9, 128.6, 127.7, 127.6, 127.5, 126.7, 126, 125.4, 123.6, 123.5, 123.3, 123.2, 69.4, 64.5, 58.3, 35.4, 30.4, 24.4, 23.0 and 18.2.; ES+ *m/z* 351 (M + Na); HRMS found 351.1933, $C_{21}H_{28}O_3$ Na requires 351.1931.

Also synthesised by treatment of ketone **246** (0.057 g, 0.17 mmol, 1 equiv.) with L-Selectride (1 M solution in THF) (0.2 cm^3, 0.18 mmol, 1.1 equiv.) and THF (10 cm^3) at 0 °C as described in general procedure K. The crude product (0.055 g, 98 %) was taken unpurified. Crude ^{1}H NMR shows mixture of diastereomers in the ratio of 88:12.
HPLC: Sphereclone, hexane:IPA 97:03, 1.0 ml/min, retention times 5.4 min (major) and 5.9 min (minor).

Also synthesised by treatment of ketone **246** (0.08 g, 0.24 mmol, 1 equiv.) with Super-Hydride® (1 M solution in hexane) (0.30 cm^3, 0.27 mmol, 1.1 equiv.) and THF (10 cm^3)

at 0 °C as described in general procedure K. The crude product (0.078 g, 98%) was taken unpurified. Crude ^{1}H NMR shows mixture of diastereomers in the ratio of 57:43. *HPLC*: Sphereclone, hexane:IPA 97:03, 1.0 ml/min, retention times 5.4 min (major) and 5.9 min (minor).

(2-(2-tert-butyl-6-methylphenoxy)-3-(methoxymethyl)phenyl)(phenyl)methanol (245)



PhMgBr (1M solution in THF) (0.5 cm^3, 0.5 mmol, 1.2 equiv.), monoaldehyde 31 (0.13 g, 0.42 mmol, 1 equiv.) and anhydrous THF (10 cm^3) were treated as described in general procedure J. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a light yellow oil (0.10 g, 63 %), and as seperable mixture of 2 diastereomers (55:45) by ^{1}H crude NMR.

Diastereomer 1 (first eluted): white solid, m.p. 120 – 123 °C; R_f = 0.33 (9:1 petrol:EtOAc); δ_H (300 MHz; $CDCl_3$) 7.51 (1H, d, *J* 7.5 H-1 or H-3), 7.28-7.22 (3H, m, H-12 and H-1 or H-3), 7.22-7.11 (4H, m, H-4 and H-13 and H-14), 7.06 (1H, t, *J* 7.5, H-2), 6.89 (1H, t, *J* 8, H-5), 6.72 (1H, br d, *J* 8, H-6), 6.16 (1H, s, H-8), 3.81 - 3.60 (2H, AB m, H-9), 2.95 (3H, s, H-11), 1.38 (9H, s, H-10) and 1.18 (3H, s, H-7).; δ_C (75 MHz; $CDCl_3$) 154.2, 151.2, 142.7, 140.2, 130.3, 129.1, 128.7, 128.4, 127.6, 127.3, 127.1, 126.5, 125.1, 123.7, 122.7, 72.0, 69.0, 58.1, 35.3, 30.7 and 17.2; ES+ *m/z* 413 (M + Na); HRMS found M + Na 413.2084, $C_{26}H_{30}O_3$ Na requires 413.2088.

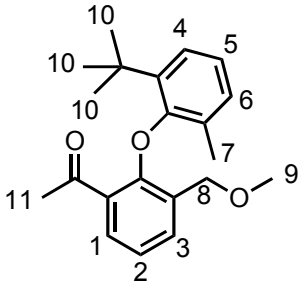
Diastereomer 2 (second eluted): light yellow oil; R_f = 0.27 (9:1 petrol:EtOAc); δ_H (300 MHz; $CDCl_3$) 7.4-7.16 (8H, m, H-1, H-3, H-12, H-13, H-14 and H-4), 7.27 (1H, d, *J* 8, H-3), 7.06 (1H, t, *J* 7.5, H-2), 6.98-6.93 (2H, m, H-5 and H-6), 6.17 (1H, s, H-8), 4.04 - 3.83 (2H, AB m, H-9), 3.05 (3H, s, H-11), 1.74 (3H, s, H-7) and 1.19 (9H, s, H-10).; δ_C

(75 MHz; $CDCl_3$) 154.9, 151.7, 143.3, 140.1, 133.4, 130.4, 129.2, 128.5, 128.3, 128.1, 127.4, 127.3, 127.0, 125.4, 123.7, 123.0, 70.6, 69.3, 58.3, 35.2, 30.6 and 18.1.; ES+ *m/z* 413 (M + Na); HRMS found M + Na 413.2084, $C_{26}H_{30}O_3$ Na requires 413.2088.

Also synthesised by treatment of ketone **247** (0.064 g, 0.16 mmol, 1 equiv.) with L-Selectride (1 M solution in THF) (0.2 cm^3, 0.18 mmol, 1.1 equiv.) and THF (10 cm^3) at 0 °C as described in general procedure K. The crude product (0.062 g, 98%) was taken unpurified. Crude ^1H NMR shows mixture of diastereomers in the ratio of >95:5.
HPLC: Sphereclone, hexane:IPA 97:03, 1.0 ml/min, retention times 4.4 min (major) and 4.7 min (minor).

Also synthesised by treatment of ketone **247** (0.068 g, 0.18 mmol, 1 equiv.) with Super-Hydride® (1 M solution in hexane) (0.22 cm^3, 0.19 mmol, 1.1 equiv.) and THF (10 cm^3) at 0 °C as described in general procedure K. The crude product (0.062 g, 92 %) was taken unpurified. . Crude ^1H NMR shows mixture of diastereomers in the ratio of >95:5.
HPLC: Sphereclone, hexane:IPA 97:03, 1.0 ml/min, retention times 4.4 min (major) and 4.7 min (minor), >99:1 dr.

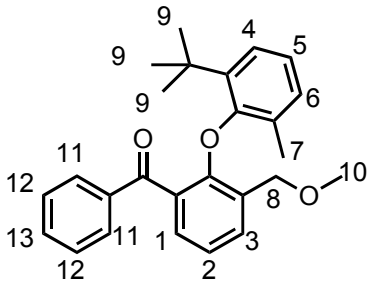
1-(2-(2-tert-butyl-6-methylphenoxy)-3-(methoxymethyl)phenyl)ethanone (246)



Dess-martin periodinane (15 wt % solution in DCM) (1.7 cm^3, 0.76 mmol, 1 equiv.), alcohol 32 (0.25 g, 0.76 mmol, 1 equiv.) and anhydrous DCM (20 cm^3) were treated as described in general procedure L. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a light yellow oil (0.24 g, 97 %).

R_f = 0.41 (9:1 petrol:EtOAc); δ_H (300 MHz; $CDCl_3$) 7.6 (1H, d, *J* 7.5, H-3), 7.51 (1H, dd, *J* 7.5 and 1.5, H-1), 7.32 (1H, d, *J* 8, H-4), 7.15 (1H, t, *J* 7.5, H-2), 7.06 (1H, t, *J* 8, H-5), 7.0 (1H, d, *J* 8, H-6), 4.13 - 3.92 (2H, AB m, H-8), 3.17 (3H, s, H-9), 2.56 (3H, s, H-11), 1.94 (3H, s, H-7) and 1.48 (9H, s, H-10).; δ_C (75MHz; $CDCl_3$) 201.2, 154.1, 152.4, 140.8, 132.9, 132.0, 130.7, 129.1, 128.2, 125.9, 124.5, 122.7, 58.5, 53.7, 35.7, 30.9 and 18.8.; ES+ *m/z* 349 (M + Na); HRMS found M + Na 349.1777, $C_{21}H_{26}O_3$ requires 349.1775.

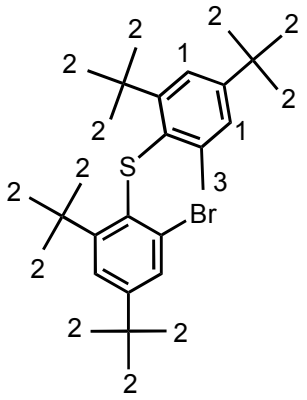
(2-(2-tert-butyl-6-methylphenoxy)-3-(methoxymethyl)phenyl)(phenyl)methanone (247)



Dess-martin periodinane (15 wt % solution in DCM) (0.56 cm^3, 0.26 mmol, 1 equiv.), alcohol **245** (0.1 g, 0.26 mmol, 1 equiv.) and anhydrous DCM (20 cm^3) were treated as described in general procedure L. The crude product was purified by flash column chromatography (9:1 Petrol : EtOAc) to yield the product as a light yellow oil (0.09 g, 90 %).

R_f = 0.44 (9:1 petrol:EtOAc); δ_H (300 MHz; $CDCl_3$) 7.81 (2H, dd, *J* 8 and 1.5, H-1 and H-3), 7.64-7.55 (2H, m, H-11), 7.44 (2H, t, *J* 7.5, H-12 or H-13), 7.28 (1H, dd, *J* 7.5 and 2, H-4), 7.23-7.15 (2H, m, H-13 and H-12), 6.94 (1H, t, *J* 7.5, H-5), 6.79 (1H, dd, *J* 7.5 and 1, H-6), 4.15 - 3.92 (2H, AB m, H-8), 3.2 (3H, s, H-10) and 1.2 (9H, s, H-9).; δ_C (75MHz; $CDCl_3$) 196.3, 154.2, 151.8, 140.8, 137.8, 133.5, 130.9, 130.2, 128.6, 128.4, 128.0, 127.4, 127.0, 125.3, 124.3, 122.3, 58.6, 53.7, 35.4, 30.4 and 18.2.; ES+ *m/z* 411 (M + Na); HRMS found M + Na 411.1946, $C_{26}H_{28}O_3Na$ requires 411.1931.

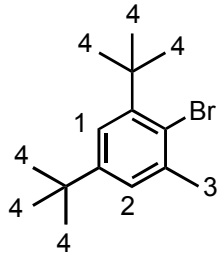
(2,4-di-tert-butyl-6-bromophenyl)(2,4-di-tert-butyl-6-methylphenyl)sulfane (250)



Following a modified procedure reported by Buchwald,[143] solid reagents: thiophenol **256** (0.57 g, 2.4 mmol, 1.2 equiv.), copper(I) iodide (0.46 g, 2.4 mmol, 1.2 equiv.) and potassium carbonate (560 mg, 4.0 mmol, 2 equiv.) were charged to a flask fitted with a reflux condenser and evacuated / back filled with nitrogen × 3. A solution of iodide **258** (0.8 g, 2.0 mmol, 1 equiv.) and ethylene glycol (0.23 cm^3) in *tert*-amyl alcohol (6 mL) was added via syringe and the reaction mixture heated to reflux for 24 h. The reaction mixture was allowed to cool to RT, diluted with ethyl acetate (40 cm^3) and filtered through a glass sinter. Organics were washed with water (3 × 50 cm^3) and brine (50 cm^3) dried over $MgSO_4$ and solvents removed under reduced pressure. The crude product was purified by flash chromatography (petrol) to yield the title compound as a white solid that was then recrystalised from acetone (1.07 g, 64%).

m.p 125-129 ˚C (acetone). R_f = 0.69 (petrol); δ_H (400 MHz, $CDCl_3$) 7.45 (1H, d, *J* 2, H-1), 7.36 (1H, d, *J* 2, H-1), 7.33 (1H, d, *J* 2, H-1), 6.93 (1H, d, *J* 2, H-1), 1.75 (3H, s, H-3), 1.65 (9H, s, H-4), 1.64 (9H, s, H-2), 1.30 (9H, s, H-2) and 1.28 (9H, s, H-2).; δ_C (100 MHz, $CDCl_3$) 150.8, 150.2, 149.0, 148.5, 139.0, 133.1, 131.8, 129.7, 127.0, 126.1, 123.6, 122.5, 38.3, 37.5, 34.7, 34.5, 31.3, 31.3, 31.1, 30.9 and 23.0.; *m/z* CI 502 (40 %, $[^{79}Br\ M]^+$), 504 (40 %, $[^{81}Br\ M]^+$) 503 (50 %, $[^{79}BrM+H]^+$), 505 (50 %, $^{81}BrM+H]^+$) HRMS found 502.2264, $C_{29}H_{43}BrS$ requires 502.2263.

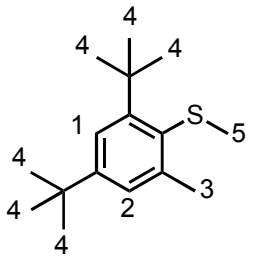
2-bromo-1,5-di-tert-butyl-3-methylbenzene (254)[165]



Using a modified procedure reported by Wieghardt.[152] A solution of bromine (12.6 cm^3, 480 mmol, 2 equiv.) in chloroform (100 cm^3) was added via syringe pump to a suspension of iron powder (4.1 g, 73.4 mmol, 0.3 equiv.) in a solution of 3,5-di-*tert*-butyl toluene (50 g, 240 mol, 1 equiv.) in chloroform (400 cm^3) at 0 ˚C over 2 hours. The reaction mixture was stirred for a further 2 hours at 0 ˚C. The reaction was quenched by addition of saturated $Na_2O_3S_2$ solution (150 cm^3). The organic phases were washed with $Na_2O_3S_2$ solution (3 × 100 cm^3), water (2 × 100 cm^3) and brine (100 cm^3), dried over $MgSO_4$ and solvents removed under reduced pressure. The resultant oil was purified by distillation under reduced pressure to yield the product as a colourless oil (40 g, 55 %).

b.p. 100-104 ˚C (1 mmHg); δ_H (200 MHz; $CDCl_3$) 7.42 (1H, d, *J* 2.5, H-1), 7.22 (1H, d, *J* 2.5, H-2), 2.52 (3H, s, H-3), 1.63 (9H, s, H-4) and 1.38 (9H, s, H-4).; Analyses matched the reported data.

(2,4-di-tert-butyl-6-methylphenyl)(methyl)sulfane (255)

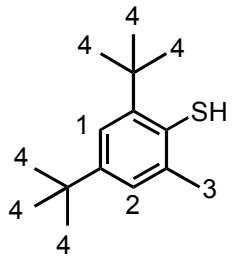


A flame dried flask was evacuated / back filled with nitrogen × 3. Bromide **254** (6 g, 21.2 mmol, 1 equiv.) was charged to the flask and dissolved in anhydrous THF (150 cm^3) and the solution cooled to –78 ˚C. *t*-BuLi solution (2.2 M in hexanes) (46.6 cm^3, 46.6 mmol, 2.2 equiv.) was added over 5 mins and stirred for a further 5 mins. Dimethyl

disulfide (4.79 cm^3, 53 mmol, 2.5 equiv.) was added dropwise and the reaction stirred and allowed to warm to RT over 16 h. The reaction was quenched by addition of saturated NH_4Cl solution (35 cm^3) and diluted with with ether (200 cm^3). The organic phase was washed with water (2 × 200 cm^3) and brine (100 cm^3), dried over $MgSO_4$ and solvents removed under reduced pressure to yield the product as a colourless oil which slowly crystallised on standing (4.95 g, 93 %).

m.p 32-34 ˚C; δ_H (400 MHz, $CDCl_3$) 7.26 (1H, s, H-1), 7.05 (1H, s, H-2), 2.97 (3H, s, H-5), 2.37 (3H, s, H-3) and 1.34 (18H, s, H-4).; δ_C (100 MHz, $CDCl_3$) 152.8, 150.4, 144.1, 131.8, 125.8, 121.8, 37.5, 34.6, 31.5, 31.3, 22.1 and 19.9.; CI *m/z* 250 (100 %, [M]+); HRMS found 250.1757, $C_{16}H_{26}S$ requires 250.1750.

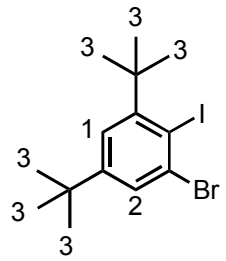
2,4-di-tert-butyl-6-methylbenzenethiol[166] (256)



Sulfide **255** (4.47 g, 17.8 mmol, 1 equiv.) was added to a solution of Sodium 2-methyl-2-propanethiolate (10 g, 89.2 mmol, 5 equiv.) in DMF (85 cm^3) under an atmosphere of nitrogen. The reaction was heated to reflux for 18 h. The reaction mixture was cooled in ice for 20 mins. 3 M HCl solution (100 m cm^3) was added and a stream of nitrogen blown over the reaction mixture for 10 mins. The reaction mixture was poured into a conical flask containing 3 M HCl solution (500 cm^3) and stirred for 15 mins, and diluted with DCM. Organic phase was washed with water (300 cm^3), dried over $MgSO_4$ and solvent evaporated by blowing a stream of nitrogen over the solution. The crude product was purified by column chromatography (petrol) to yield the title compound as a waxy white solid (3.65 g, 87%).

R_f = 0.34 (petrol); δ_H (500 MHz, $CDCl_3$) 7.34 (1H, d, *J* 1.5, H-1), 7.14 (1H, d, *J* 1.5, H-2), 3.28 (1H, s, S*H*), 3.42 (3H, s, H-3), 1.54 (9H, s, H-4) and 1.30 (9H, s, H-4).; Analyses matched the reported data.[153]

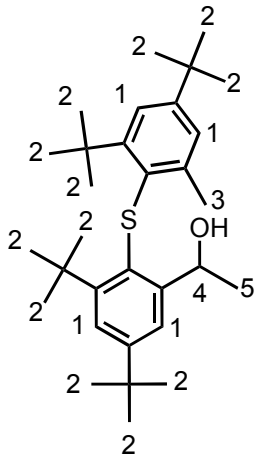
1,5-di-tert-butyl-3-bromo-2-iodobenzene (258)



Following a modified procedure reported by Stavber[138], 1-Bromo-3,5-di-*tert*-butyl benzene (11.2 g, 41.6 mmol, 1 equiv.) and selectfluor® (16.3 g, 45.9 mmol, 1.1 equiv.) were charged to a flask and dissolved in acetonitrile (300 cm^3). The reaction mixture was heated to reflux for 5 hours. The reaction was allowed to cool to room temperature and quenched by addition solid $Na_2O_3S_2$ (~10 g) and water (~30 cm^3) and stirred for 10 min. Solvents were removed under reduced pressure and the resultant residue dissolved in dichloromethane (200 cm^3), washed with water (3 × 150 cm^3), saturated $Na_2O_3S_2$ solution (100 cm^3L) and brine (100 cm^3), dried over $MgSO_4$ and solvents removed under reduced pressure. The crude product was purified by distillation under reduced pressure yielding 1-bromo-3,5-di-*tert*-butyl benzene (bp 85-95 ˚C (1 mmHg) and the title compound as a yellow oil (6.9 g, 42 %),

bp 125-130 ˚C (1 mmHg); δ_H (300 MHz, $CDCl_3$) 7.59 (1H, d, *J* 2.5, H-1), 7.37 (1H, d, *J* 2.5, H-2), 1.58 (9H, s, H-3) and 1.29 (9H, s, H-3).; δ_C (125 MHz, $CDCl_3$) 153.4, 152.0, 134.4, 128.0, 123.5, 99.1, 38.5, 31.3, 31.0 and 30.2.; EI *m/z* 394 (30 %, $[^{79}BrM+H]^+$), 396 (30 %, $[^{81}BrM+H]^+$); HRMS found 393.9793, $C_{14}H_{20}BrI$ requires 393.9788.

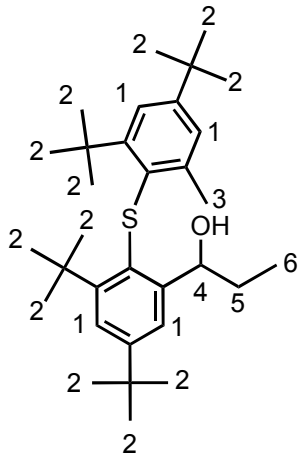
1-(3,5-di-*tert*-butyl-2-(2,4-di-*tert*-butyl-6-methylphenylthio)phenyl)ethanol (259)



Bromide **150** (0.08 g, 0.16 mmol, 1 equiv.), *n*-BuLi (2.1 M in hexanes) (0.08 cm^3, 0.16 mmol, 1 equiv.) and acetaldehyde (0.03 cm^3, 0.4 mmol, 2.5 equiv.) were treated as described in general procedure L. Reaction mixture was diluted using ether and the organic phase washed with water (3 × 20 cm^3) and brine (20 cm^3), dried over $MgSO_4$ and solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (25:1 petrol:ethyl acetate) to yield the title compound as a colourless oil (13 mg, 18%) and as a mixture of diastereomers: crude ^1H NMR shows the ratio as 2:1.

Major diastereomer: R_f = 0.40 (9:1 petrol:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.41-7.35 (2H, m, H-1), 7.31 (1H, d, *J* 2, H-1), 6.94 (1H, d, *J* 2, H-1), 4.94 (1H, dq, *J* 6.5 and 2.5, H-4), 1.66 (9H, s, H-2), 1.65 (9H, s, H-2), 1.64 (3H, s, H-3), 1.32 (9H, s, H-2), 1.29 (9H, s, H-2) and 1.16 (3H, d, *J* 6.5, H-5).; ES+ *m/z* 491.5 (M + Na);

1-(3,5-di-*tert*-butyl-2-(2,4-di-*tert*-butyl-6-methylphenylthio)phenyl)propan-1-ol (260)

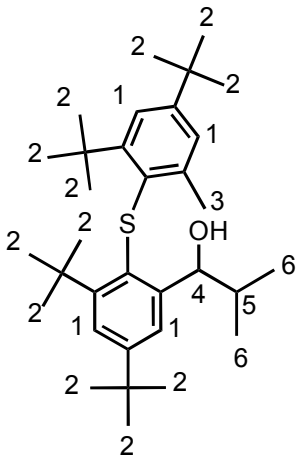


Bromide **250** (0.8 g, 0.16 mmol, 1 equiv.), *n*-BuLi (2.1 M in hexanes) (0.08 cm^3, 0.16 mmol, 1 equiv.) and propionaldehyde (0.03 cm^3, 0.4 mmol, 2.5 equiv.) were treated as described in general procedure L. Reaction mixture was diluted using ether and the organic phase washed with water (3 × 20 cm^3) and brine (20 cm^3), dried over $MgSO_4$ and solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (25:1 petrol:ethyl acetate) to yield the title compound as a colourless oil (18 mg, 23%) and as a mixture of diastereomers; Crude ^1H NMR shows the ratio as 2:1.

First eluted diastereomer (major diastereomer) (11mg, 14%); R_f = 0.6 (4:1 petrol:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.45 (1H, d, *J* 2, H-1), 7.39 (1H, d, *J* 2, H-1), 7.24 (1H, d, *J* 2, H-1), 6.90 (1H, d, *J* 2, H-1), 4.77 (1H, dd, *J* 10 and 2, H-4, 1.69 (9H, s, H-2), 1.68 (3H, s, H-3), 1.66 (9H, s, H-2), 1.42-1.40 (2H, m, H-5), 1.30 (9H, s, H-2), 1.29 (9H, s, H-2) and 0.41 (3H, t, *J* 7, H-6).; ES+ *m/z* 505.5 (M + Na).

Second eluted diastereomer (minor diastereomer): (7 mg, 9%); R_f = 0.55 (4:1 petrol:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.41 (1H, d, *J* 2, H-1), 7.38 (1H, d, *J* 2, H-1), 7.22 (1H, d, *J* 2, H-1), 6.92 (1H, d, *J* 2, H-1), 4.63 (1H, dt, *J* 7 and 3, H-4, 1.67 (9H, s, H-2), 1.65 (9H, s, H-2), 1.60 (3H, s, H-3), 1.40-1.37 (2H, m, H-5), 1.30 (9H, s, H-2), 1.28 (9H, s, H-2) and 0.60 (3H, t, *J* 7, H-6).; ES+ *m/z* 505.5 (M + Na).

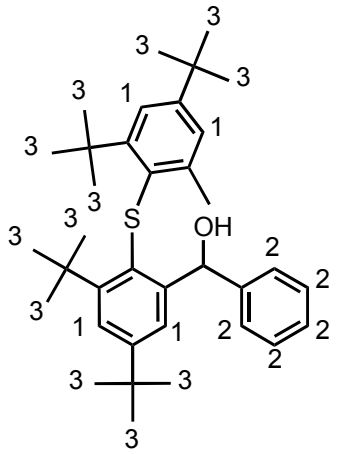
1-(3,5-di-*tert*-butyl-2-(2,4-di-*tert*-butyl-6-methylphenylthio)phenyl)-2-methylpropan-1-ol (261)



Bromide **250** (0.08 g, 0.16 mmol, 1 equiv.), *n*-BuLi (2.1 M in hexanes) (0.08 cm^3, 0.16 mmol, 1 equiv.) and isobutryaldehyde (0.04 cm^3, 0.4 mmol, 2.5 equiv.) were treated as described in general procedure L. Reaction mixture was diluted using ether and the organic phase washed with water (3 × 20 cm^3) and brine (20 cm^3), dried over $MgSO_4$ and solvent evaporated under reduced pressure .The crude product was purified by flash chromatography (25:1 petrol:ethyl acetate) to yield the title compound as a colourless oil (30 mg, 38%) and as a mixture of diastereomers; Crude ^1H NMR shows the ratio as 6:1.

Major diastereomer: R_f = 0.48 (9:1 petrol:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.4 (1H, d, *J* 2, H-1), 7.37 (1H, d, *J* 2, H-1), 7.18 (1H, d, *J* 2, H-1), 6.9 (1H, d, *J* 2, H-1), 4.23 (1H, dd, *J* 9.8 and 3.3, H-4), 1.67 (9H, s, H-2), 1.64 (9H, s, H-2), 1.56 (3H, s, H-3), 1.30 (9H, s, H-2, 1.28 (9H, s, H-2), 0.90 (3H, d, *J* 6.5, H-6), 0.75-0.73 (1H, m, H-5) and 0.37 (3H, d, *J* 6.5, H-6).; ES+ *m/z* 519.6 (M+ Na).

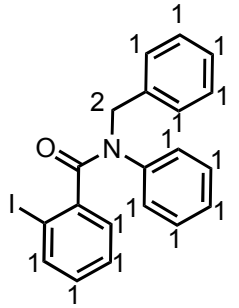
(3,5-di-tert-butyl-2-(2,4-di-tert-butyl-6- ethylphenylthio)phenyl)(phenyl)methanol (262)



Bromide **250** (0.03 g, 0.06 mmol, 1 equiv.), *n*-BuLi (2.1 M in hexanes) (0.03 cm^3, 0.06 mmol, 1 equiv.) and benzaldehyde (0.015 cm^3, 0.15 mmol, 2.5 equiv.) were treated as described in general procedure L. Reaction mixture was diluted using ether and the organic phase washed with water (3 × 20 cm^3) and brine (20 cm^3), dried over $MgSO_4$ and solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (25:1 petrol:EtOAc) to yield the title compound as a white foam (21 mg, 68%).

R_f = 0.71 (4:1 petrol:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.41 (1H, d, *J* 2, H-1), 7.36 (1H, d, *J* 2, H-1), 7.21-7.17 (2H, m, H-2), 7.14-7.07 (3H, m, H-2), 7.00 (1H, d, *J* 2, H-1), 6.93 (1H, d, *J* 2, H-1), 5.97 (1H, d, *J* 4, H-4, 1.72 (3H, s, H-5), 1.68 (9H, s, H-3), 1.63 (9H, s, H-3), 1.30 (9H, s, H-3) and 1.15 (9H, s, H-3).; δ_C (100 MHz, $CDCl_3$) 150.0, 149.7, 149.6, 148.7, 145.3, 144.8, 139.7, 135.3, 133.14, 127.7, 127.1, 126.0, 125.8, 125.3, 123.6, 122.9, 72.5, 37.7, 37.7, 34.6, 34.6, 31.3, 31.2, 31.1, 30.9 and 22.5.; CI *m/z* 513 (20 %, $[M\text{-}OH]^+$), 530 (30 %, $[M]^+$); HRMS found 530.3578, $C_{36}H_{50}OS$ requires 530.3577.

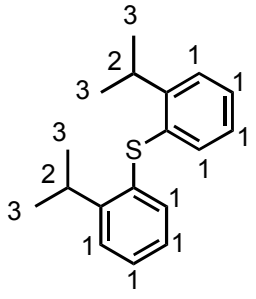
N-benzyl-2-iodo-N-phenylbenzamide (272)



2-iodobenzoylchloride (0.29 g, 1.09 mmol, 1 equiv) was dissolved in DCM (10 cm^3) and a solution of *N*-phenylbenzylamine (0.20 g, 1.09 mmol, 1.0 equiv) and triethylamine (1 cm^3) in DCM (6 cm^3) added dropwise at RT and stirred for 16 hours. The organic phase was washed with water and brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (9:1 petrol:EtOAc) to yield the amide as light yellow oil (0.02 g, 5%).

R_f = 0.32 (4:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 1646 (amide C=O).; δ_H (400 MHz; $CDCl_3$) 7.70 (1H, d, *J* 8, H-1), 7.40-7.34 (3H, m, H-1), 7.32-7.25 (3H, m, H-1), 7.12-6.99 (6H, m, H-1), 6.80 (1H, dt, *J* = 8 and 1.5, H-1), and 5.14 (2H, s, H-2, H-2).; ES+ *m/z* 436 (M+Na). *VT NMR;* In $CDCl_3$ run from -50 to 40 ºC, modeling benzylic protons decoalescence observed at 0 and -20 ºC.

bis(2-isopropylphenyl)sulfane[135,167] **(289a)**

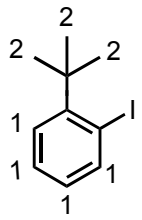


Following the procedure reported by Buchwald[135] 2-*i*-propyl thiophenol (1 g, 5.5 mmol, 1.2 equiv.), 2-*i*-propyl iodobenzene (1.21 g, 4.6 mol, 1.0 equiv.), copper(I) iodide (1.05 g, 5.5 mmol, 1.2 equiv.), ethylene glycol (0.55 cm^3) and *tert*-amyl alcohol (6 cm^3) were charged to a flask fitted with a reflux condenser and stirred at 120 ºC under an

atmosphere of nitrogen for 18 h. The reaction was allowed to cool to RT and diluted with EtOAc (20 cm^3). Organic phase was washed with water (3 × 20 cm^3) and brine (20 cm^3) dried over $MgSO_4$ and solvents removed under reduced pressure. The crude product was purified by flash chromatography (petrol) to yield the title compound as a colourless oil (1.13 g, 85%).

δ_H (500 MHz, $CDCl_3$) 7.21 (2H, d, 8, H-1), 7.13-7.10 (2H, m, H-1), 6.96-6.95 (4H, m, H-1), 3.41 (2H, sept, *J* 6.5, H-2) and 1.13 (12H, d, *J* 6.5, H-3).; δC (125 MHz, $CDCl_3$) 149.0, 134.1, 131.9, 127.4, 126.5, 125.7, 30.5, 23.4; Analyses matched the reported data.[135]

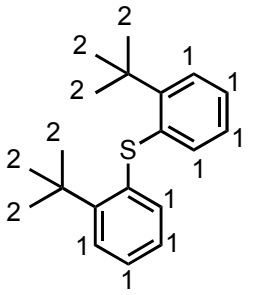
1-tert-butyl-2-iodobenzene[168]



Following the procedure reported by Howell *et al.*[155] *t*-butyl aniline (25 g, 0.17 mol, 1 equiv.) was slowly added to 3 M H_2SO_4 solution (250 cm^3) at -15 °C with overhead mechanical stirring. A saturated solution of sodium nitrite (12.1 g, 0.18 mol, 1.05 equiv.) was added dropwise over 30 min with vigorous stirring. The reaction mixture was rapidly added to a solution of potassium iodide (75 g) in water (100 cm^3) at 0 °C and stirred for 2 h. Reaction mixture was diluted using ether and the organic phase washed with water (2 × 100 cm^3) and brine (100 cm^3), dried over $MgSO_4$ and solvents removed under reduced pressure. The crude product was purified by flash chromatography (petrol) to yield the title compound as a colourless oil (8.8 g, 20 %).

δ_H (500 MHz, $CDCl_3$) 8.09 (1H, d, *J* 7.5, H-1), 7.53 (1H, d, *J* 7.5, H-1), 7.36 (1H, t, *J* 7.5, AH-1), 6.89 (1H, t, *J* 7.5, H-1) and 1.65 (9H, s, H-2).; Analyses matched the reported data.[168]

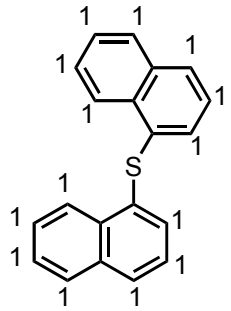
bis(2-tert-butylphenyl)sulfane (189b)



Following a modified procedure reported by Buchwald[135] 2-*t*-Butyl thiophenol (1 g, 5.1 mmol, 1.2 equiv.), 2-*t*-Butyl iodobenzene (1.30 g, 4.24 mmol, 1 equiv.), copper(I) iodide (0.23 g, 5.1 mmol, 1.2 equiv.), ethylene glycol (0.67 cm^3) and *tert*-amyl alcohol (6 cm^3) were charged to a flask fitted with a reflux condenser and stirred at 120 ºC under an atmosphere of nitrogen for 18 h. The reaction mixture was allowed to cool to RT and diluted with ethyl acetate (20 cm^3). Organic phase was washed with water (3 × 20 cm^3) and brine (20 cm^3), dried over $MgSO_4$ and solvents removed under reduced pressure. The crude product was purified by flash chromatography (petrol) to yield the title compound as a colourless oil (1.31 g, 88%).

R_f = 0.37 (petrol); δ_H (500 MHz, $CDCl_3$) 7.54 (2H, d, 8, H-1), 7.28-7.20 (2H, m, H-1), 7.16-7.10 (4H, m, H-1) and 1.68 (18H, s, H-2).; δ_C (125 MHz, $CDCl_3$) 150.0, 137.0, 135.1, 126.7, 126.6, 126.5, 36.5 and 30.5; EI *m/z* 298 (70 %, $[M]^+$); HRMS found 298.1751, $C_{20}H_{26}S$ requires 298.1750.

Dinaphthalen-1-ylsulfane[169](289c)

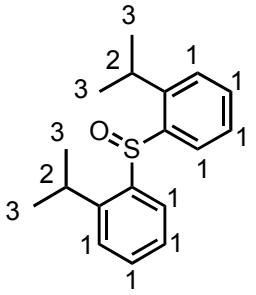


Following a modified procedure reported by Buchwald[135] naphthalene-1-thiol (1.0 g, 6.24 mmol, 1.2 equiv.), 1-iodonaphthalene (1.0 cm^3, 5.2 mmol, 1 equiv.), copper(I)

iodide (0.24 g, 6.24 mmol, 1.2 equiv.), ethylene glycol (0.70 cm^3) and *tert*-amyl alcohol (6.5 cm^3) were charged to a flask fitted with a reflux condenser and stirred at 120 ºC under an atmosphere of nitrogen for 18 h. The reaction was allowed to cool to RT and diluted with EtOAc (20 cm^3). Organic phase was washed with water (3 × 20 cm^3) and brine (20 cm^3) dried over $MgSO_4$ and solvents removed under reduced pressure. The crude product was purified by flash chromatography (petrol) to yield the title compound as a white solid (1.60 g, 90 %).

m.p. found 108-111 ˚C, lit. 110 ˚C;[169] δ_H (400 MHz, $CDCl_3$) 8.42-8.39 (2H, m, H-1), 7.90-7.86 (2H, m, H-1), 7.54-7.48 (4H, m, H-1), and 7.33-7.27 (4H, m, H-1).; δ_C (100 MHz, $CDCl_3$) 129.9, 128.6, 128.0, 126.8, 126.4, 125.9 and 125.1. Analyses matched the published data.[169]

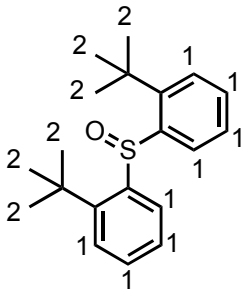
2,2'-sulfinylbis(isopropylbenzene (190a)



Sulfide **189a** (0.09 g, 0.33 mmol, 1 equiv.), *m*CPBA (0.057 g, 0.33 mmol, 1 equiv.) and DCM were treated as described in general procedure N for 2 hours. The crude product was purified by flash column chromatography (9:1 petrol:EtOAc) to yield the title compound as a clear film (0.089 g, 95%).

R_f = 0.15 (9:1 petrol:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.67 (2H, dd, *J* 8 and 1, H-1), 7.45 (2H, dd *J* 8 and 1, H-1), 7.32-7.28 (4H, m, H-1), 3.44 (2H, sept, *J* 6.5, H-2), 1.33 (6H, d, *J* 6.5, H-3) and 1.00 (6H, d, *J* 6.5, H-3).; δ_C (100 MHz, $CDCl_3$)147.3, 133.5, 131.6, 127.2, 126.3, 126.2, 29.4, 24.5 and 22.7.; ES+ *m/z* 309.2 (M + Na); HRMS found M 287.1467, $C_{18}H_{23}OS$ requires 287.1465.

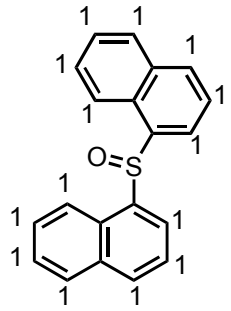
2,2'-sulfinylbis(*tert*-butylbenzene) (190b)



Sulfide **189b** (0.19 g, 0.65 mmol, 1 equiv.) *m*CPBA (0.11 g, 0.65 mmol, 1 equiv.) and DCM were treated as described in general procedure N for 2 hours. The crude product was purified by flash column chromatography (9:1 petrol:EtOAc) to yield the title compound as a white solid (0.19 g, 93%).

m.p. 150 – 152 °C; Rf = 0.20 (9:1 petrol:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* 8, H-1), 7.59-7.54 (2H, m, H-1), 7.46-7.41 (2H, m, H-1), 7.35-7.31 (2H, m, H-1) and 1.54 (18H, s, H-2).; δ_C (100 MHz, $CDCl_3$) 149.7, 142.2, 133.6, 128.9, 127.9, 37.0 and 32.5.; ES+ *m/z* 315.2 (M) and 337.2 (M + Na); HRMS found M 315.1772, $C_{20}H_{26}OS$ requires 315.1778.

1,1'-sulfinyldinaphthalene (190c)



Sulfide **189c** (0.10 g, 0.35 mmol, 1 equiv.), *m*CPBA (0.06 g, 0.35 mmol, 1 equiv.) and DCM were treated as described in general procedure N for 2 hours. The crude product was purified by flash column chromatography (9:1 petrol:EtOAc) to yield the title compound as a white solid (95 mg, 90%).

m.p. 162 – 164 °C; R_f = 0.19 (9:1 petrol:EtOAc); δ_H (400 MHz, $CDCl_3$) 8.36-8.33 (2H, m, H-1), 8.07 (2H, dd, *J* 8 and 1, H-1), 7.97 (2H, d, *J* 8, H-1), 7.90-7.88 (2H, m, H-1) and 7.60-7.50 (6H, m, H-1).; δ_C (100 MHz, $CDCl_3$) 139.5, 133.7, 132.1, 129.9, 129.0, 127.7, 126.8, 125.7, 125.6 and 122.6.; ES+ *m/z* 303.1 (M + Na); HRMS found M 303.0837, $C_{20}H_{14}OS$ requires 303.0839.

5.3 Biocatalysis Procedures

Galactose oxidase (GOase) expression and purification

Cultures of 800 ml LB media (containing 100 μg/ml ampicillin) were inoculated with 5 ml preculture (OD = 0.5-0.6) containing the GOase M_{3-5} *Escherichia coli* clone. The cells were harvested after overnight incubation at 26 °C and lysed by sonification. The Ni-NTA purification and subsequent copper activation of the proteins were performed as previously described.[101] From SDS-PAGE analysis and subsequent Coomassie staining more than 95% pure protein was acquired with a molecular mass of approximately 71 KDa, identical to the theoretical mass of the histidine-tagged GOase variants. Protein concentrations were determined by measuring the absorbance at 280 nm (ε = 1.05 x 105 M-1). Yields of approximately 7-8 mg pure protein/L culture were obtained.

Determination of GOase activity for diols 119a-d

The specific activity, kinetics constants and conversion rates of the purified enzymes were measured using a ABTS-HRP coupled assay.[170] For the initial activity measurements, 20 μl protein (12.5 nM final concentration) were mixed with 50 mM substrate in 250 mM NaP (pH 7.0) that contained 0.5 U HRP (Sigma Aldrich) and 0.1 mg ABTS (Pierce) in a 96-well plate (200 μl total volume). Product formation was measured at 420 nm in a SpectraMax M2 (Molecular Devices) plate reader at 30°C in triplicate in at least three independent experiments.

***Cu^{2+} preincubation**:*

Cu^{2+} preincubation of old M_{3-5} sample: Galactose oxidase is a copper dependent oxidase. The enzyme needs to be preincubated with copper prior to the assay:

6.06 μL $GaoAM_{3-5}$ (5.69 mg/mL) + 994 μL water + 0.62 μL $CuSO_4$ 80 mM

→ $GaoAM_{3-5}$ final concentration: 34.5 μg/mL ↔ 0.5 μM (MW = 68000 Da)

→ Cu^{2+} final concentration: 50 μM

The mixture was vortexed for 30 min at room temperature and then diluted 5 times with water (final concentration: 6.9 μg/mL ↔ 0.1 μM)

***Colorimetric assay protocol**:*

The enzymatic assay is based on the oxidase-catalysed H_2O_2 formation; H_2O_2 release is then coupled with a peroxidase-based assay (peroxidase + peroxidase substrate ↔

ABTS) producing a coloured pigment (green colour using ABTS as peroxidase substrate). The kinetics can be measured by following the absorbance increase at 420 nm when ABTS is used.

Since the 4 compounds ***119a-d*** are not soluble in water, a 0.4 M stock solution in DMSO was prepared.

Assay components	Assay	Control – GaoA	Control - substrate
ABTS solution	100 µL	100 µL	100 µL
water	74 µL	94 µL	74 µL
DMSO	-	-	5 µL
Peroxidase (1 mg/mL)	1 µL	1 µL	1 µL
Substrate (0.4 M in DMSO)	5 µL	5 µL	-
$GaoAM_{3\text{-}5}$ (6.9 µg/mL)	20 µL	-	20 µL

For each substrate, solution corresponding to 5 assays prepared and aliquoted in wells (3 x 175 µL or 3 x 195 µL for control - GaoA), then 5 µL of substrate added to the assay mixture and 20 µL of GaoA protein added to initiate the reaction using a multi-channel pipetman.

Measurement and rate calculation

- λ = 420 nm, length: 0-3600 sec
- Plate and GaoA samples preincubated at 30˚C for 15 min before assay
- Rate calculation:

$Vi_{max} = Vi_{max\text{-}obs}$ – control without GaoA – control without Substrate

Then average on the triplicate

GOase catalysed oxidation of diaryl ethers 119d and 140

For the desymmetrisation of diol **119d** and kinetic resolution of monoaldehyde **140**, the following components were placed in a glass tube; substrate (10 mM), DMSO (30% v/v), horse radish peroxidase (1mg), catalase (0.1mg), in sodium phosphate buffer (100mM, pH 7.0) total volume = 1mL. Oxygen was bubbled through the solution for 5 min prior to the addition of purified GOase $M_{3\text{-}5}$ variant (2mg). Parafilm was wrapped around the rubber septum of the tube in order to reduce leakage of oxygen. The reaction was shaken at 30 °C and 250 rpm. The desymmetrisation reactions were monitored by

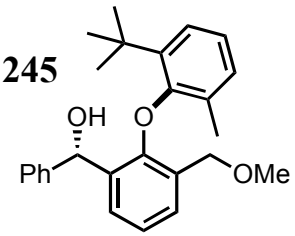
normal phase HPLC; 50 µl of sample were taken and 200 µl of MTBE was added. The sample was then thoroughly mixed in an Eppendorf tube and the upper-layer was transferred to another Eppendorf tube, volatiles were removed under reduced pressure and 100µl of ethanol was added. The solution was then transferred into a 2 mL HPLC vial with 0.2 mL insert and both conversion and ee determined.

The kinetic resolution reactions were monitored by both reverse phase HPLC (conversion) and normal phase HPLC (ee) analysis; For reverse phase analysis, 50 µl of sample was taken and 50 µl of acetonitrile was added. The sample was then thoroughly mixed in an Eppendorf tube and centrifuged for 2 minutes. The supernatant was taken and transferred to a 2 ml HPLC vial with a 0.45 µm filter and analysed by reverse phase HPLC.

Reduction of dialdehyde 118d using ketoreductases (KREDs)

For the reduction of the dialdehyde **118d** using ketoreductases the following components were placed in a glass tube; substrate **118d** (5mg, 17 mM), DMSO (30% v/v), KRED enzyme (5mg), glucose dehydrogenase (CDX-901, 1mg), $NADP^+$ (1mg), glucose (3.8 mg, 1.25 mol excess relative to substrate), in potassium phosphate buffer (100 mM, pH 7.0), total volume = 1 ml. The reaction mixture was shaken at 30 °C and 250 rpm. Both conversion and ee were monitored by normal phase HPLC.

5.4 X-Ray Crystal Data and structure refinement for 245



Identification code	s2953m
Empirical formula	C26 H30 O3
Formula weight	390.50
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 9.7218(9) A alpha = 90 deg. b = 15.3255(15) A beta = 108.148(2) deg. c = 14.8135(15) A gamma = 90 deg.
Volume	2097.3(4) A^3
Z, Calculated density	4, 1.237 Mg/m^3
Absorption coefficient	0.079 mm^-1
F(000)	840
Crystal size	0.35 x 0.30 x 0.15 mm
Theta range for data collection	1.96 to 28.31 deg.
Limiting indices	-12<=h<=12, -20<=k<=19, -19<=l<=19
Reflections collected / unique	17951 / 4993 [R(int) = 0.0568]
Completeness to theta = 25.00	100.0 %
Absorption correction	None
Max. and min. transmission	0.9882 and 0.9728
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4993 / 0 / 268
Goodness-of-fit on F^2	1.016
Final R indices [I>2sigma(I)]	R1 = 0.0532, wR2 = 0.1006
R indices (all data)	R1 = 0.0773, wR2 = 0.1092
Largest diff. peak and hole	0.297 and -0.264 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for s2953m.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	6096(2)	2517(1)	3737(1)	15(1)
C(2)	7461(2)	2606(1)	3598(1)	15(1)
C(3)	7573(2)	3240(1)	2949(1)	18(1)
C(4)	6406(2)	3757(1)	2467(1)	20(1)

C(5)	5104(2)	3660(1)	2638(1)	19(1)
C(6)	4913(2)	3053(1)	3289(1)	16(1)
C(7)	8788(2)	2048(1)	4127(1)	16(1)
C(8)	10131(2)	2300(1)	3849(1)	23(1)
C(9)	8495(2)	1075(1)	3879(1)	22(1)
C(10)	9176(2)	2178(1)	5204(1)	24(1)
C(11)	3478(2)	3031(1)	3486(1)	21(1)
C(12)	4823(2)	1371(1)	4319(1)	15(1)
C(13)	4075(2)	948(1)	3475(1)	16(1)
C(14)	2898(2)	429(1)	3478(1)	18(1)
C(15)	2537(2)	288(1)	4295(1)	20(1)
C(16)	3346(2)	682(1)	5138(1)	17(1)
C(17)	4484(2)	1232(1)	5160(1)	15(1)
C(18)	4498(2)	1006(1)	2580(1)	18(1)
C(19)	4461(2)	151(1)	1239(1)	29(1)
C(20)	5332(2)	1699(1)	6075(1)	16(1)
C(21)	4872(2)	2647(1)	6038(1)	17(1)
C(22)	5802(2)	3320(1)	5992(1)	24(1)
C(23)	5344(2)	4182(1)	5947(1)	30(1)
C(24)	3960(2)	4376(1)	5949(1)	31(1)
C(25)	3025(2)	3708(1)	5996(1)	28(1)
C(26)	3482(2)	2847(1)	6042(1)	21(1)
O(1)	6020(1)	1901(1)	4419(1)	16(1)
O(2)	4002(1)	228(1)	2051(1)	21(1)
O(3)	5053(1)	1331(1)	6883(1)	21(1)

Table 3. Bond lengths [A] and angles [deg] for s2953m.

C(1)-C(6)	1.401(2)
C(1)-O(1)	1.4014(17)
C(1)-C(2)	1.411(2)
C(2)-C(3)	1.395(2)
C(2)-C(7)	1.543(2)
C(3)-C(4)	1.386(2)
C(3)-H(3)	0.9500
C(4)-C(5)	1.374(2)
C(4)-H(4)	0.9500
C(5)-C(6)	1.394(2)
C(5)-H(5)	0.9500
C(6)-C(11)	1.512(2)
C(7)-C(10)	1.534(2)
C(7)-C(8)	1.535(2)
C(7)-C(9)	1.541(2)
C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-O(1)	1.3883(17)
C(12)-C(13)	1.396(2)
C(12)-C(17)	1.400(2)
C(13)-C(14)	1.395(2)
C(13)-C(18)	1.508(2)
C(14)-C(15)	1.377(2)
C(14)-H(14)	0.9500
C(15)-C(16)	1.390(2)
C(15)-H(15)	0.9500
C(16)-C(17)	1.383(2)
C(16)-H(16)	0.9500

C(17)-C(20)	1.527(2)
C(18)-O(2)	1.4255(17)
C(18)-H(18A)	0.9900
C(18)-H(18B)	0.9900
C(19)-O(2)	1.4127(18)
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(20)-O(3)	1.4229(17)
C(20)-C(21)	1.517(2)
C(20)-H(20)	1.0000
C(21)-C(26)	1.387(2)
C(21)-C(22)	1.388(2)
C(22)-C(23)	1.389(2)
C(22)-H(22)	0.9500
C(23)-C(24)	1.379(3)
C(23)-H(23)	0.9500
C(24)-C(25)	1.385(3)
C(24)-H(24)	0.9500
C(25)-C(26)	1.386(2)
C(25)-H(25)	0.9500
C(26)-H(26)	0.9500
O(3)-H(3A)	0.8400

C(6)-C(1)-O(1)	121.04(13)
C(6)-C(1)-C(2)	123.02(14)
O(1)-C(1)-C(2)	115.73(13)
C(3)-C(2)-C(1)	116.54(14)
C(3)-C(2)-C(7)	120.24(13)
C(1)-C(2)-C(7)	123.22(13)
C(4)-C(3)-C(2)	121.78(15)
C(4)-C(3)-H(3)	119.1
C(2)-C(3)-H(3)	119.1
C(5)-C(4)-C(3)	119.76(14)
C(5)-C(4)-H(4)	120.1
C(3)-C(4)-H(4)	120.1
C(4)-C(5)-C(6)	121.91(14)
C(4)-C(5)-H(5)	119.0
C(6)-C(5)-H(5)	119.0
C(5)-C(6)-C(1)	116.89(14)
C(5)-C(6)-C(11)	118.55(14)
C(1)-C(6)-C(11)	124.54(14)
C(10)-C(7)-C(8)	107.05(13)
C(10)-C(7)-C(9)	109.89(13)
C(8)-C(7)-C(9)	106.78(13)
C(10)-C(7)-C(2)	110.66(12)
C(8)-C(7)-C(2)	111.78(12)
C(9)-C(7)-C(2)	110.55(12)
C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
C(7)-C(9)-H(9A)	109.5
C(7)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(7)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(7)-C(10)-H(10A)	109.5
C(7)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(7)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(6)-C(11)-H(11A)	109.5
C(6)-C(11)-H(11B)	109.5

H(11A)-C(11)-H(11B)	109.5
C(6)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
O(1)-C(12)-C(13)	123.50(13)
O(1)-C(12)-C(17)	114.61(13)
C(13)-C(12)-C(17)	121.70(13)
C(14)-C(13)-C(12)	117.40(14)
C(14)-C(13)-C(18)	119.06(14)
C(12)-C(13)-C(18)	123.52(13)
C(15)-C(14)-C(13)	121.76(15)
C(15)-C(14)-H(14)	119.1
C(13)-C(14)-H(14)	119.1
C(14)-C(15)-C(16)	119.58(15)
C(14)-C(15)-H(15)	120.2
C(16)-C(15)-H(15)	120.2
C(17)-C(16)-C(15)	120.68(14)
C(17)-C(16)-H(16)	119.7
C(15)-C(16)-H(16)	119.7
C(16)-C(17)-C(12)	118.70(14)
C(16)-C(17)-C(20)	120.84(14)
C(12)-C(17)-C(20)	120.44(13)
O(2)-C(18)-C(13)	107.21(12)
O(2)-C(18)-H(18A)	110.3
C(13)-C(18)-H(18A)	110.3
O(2)-C(18)-H(18B)	110.3
C(13)-C(18)-H(18B)	110.3
H(18A)-C(18)-H(18B)	108.5
O(2)-C(19)-H(19A)	109.5
O(2)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
O(2)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
O(3)-C(20)-C(21)	106.19(12)
O(3)-C(20)-C(17)	111.67(12)
C(21)-C(20)-C(17)	110.20(12)
O(3)-C(20)-H(20)	109.6
C(21)-C(20)-H(20)	109.6
C(17)-C(20)-H(20)	109.6
C(26)-C(21)-C(22)	119.08(15)
C(26)-C(21)-C(20)	119.27(14)
C(22)-C(21)-C(20)	121.65(14)
C(21)-C(22)-C(23)	120.36(16)
C(21)-C(22)-H(22)	119.8
C(23)-C(22)-H(22)	119.8
C(24)-C(23)-C(22)	120.21(16)
C(24)-C(23)-H(23)	119.9
C(22)-C(23)-H(23)	119.9
C(23)-C(24)-C(25)	119.78(16)
C(23)-C(24)-H(24)	120.1
C(25)-C(24)-H(24)	120.1
C(24)-C(25)-C(26)	120.07(16)
C(24)-C(25)-H(25)	120.0
C(26)-C(25)-H(25)	120.0
C(25)-C(26)-C(21)	120.51(16)
C(25)-C(26)-H(26)	119.7
C(21)-C(26)-H(26)	119.7
C(12)-O(1)-C(1)	123.27(11)
C(19)-O(2)-C(18)	113.31(12)
C(20)-O(3)-H(3A)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for s2953m.
The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(1)	18(1)	14(1)	12(1)	1(1)	5(1)	-3(1)
C(2)	15(1)	15(1)	14(1)	-3(1)	4(1)	-1(1)
C(3)	19(1)	17(1)	20(1)	-2(1)	9(1)	-3(1)
C(4)	28(1)	15(1)	19(1)	4(1)	9(1)	1(1)
C(5)	20(1)	16(1)	19(1)	0(1)	3(1)	4(1)
C(6)	17(1)	17(1)	15(1)	-4(1)	5(1)	0(1)
C(7)	14(1)	17(1)	18(1)	2(1)	5(1)	0(1)
C(8)	16(1)	25(1)	27(1)	4(1)	7(1)	1(1)
C(9)	20(1)	19(1)	28(1)	3(1)	8(1)	3(1)
C(10)	17(1)	32(1)	20(1)	2(1)	3(1)	1(1)
C(11)	16(1)	23(1)	23(1)	2(1)	5(1)	4(1)
C(12)	11(1)	13(1)	21(1)	2(1)	5(1)	1(1)
C(13)	14(1)	14(1)	20(1)	3(1)	4(1)	3(1)
C(14)	15(1)	17(1)	20(1)	-1(1)	3(1)	1(1)
C(15)	15(1)	16(1)	28(1)	1(1)	8(1)	-1(1)
C(16)	17(1)	16(1)	22(1)	3(1)	10(1)	2(1)
C(17)	14(1)	13(1)	19(1)	2(1)	5(1)	4(1)
C(18)	18(1)	17(1)	18(1)	0(1)	4(1)	-3(1)
C(19)	42(1)	26(1)	24(1)	-6(1)	17(1)	-7(1)
C(20)	15(1)	19(1)	16(1)	1(1)	7(1)	0(1)
C(21)	20(1)	19(1)	10(1)	-1(1)	3(1)	0(1)
C(22)	22(1)	24(1)	22(1)	1(1)	2(1)	-2(1)
C(23)	35(1)	20(1)	27(1)	0(1)	-3(1)	-8(1)
C(24)	43(1)	19(1)	25(1)	-4(1)	0(1)	7(1)
C(25)	29(1)	30(1)	25(1)	-3(1)	8(1)	10(1)
C(26)	23(1)	23(1)	19(1)	0(1)	7(1)	1(1)
O(1)	14(1)	19(1)	16(1)	4(1)	4(1)	-3(1)
O(2)	27(1)	19(1)	19(1)	-5(1)	9(1)	-6(1)
O(3)	25(1)	21(1)	18(1)	4(1)	10(1)	5(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for s2953m.

	x	y	z	U(eq)
H(3)	8474	3320	2835	22
H(4)	6506	4177	2020	24
H(5)	4311	4018	2303	23
H(8A)	10372	2913	4011	34
H(8B)	9929	2217	3164	34
H(8C)	10948	1930	4194	34
H(9A)	9341	730	4229	33
H(9B)	8305	992	3195	33
H(9C)	7650	885	4055	33
H(10A)	9364	2797	5357	36
H(10B)	10042	1837	5526	36
H(10C)	8368	1982	5417	36
H(11A)	2966	3583	3283	32
H(11B)	3647	2949	4169	32
H(11C)	2892	2548	3135	32
H(14)	2330	166	2902	22
H(15)	1741	-77	4282	24
H(16)	3114	573	5705	21
H(18A)	4047	1524	2204	22
H(18B)	5562	1057	2739	22
H(19A)	4134	661	829	44
H(19B)	4047	-379	889	44

H(19C)	5520	117	1435	44
H(20)	6391	1665	6158	20
H(22)	6757	3191	5990	29
H(23)	5987	4640	5914	36
H(24)	3648	4966	5919	38
H(25)	2071	3840	5996	33
H(26)	2838	2392	6076	26
H(3A)	5480	849	7014	31

Table 6. Torsion angles [deg] for s2953m.

C(6)-C(1)-C(2)-C(3)	-2.8(2)
O(1)-C(1)-C(2)-C(3)	-177.52(13)
C(6)-C(1)-C(2)-C(7)	176.77(14)
O(1)-C(1)-C(2)-C(7)	2.0(2)
C(1)-C(2)-C(3)-C(4)	0.1(2)
C(7)-C(2)-C(3)-C(4)	-179.45(14)
C(2)-C(3)-C(4)-C(5)	1.2(2)
C(3)-C(4)-C(5)-C(6)	0.1(2)
C(4)-C(5)-C(6)-C(1)	-2.6(2)
C(4)-C(5)-C(6)-C(11)	175.75(14)
O(1)-C(1)-C(6)-C(5)	178.44(13)
C(2)-C(1)-C(6)-C(5)	4.0(2)
O(1)-C(1)-C(6)-C(11)	0.2(2)
C(2)-C(1)-C(6)-C(11)	-174.24(14)
C(3)-C(2)-C(7)-C(10)	119.84(15)
C(1)-C(2)-C(7)-C(10)	-59.70(18)
C(3)-C(2)-C(7)-C(8)	0.6(2)
C(1)-C(2)-C(7)-C(8)	-178.91(14)
C(3)-C(2)-C(7)-C(9)	-118.18(15)
C(1)-C(2)-C(7)-C(9)	62.29(18)
O(1)-C(12)-C(13)-C(14)	179.44(13)
C(17)-C(12)-C(13)-C(14)	4.7(2)
O(1)-C(12)-C(13)-C(18)	1.2(2)
C(17)-C(12)-C(13)-C(18)	-173.51(14)
C(12)-C(13)-C(14)-C(15)	-4.2(2)
C(18)-C(13)-C(14)-C(15)	174.13(14)
C(13)-C(14)-C(15)-C(16)	1.1(2)
C(14)-C(15)-C(16)-C(17)	1.6(2)
C(15)-C(16)-C(17)-C(12)	-1.1(2)
C(15)-C(16)-C(17)-C(20)	177.21(13)
O(1)-C(12)-C(17)-C(16)	-177.32(12)
C(13)-C(12)-C(17)-C(16)	-2.2(2)
O(1)-C(12)-C(17)-C(20)	4.37(19)
C(13)-C(12)-C(17)-C(20)	179.51(13)
C(14)-C(13)-C(18)-O(2)	-25.12(18)
C(12)-C(13)-C(18)-O(2)	153.10(13)
C(16)-C(17)-C(20)-O(3)	14.83(19)
C(12)-C(17)-C(20)-O(3)	-166.89(13)
C(16)-C(17)-C(20)-C(21)	-102.94(16)
C(12)-C(17)-C(20)-C(21)	75.33(17)
O(3)-C(20)-C(21)-C(26)	-53.97(17)
C(17)-C(20)-C(21)-C(26)	67.14(17)
O(3)-C(20)-C(21)-C(22)	126.61(15)
C(17)-C(20)-C(21)-C(22)	-112.28(16)
C(26)-C(21)-C(22)-C(23)	-0.2(2)
C(20)-C(21)-C(22)-C(23)	179.23(14)
C(21)-C(22)-C(23)-C(24)	0.1(3)
C(22)-C(23)-C(24)-C(25)	0.0(3)
C(23)-C(24)-C(25)-C(26)	0.1(3)
C(24)-C(25)-C(26)-C(21)	-0.3(2)
C(22)-C(21)-C(26)-C(25)	0.3(2)
C(20)-C(21)-C(26)-C(25)	-179.15(14)
C(13)-C(12)-O(1)-C(1)	43.4(2)
C(17)-C(12)-O(1)-C(1)	-141.59(14)
C(6)-C(1)-O(1)-C(12)	42.6(2)

C(2)-C(1)-O(1)-C(12)	-142.54(13)
C(13)-C(18)-O(2)-C(19)	-173.64(13)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for s2953m [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3A)...O(2)#1	0.84	2.11	2.8539(15)	147.0

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,-y,-z+1

6. References

1. Eliel, E. L., Wilen, S. H. *Stereochemistry of organic compounds*, Wiley: New York, **1994**, 1119 and 1142
2. Christie, H.G., Kenner, J. H. *J. Chem. Soc*., **1922**, 121, 614
3. Ariens, E. J., Soudijn, W., Timmermans, P. B. M. W. M. Eds. *Stereochemistry and Biological Activity of Drugs* Blackwell Scientific Publications: Oxford, **1983**
4. Aitken, R. A., Kilenyi, S. N. *Asymmetric Synthesis* **1994**, 2
5. Crosby, J. *Tetrahedron* **1991**, 47, 4789
6. Kuhn, R. *Stereochemie* Frendenberg, K. Ed. Deutike, F. **1933**, 803
7. Bringmann G., Price Mortimer, A. J., Keller P. A., Gresser, M. J., Garner J., Breuning, M. *Angew. Chem. Int. Ed.* **2005**, 44, 5384
8. Aitken, R. A., Kilenyi, S. N. In *Asymmetric Synthesis* **1994**, 15
9. Oki, M; *Topics in Stereochemistry* **1983**, 1
10. Cooke, A. S., Harris, M. M. *J. Chem. Soc.* **1963**, 2365
11. Adams, R., Yuan, H. C., *Chem. Rev.* **1933**, 12, 261
12. Bennett, D. J., Blake, A. J., Cooke, P. A., Godfrey, C. R. A., Pickering, P. L., Simpkins, N. S., Walker, M. D., Wilson, C. *Tetrahedron* **2004**, 60, 4491; Kitagawa, O., Yoshikawa, M., Tamnabe, H., Morita, T., Takahashi, M., Dobashi, Y., Taguchi, T. *J. Am. Chem. Soc.* **2006**, 128, 12923, and references therein
13. Clayden, J., Turner, H., Helliwell, M., Moir, E. *J. Org. Chem*. **2008**, 73, 4415
14. Clayden, J., Senior, J., Helliwell, M. *Angew. Chem. Int. Ed.* **2009**, 48, 6270
15. Clayden, J., Senior, J. *Synlett* **2009**, 2769
16. Noyori, R., *Acta Chem. Scand.* **1996**, 50, 380
17. Brown, J. M., Hulmes, D. I., Guiry, P. J. *Tetrahedron* **1994**, 50, 4493; Alcock, N. W., Brown, J. M., Hulmes, D. I. *Tet. Asym*. **1993**, 4, 743-756
18. (a) Nicolaou, K. C., Boddy, C. N. C., Bräse, S., Winssinger, N. *Angew. Chem. Int. Ed.* **1999,** 38, 2096; (b) Nicolaou, K. C., Body, C. N. C. *J. Am. Chem Soc.* **2002**, 124, 10451
19. (a) Boger, D. L., Weng, J.-H., Miyazaki, S., McAtee, J. J., Castle, S. L., Kim, S. H., Mori, Y., Rogel, O., Strittmatter, H., Jin, Q. *J. Am. Chem. Soc.* **2000**, 122, 10047; Boger, D. L., Miyazaki, S., Loiseleur, O., Beresis, R. T., Castle, S. L., Win, J. H., Jin, Q. *J. Am. Chem. Soc.* **1998**, 120, 8920; Boger, D. L., Miyazaki, S., Kim, S. H., H.Wu, J., Loiseleur, O., Castle, S. L. *J. Am. Chem. Soc.* **1999**, 121, 3226; Boger, D. L., Miyazaki, S., Kim, S. H., H.Wu, J., Castle, S. L., Loiseleur, O., Jin, Q. *J. Am. Chem. Soc.* **1999**, 121, 10004; (b) Evans, D. A., Wood, M. R., Trottter, B. W., Richardson, T. I., Barrow, J. C., Katz, J. K. *Angew. Chem.* **1998**, 110, 2864; *Angew. Chem. Int. Ed.* **1998**, 37, 2700; (c) Boger, D. L., Nomoto, Y., Teegarden, B. R. *J. Org. Chem.* **1993**, 58, 1425
20. Couladouros, E. A., Pitsinos, E. N., Moutsos, V. I., Sarakinos, G. *Chem. Eur. J.* **2005**, 11, 406
21. Teague, S., Davis, A. M. *Angew. Chem. Int. Ed.* **1999**, 38, 737
22. Albert, J. S., Ohnmacht, C., Bernstein, P. R., Rumsey, W. L., Aharony, D., Masek, B. B., Dembofsky, B. T., Koether, G. M., Potts, W., Evenden, J. *Tetrahedron* **2004**, 60, 4337; Ikeura, Y., Ishimaru, T., Doi, T., Kawada, M., Fujishima, A., Natsugari, H. *Chem. Commun.* **1998**, 2141; Ishichi, Y., Ikeura, Y., Natsugari, H. *Tetrahedron* **2004**, 60, 4481
23. Ikeura, Y., Ishichi, Y., Tanaka, T., Fujishima, A., Murabayashi, M., Kawada, M., Ishimaru, T., Kamo, I., Doi, T. & Natsugari, H. *J. Med. Chem*. **1998**, 41, 4232
24. Giralt, E., Lloyd-Williams, P. *Chem. Soc. Rev.* **2001**, 30, 147
25. Kessler, H., Rieker, A., Rundel, W. *Chem. Commun.* **1968**, 475

26. Betson, M. S., Clayden, J., Worrall, C. P., Peace, S. *Angew. Chem. Int. Ed.* **2006**, 45, 5803

27. Adler, T., Bonjoch, J., Clayden, J., Font-Bardfa, M., Pickworth, M., Solans, X., Sole, D., Vallverdu, L. *Org. Biomol. Chem.* **2005**, 3, 3173

28. Curran, D. P., Qi, H., Geib, S. J., DeMello, N. C. *J. Am. Chem. Soc.* **1994**, 116, 3131

29. Clayden, J. P., Lai, L. W. *Angew. Chem. Int. Ed.* **1999**, 38, 2556

30. Cuyegkeng, M. A., Mannschreck, A. *Chem. Ber.* **1987**, 120, 803

31. Pinkus, A. G., Riggs, J. I., Broughton, S. M., *J. Am. Chem. Soc.* **1968**, 90, 5043; Michalik, J. *Chem. Soc. Perkin Trans. 2* **2002**, 114

32. Lam, W. Y., Martin, J. C. *J. Org. Chem.* **1981**, 46, 4458

33. Furusho, Y., Aida, T., Inoue, S. *Chem. Commun.* **1994**, 653

34. See for example Eveleigh, P., Hulme, E. C., Schudt, C., Birdsall, N. J. M. *Mol. Pharmacol.* **1989**, 35, 477; Guile, S. D., Bantick, J. R., Cooper, M. E., Donald, D. K., Eyssade, C., Ingall, A. H., Lewis, R. J., Martin, B. P., Mohammed, R. T., Potter, T. J., Reynolds, R. H., St-Gallay, S. A., Wright, A. D. J. *Med. Chem.* **2007**, 50, 254; Palani, A., Shapiro, S., Clader, J. W., Greenlee, W. J., Blythin, D., Cox, K., E.Wagner, N., Strizki, J., Baroudy, B. M., Dan, N. *Bioorg. Med. Chem. Lett*. **2003**, 13, 705

35. Clayden, J., Helliwell, M., Pink , J. H., Westlund, N. *J. Am. Chem. Soc.* **2001**, 123, 12449

36. Clayden, J., Stimson, C. C., Keenan, M., Wheatley, A. E. H. *Chem. Commun.* **2004**, 228

37. Beak, P., Kerrick, S. T., Gallagher, D. J. *J. Chem. Soc.* **1993**, 115, 10628

38. Betson, M. S., Clayden, J., Ho Kam Lam, Helliwell, M. *Angew. Chemie Int. Ed*. **2005**, 44, 1241

39. Clayden, J., Menet, C. J., Mansfield, D. J. *Org. Lett.* **2000**, 2, 4229

40. Clayden, J., Lund, A., Vallverdu, L., Helliwell, M. *Nature (London)*, **2004**, 431, 966

41. Fuji, K., Kawabata, T. *Chem. Eur. J.* **1998**, 373

42. Clayden, J., Stimson, C. C., Keenan, M. *Synlett* **2005**, 1716

43. Clayden, J., Worrall, C. P., Moran, W. J., Helliwell, M. *Angew. Chemie Int Ed.* **2008**, 47, 3234

44. Clayden, J. *Synlett*. **1998**, 810

45. Curran, D. P., Qi, H., Geib, S J., DeMello, N. C. *J. Am. Chem. Soc.* **1994**, 116, 3131; Hughes, A. D., Price, D. A., Shishkin O., Simpkins, N. S. *Tet. Lett*. **1996**, 37, 7607; Kitagawa, O., Izawa, H., Taguchi, T., Shiro, M. *Tet. Lett.* **1997**, 38, 4447

46. Bull, S. D., Davies, S. G., Epstein, S. W., Ouzman, J. V. A., *Chem. Commun.* **1998**, 659; Bull, S. D., Davies, S. G., Epstein, S. W., Leech, M. A., Ouzman, J. V. A. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 2321; Bull, S. D., Davies, S. G., Epstein, S. W., Fox, D. J., Sellers, T. G. R. *Tetrahedron: Asymmetry*, **1998**, 9, 1483

47. Corminboeuf, O., Quaranta, L., Renaud, P., Liu, M., Jasperse, C. P., Sibi, M. P. *Chem. Eur. J.* **2003**, 9, 29

48. Clayden, J. *Chem. Soc. Rev.* **2009**, 38, 817

49. Noyori, R. *Asymmetric catalysis in organic synthesis*; Wiley:New York, **1994**

50. Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503; Pu, L. *Chem. Rev*. **1998**, 98, 2405

51. For uses of non-biaryl atropisomers in catalysis, see: (a) Brandes, S., Niess, B., Bella, M., Prieto, A., Overgaard, J., Jørgensen, K. A. *Chem. Eur. J.* **2006**, 12, 6039; (b) Honda, A., Waltz, K. M., Carroll, P. J., Walsh, P. J. *Chirality* **2003**, 15, 615; Dai, W.-M., Yeing, K. K. Y., Liu, J.-T., Zhang, Y., Williams, I. D. *Org. Lett.* **2002**, 4, 1615; Dai, W.-M., Yeing, K. K. Y., Wang, Y. *Tetrahedron* **2004**, 60, 4425; Dai, W.-M., Li, Y., Zhang, Y., Yue, Z., Wu, J. H. *Chem. Eur. J.* **2008**, 14, 5538

52. (a) Birkholz, M.-N., Freixa, Z., van Leeuwen, P. W. N. *Chem. Soc. Rev.* **2009**, 38, 1099; Kamer, P. C. J., van Leeuwen, P. W. N. M., Reek, J. N. H. *Acc. Chem. Res.* **2001**, 34, 895; Kranenburg, M., ven der Burgt, Y. E. M., Kamer, P. C. J., van Leeuwen, P.W. N. M., Goubitz, K., J. Fraanje, J. *Organometallics***, 1995**, 14, 3081; (b) Kim, D., Park, B.-M., Yun, *J. Chem. Commun*. **2005**, 1755; Chea, H., Sim, H.-S., Yun, J. *Adv. Synth. Catal*. **2009**, 351, 855; (c) Takemiya, A., Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, 128, 14800; (d) Ward, A. F., Wolfe, J. P. *Org. Lett*. **2009**, 11, 2209; Hat, M. B., Hardin, A. R., Wolfe, J. P. *J. Org. Chem.* **2005**, 70, 3099; Peng, J., Lin, W., Yuan, S., Chen, Y. *J. Org. Chem*. **2007**, 72, 3145; (e) Utsunomiya, M., Miyamoto, Y., Ipposhi, J., Ohshima, T., Mashima, K. *Org. Lett.* **2007**, 9, 3371, Hamid, M. H. S. A., Allen, C. L., Lamb, G. W., Maxwell, A. C., Maytum, H. C., Watson, A. J. A., Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, 131, 1766; Johns, A. M., Utsunomiya, M., Incarvito, C. D., Hartwig, J. F. *J. Am. Chem. Soc*. **2006**, 128, 1828; Clayden, J., Hennecke, U. *Org. Lett*. **2008**, 10, 3567

53. Hamada, Y., Matsuura, F., Oku, M., Hatano, K., Shioiri, T. *Tetrahedron Lett.* **1997**, 38, 8961; Ramdeehul, S., Dierkes, P., Aguado, R., Kamer, P. C. J., van Leeuwen, P. W. N. M.; Osborn, J. A. *Angew. Chem., Int. Ed.* **1998**, 37, 3118; Dierkes, P., Ramdeehul, S., Barloy, L., De Cian, A., Fischer, J., Kamer, P. C. J., van Leeuwen, P. W. N. M., Osborn, J. A. *Angew. Chem., Int. Ed*. **1998**, 37, 3116

54. Clayden, J., Johnson, P., Pink, J. H., Helliwell, M. *J. Org. Chem*. **2000**, 65, 7033

55. Dai, W.-M., Yeing, K. K. Y., Liu, J.-T., Zhang, Y., Williams, I. D. *Org. Lett*. **2002**, 4, 1615; Dai, W.-M., Yeung, K. K. Y., Wang, Y. *Tetrahedron* **2004**, 60, 4425; Mino, T., Tanaka, Y., Hattori, Y., Yabusaki, T., Saotome, H., Sakamoto, M., Fujita, T. *J. Org. Chem*. **2006**, 71, 7346

56. Dalko, P. I., Moison, L., *Angew. Chem. Int. Ed.* **2000**, 40, 3726

57. Kitagawa, O., Yoshikawa, M., Tanabe, H., Monita, T., Takahashi, M., Dobashi, Y., Taguchi, T. *J. Chem. Soc.* **2006**, 128, 12923

58. Kitagawa, O., Kurihara, D., Tanabe, H., Shibuya, T., Taguchi, T. *Tetrahedron Lett.* **2008**, 49, 471

59. Bringmann G., Walter, R., Weirich, R. *Angew. Chem. Int. Ed.* **1990**, 29, 977

60. Bringmann G., Breuning, M., Tasler, S. *Synthesis* **1999**, 525

61. Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth*. **1989**, 67, 20.

62. Toda, F.; Tanaka, K.; Stein, Z.; Golderberg, I. *J. Org. Chem*. **1994**, 59, 5748

63. Bringman, G., Tasler, S., Endress, H., Kraus, J., Messer, K., Wohlfarth, M. Lobin, W. *J. Am. Chem. Soc.* **2001**, 123, 12, 2703

64. Malkov, A. V., Dufkova, L., Farrugia, L., Kocovsky, P. *Angew. Chem. Int. Ed.* **2003**, 42, 3674

65. Clayden, J., Turner, H. *Tetrahedron Lett.* **2009**, *50*, 3216

66. Itoh, T. *J. Org. Chem.* **1995**, 60, 4968; Kitagawa O., Fujita, M., Kohriya, M., Hasegawa, H., Taguchi, T. *Tetrahedron Lett.* **2000**, 41, 8539; Watanabe, T., Kamikawa, K., Uemura, M. *Tetrahedron Lett.* **1995**, 36, 6695; Rios, R., Jimeno, C., Carroll, P. J., Walsh, P. J. *J. Am. Chem. Soc.* **2002**, 124, 10272; Pamperin, D., Hopf, H., Syldatk, C., Pietzsch, M. *Tetrahedron Asymm.* **1997**, 8, 319; Pamperin, D., Schulz, C., Hopf, H., Syldatk, C., Pietzsch, M. *Eur. J. Org. Chem.* **1998**, 1441

67. Bracegirdle, A., Clayden, J., Lai, L. W. *Beilstein J. Org. Chem.* **2008**, 4, 47

68. (a) Bringmann, G., Pabst, T., Henschel, P., Kraus, J., Peters, K., Peters, E.-M., Rycroft, D. S., Connolly, J. D. *J. Am. Chem. Soc.* **2000,** 38, 9127; (b) Bringmann, G., Pfeifer, R.-M., Schreiber, P., Hartner, K., Schraut, M., Breuning, M. *Tetrahedron* **2004**, *60*, 4349; Bringmann, G., Menche, D. *Acc. Chem. Res.* **2001**, *34*, 615; Bringmann, G., Hinrichs, J., Pabst, T., Henschel, P., Peters, K., Peters, E.-M. *Synthesis* **2001**, 155

69. (a) Clayden, J. Lai, L. W. *Tetrahedron Lett.* **2001**, 42, 3163; (b) Clayden, J., Mitjans, D., Youssef, L. H., *J. Am. Chem. Soc.* **2002**, 124, 5266; (c) Clayden, J., Lai, L. W. *Angew. Chem., Int. Ed.* **1999**, 38, 2556; Clayden, J., Lai, L. W., Helliwell, M. *Tetrahedron* **2004**, 60, 4399; Clayden, J., Kubinski, P. M., Sammiceli, F., Helliwell, M., Diorazio, L. *Tetrahedron* **2004**, 60, 4387; Clayden, J., Lai, L. W., Helliwell, M. *Tetrahedron* **2004**, *60*, 4399

70. Clayden, J., Fletcher, S. P., McDouall, J. J. W., Rowbottom S. J. M. *J. Am. Chem. Soc.* **2009**, 131, 5331

71. Meyers, A. I., Nelson, T. D., Moorlag,H., Rawson, D. J., Meier, A. *Tetrahedron* **2004**, 60, 4459

72. Gutnov, A., Heller, B., Fischer, C., Drexler, H.-J., Spannenberg, A., Sundermann, B., Sundermann, C. *Angew. Chem.* **2004,** 116, 3883; *Angew. Chem. Int. Ed.* **2004**, 43, 3795

73. Tanaka, K., Takeishi, K. K., Noguchi, K. *J. Am. Chem. Soc.* **2006**, 128, 4586

74. Clayden, J. In *Organolithiums in Enantioselective Synthesis,* Hodgson, D. M., Ed. Springer Verlag: Berlin, **2003**, vol.5, 251

75. Koide, H., Hata, T., Uemura, M. *J. Org. Chem.* **2002**, 67, 1929

76. Schoffers, E. *Tetrahedron* **1996***,* 52, 3769

77. Garcia-Urdiales, E., Ingnacio, A., Gotor, V., *Chem. Rev.* **2005**, 105, 313

78. Matsumoto, T., Konegawa, T., Nakamura, T., Suzuki, N. *Synlett.* **2002**, 122

79. Montaudo, G., Finocchiaro, P., Trivellone, E., Bottino, F., Maravigna, P. *Tetrahedron* **1971**, 27, 2125; Kessler, H., Rieker, A., Rundel, W. *Chem. Commun*. **1968**, 475; Bergman, J. J., Chandlwe, W. D. *Can. J. Chem*. **1972**, 50, 353; Lehman, P. A., Jorgensen, E. C. *Tetrahedron* **1965**, 21, 363

80. Duggan, B. M., Craik, D. J. *J. Med. Chem.* **1997**, 40, 2259

81. (a) Boger, D. L., Weng, J.-H., Miyazaki, S., McAtee, J. J., Castle, S. L., Kim, S. H., Mori, Y., Rogel, O., Strittmatter, H., Jin, Q. *J. Am. Chem. Soc.* **2000**, 122, 10047; Boger, D. L., Miyazaki, S., Loiseleur, O., Beresis, R. T., Castle, S. L., Win, J. H., Jin, Q. *J. Am. Chem. Soc.* **1998**, 120, 8920; D . Boger, D. L., Miyazaki, S., Kim, S. H., H.Wu, J., Loiseleur, O., Castle, S. L. *J. Am. Chem. Soc.* **1999**, 121, 3226; Boger, D. L., Miyazaki, S., Kim, S. H., H.Wu, J., Castle, S. L., Loiseleur, O., Jin, Q. *J. Am. Chem. Soc.* **1999**, 121, 10004; (b) Evans, D. A., Wood, M. R., Trottter, B. W., Richardson, T. I., Barrow, J. C., Katz, J. K. *Angew. Chem.* **1998**, 110, 2864; *Angew. Chem. Int. Ed.* **1998**, 37, 2700

82. Theil, F. *Angew. Chem.* **1999**, 111, 2493; *Angew. Chem. Int. Ed*. **1999**, 38, 2345; Sawyer, J. S. *Tetrahedron* **2000**, 56, 5045

83. (a) Garcia-Urdiales, E., Ingnacio, A., Gotor, V. *Chem. Rev.* **2005**, 105, 313; (b) Engelhardt, L. M., Leung, W.-P., Raston, C. L., Salem, G., Twiss, P., White, A. H. *J. Chem. Soc., Dalton Trans.* **1988**, 2403. (c) Hayashi, T., Niizuma, S., Kamikawa, T., Suzuki, N., Uozumi, Y. *J. Am. Chem. Soc.* **1995**, 117, 9101; Kamikawa, T., Uozumi, Y., Hayashi, T. *Tetrahedron Lett.* **1996**, 37, 3161; (d) i) Harada, T., Ueda, S., Tuyet, T. M. T., Inoue, A., Fujita, K., Takeuchi, M., Ogawa, N., Oku, A., Shiro, M. *Tetrahedron* **1997**, 53, 16663; ii) Tuyet, T. M. T., Harada, T., Hashimoto, K., Hatsuta, M., Oku, A. *J. Org. Chem.* **2000**, 65, 1335; Harada, T., Tuyet, T. M. T., Oku, A. *Org. Lett.* **2000**, 2, 1319; (e) Matsumoto, T., Konegawa, T., Nakamura, T., Suzuki, K. *Synlett* **2002**, 122

84. Cristau, H.-J., Cellier, P. P., Hamads, S., Spindler, J.-F., Taillefer, M. *Org. Lett.* **2004**, 6, 913

85. Burgos, C. H., Barder, T. E., Huang, X., Buchwald, S. L *Angew. Chem. Int. Ed.* **2006**, 45, 4321

86. Mazzocchi, P. H., Ammon, H. L., Liu, L., Colicelli, E., Ravi, P., Burrows, E. *J. Org. Chem.* **1981,** 46, 4530

87. Krizan, T. D., Martin, J. C. *J. Org. Chem.* **1982**, 47, 2681

88. Hicks, M. G., Jones, G., York, D. C. *J. Chem. Soc. Perkin Trans I,* **1988**, 69

89. Boduszek, B., Shine, H. *J. Am. Chem. Soc.* **1988**, 110, 3247

90. Carpenter, M. S. *U. S. Patent,* 2064885, **1936**

91. James, R., Glen, J. B. *J. Med. Chem.* **1980**, 23, 1350-1357

92. Mayrargue, O., Essamkaoui, M., Moskowitz, H. *Tetrahedron Letters*, **1989**, 30, 6867

93. Chavez, F., Godinez, R. *Synth. Comm*. **1992**, 22, 159

94. Dakin, H. D. *Proc. Chem. Soc. London* **1903**, 19, 161

95. (a) Faber, K., *Biotransformations in Organic Chemistry*, 3rd ed. Springer-Verlag: Berlin **1997** (b) Drauz, K., Waldmann, H. Eds. *Enzyme Catalysis in Organic Synthesis: A Comprehensive Handbook*; VCH Publishers: New York **1995** (c) Wong C.-H. Whitesides, G. *Enzymes in Synthetic Organic Chemistry*, Pergamon: New York **1994** (d) Poppe, L.; Novak, L. *Selective Biocatalysis*; VCH Publishers: New York **1992** (e) Kazlauskas, R. J., Bornscheuer, U. T. *Biotechnology*, *Vol. 8a: Biotransformations I*, 2nd ed. Kelly, D. R. Ed., Wiley-VCH: Weinheim, Germany **1998**, 37 (f) *Preparative Biotransformations: Whole Cell and Isolated Enzymes in Organic Synthesis* Roberts S. M.; Wiggins, K., Casy, G., Phythian, S., Eds., Wiley: Chichester, U.K. **1992** (g) *Biotransformations CD-ROM*, Chapman and Hall, Electronic Publishing Division: London, U.K. (h) *BioCatalysis*; Synopsis Scientific Systems Ltd: Leeds, U.K

96. (a) Zaks, A., Dodds, D. R. *Drug Discovery Today* **1997**, 2, 513 (b) Patel, R. N. *Adv. Appl. Microbiol*. **1997**, *43*, 91-140. (c) Sheldon, R. A. *Enzymatic Reactions in Organic Media*; Koskinen, A. M. P., Klibanov, A. M. Eds. Blackie Academic and Professional: Glasgow, U.K. **1996**, 266

97. Initial deacylations carried out by Chris Worral, PhD Thesis, University of Manchester, **2006**, ch 3, 142

98. Chan, V., Kim, J.-G., Jimeno, C., Carroll, P J., Walsh, P. J. *Org. Lett.* **2004**, 6, 2051

99. Blakemore, P. R., Milicevic, S. D., Zakharov, L. N. *J. Org. Chem.* **2007**, 72, 9368

100. Morgan, B., Zaks, A., Dodds, D. R., Liu, I., Jain, R., Megati,, S., Njoroge, F. G., Girijavallabhan, V. M. *J. Org. Chem.* **2000**, 65, 5451

101. Escalettes, F., Turner, N. J. *ChemBiohem.* **2008**, 9, 857

102. Enzymatic incubations carried out at the University of Manchester MIB by the group of Prof Turner.

103. *Gaussian 03*, *Revision D.02*, Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Montgomery, J. A., Vreven, Jr., T., Kudin, K. N., Burant, J. C., Millam, J. M., Iyengar, S. S., Tomasi, J., Barone, V., Mennucci, B., Cossi, M., Scalmani, G., Rega, N., Petersson, G. A., Nakatsuji, H., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Klene, M., Li, X., Knox, J. E.,. Hratchian, H. P., Cross, J. B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R. E., Yazyev, O., Austin, A. J., Cammi, R., Pomelli, C., Ochterski, J. W., Ayala, P. Y., Morokuma, K., Voth, G. A., Salvador, P., Dannenberg, J. J., Zakrzewski, V. G., Dapprich, S., Daniels, A. D., Strain, M. C., Farkas, O., Malick, D. K.,. Rabuck, A. D., Raghavachari, K., Foresman, J. B., Ortiz, J. V., Cui, Q., Baboul, A. G., Clifford, S., Cioslowski, J., Stefanov, B. B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Martin, R. L., Fox, D. J., Keith, T., Al-Laham, M. A., Peng, C. Y., Nanayakkara, A., Challacombe, M., Gill, P. M. W., Johnson, B., Chen, W.,. Wong, M. W., Gonzalez, C., Pople, J. A. *Gaussian, Inc.* **2004**, Wallingford CT

104. X-ray crystallographic data deposited with the CCDC: deposition reference 764850

105. O'Boyle, N. M., Tenderholt, A. L., Langner, K. M. *J. Comp. Chem.* **2008**, 29, 839

106. Diedrich, C., Grimme, S. *J. Phys. Chem. A*. **2003**, 107, 2524

107. Firbank, S. J., Rogers, M. S., Wilmot, C. M., Dooley, D. M., Halcrow, M. A., Knowles, P. F., McPherson, M. J., Phillips, S. E. *Proc. Natl. Acad. Sci. USA* **2001**, 98, 12932

108. Chen, C.-S., Fujimoto, Y., Girdaukas, G., Sih, C. J. *J. Am. Chem. Soc.* **1982**, 104, 1294

109. Kroutil, W., Kleewein, A., Faber, K. *Tetrahedron: Asymm.* **1997**, 8, 3263

110. Ahmed, A., Bragg, R. A., Clayden, J., Lai, L. W., McCarthy, C., Pink, J. H., Westlund, N., Yasin, S. A. *Tetrahedron* **1998**, 54, 13277

111. Truppo, M. D., Pollard, D., Devine, P. *Org. Lett.* **2007**, 9, 335

112. All ketoreductases (KREDS) were obtained from Codexis Inc., 200 Penobscot Drive, Redwood City, CA 940643, USA

113. Bartoli, G., Marcantoni, E., Petrini, E. *Angew. Chem. Int. Ed.* **1993**, 32, 1061

114. Young, J. F., Osborn, J. A., Jardine, F. A., Wilkinson, G. *J. Chem. Soc., Chem. Commun.* **1965**, 131-132

115. Kwong, F.-Y., Yang, Q., Mak, C. W. T., Chan, S. C. A., Chan, K.-S. *J. Org. Chem.* **2002**, 67*,* 2769

116. Kim, K.-H., Jeong, C.-K., Kim, D.-H., Ha, D.-C. *Tetrahedron: Asymm*. **2006**, 17, 1688

117. Faber, K., Kroutil, W. *Curr. Opin. Chem. Biol.* **2005**, 9, 181; Höhne, M., Robins, K., Bornscheuer, U. T. *Adv. Synth. Catal.* **2008**, 350, 807. Stewart, J. D. *Curr. Opin. Chem. Biol.* **2001**, 5, 120; Koszelewski, D., Lavandera, I., Clay, D., Guebitz, G. M., Rozzell, D., Kroutil, W. *Angew. Chem.Int. Ed.* **2008**, 47, 9337; Kaulmann, U., Smithies, K., Smith, M. E. B., Hailes, H. C., Ward, J. M. *Enz. Microb. Technol*. **2007**, 41, 628

118. Savile, C. K., Janey, J. M., Mundorff, E. C., Moore, J. C., Tam, S., Jarvis, W. R., Colbeck, J. C., Krebber, A., Fleitz, F. J., Brands, J., Devine, P. N., Huisman,G. W., Hughes, G. J. *Science* **2010**, 329, 305

119. Clayden, J., Fletcher, S. P., Senior, J., Worrall, C. P. *Tetrahedron Asymm.* **2010**, 21, 1355

120. G-Choghamarani, A., Goudarziafshar, H., Nikoorazm, M., Yousefi, S. *Can. J. Chem,* **2009**, 87, 1144

121. Clark, R. D., Jahangir, J. *J. Org. Chem.* **1989**, 54, 1174

122. Derdau, V., Snieckus, V. *J. Org. Chem.* **2001**, 66, 1992

123. Thayumanavan, S., Lee, S., Liu, C., Beak, P. *J. Am. Chem. Soc.* **1994**, 116, 9755

124. Thayumanavan, S., Basu, A., Beak, P. *J. Am. Chem. Soc.* **1997**, 119, 8209

125. Clayden, J., Johnson, P., Pink, J. H. *J. Chem. Soc. Perkin Trans. 1* **2001**, 371

126. Initial reaction carried out by Chris Worral, PhD Thesis, University of Manchester, **2006**, ch 3, 201

127. Still, W. C., Streekumur, C. *J. Am. Chem. Soc.* **1993**, 115, 2516

128. Gawley, R. E. *Tetrahedron Lett.* **1999**, 40, 4297

129. Clayden, J., Pink, J. *Tetrahedron Lett.* **1997**, 38, 2565

130. Pearson, W. H., Lindbeck, A. C., Kampf, J. W. *J. Am. Chem. Soc.* **1993**, 115, 2622

131. Clayden, J. In *Organolithiums in Enantioselective Synthesis,* Hodgson, D. M., Ed. Springer Verlag: Berlin, **2003**, vol.5, 220

132. Hoppe, D., Carstens, A., Kramer, T. *Angew. Chem*. **1990**, 102, 1455 – 1456; *Angew. Chem. Int. Ed.* **1990**, 29, 1424

133. Lange, H., Huenerbein, R., Frçhlich, R., Grimme, S., Hoppe, D. *Chem. Asian J.* **2008**, 3, 78–87

134. Hoffmann, R. W., Ruhl, T., Harbach, J. *Liebigs Ann. Chem*. **1992**, 725 – 730

135. Beak, P., Basu, A., Gallagher, D. J., Park, Y.-S., Thayumanavan, S. *Acc. Chem. Res.* **1996**, 29*,* 552

136. Thayumanavan, S., Beak, P., Curren, D. *Tetrahedron Lett.* **1996**, 37. 2899

137. Seeman, J. I. *Chem. Rev.* **1983**, 83, 83

138. Basu, A., Gallagher, D. J., Beak, P. *J. Org. Chem.* **1996**, 61, 5718

139. Clayden, J. In *Organolithiums in Enantioselective Synthesis,* Hodgson, D. M., Ed. Springer Verlag: Berlin, **2003**, vol.5, 220

140. Schlosser, M., Limat, D. *J. Am. Chem. Soc.* **1995**, 117, 12342

141. Marsch, M., Harms, K., Zschage, O., Hoppe, D., Boche, G. *Angew. Chem. Int. Ed.* **1991**, 30, 321

142. Lunazzi, L., Mazzanti, A., Minzoni, M. *J. Org. Chem*. **2006**, 71, 9299

143. Kwong, F.Y., Buchwald, S. L. *Org. Lett.* **2002**, 4, 3517

144. Deng, W., Zou, Z., Wang, Y-F., Liu, L., Guo, Q-X. *Synlett*. **2004**, 1254

145. Pinchart, A., Dallaire, C., Van Bierbeek, A., Gingras, M. *Tetrahedron Lett.* **1999**, 40, 5479

146. Stavber, S., Kralj, P., Zupan, M. *Synthesis* **2002**, 1513

147. Greenberg, A., Breneman, C. M., Liebman, J. F. In *The Amide Linkage*, Eds. Wiley: New York, **2003**

148. Huc, I. *Eur. J. Org. Chem.* **2004**, 17; Li, Z.-T., Hou, J.-L., Li, C. *Acc. Chem. Res.* **2008**, 41, 1343 and references therein

149. Itai, A., Toriumi, Y., Tomioka, N., Kagechika, H., Azumaya, I., Shudo, K. *Tetrahedron Lett*. **1989**, 30, 6177

150. (a) Azumaya, I.; Kagechika, H., Fujiwara, Y., Itoh, M.; Yamaguchi, K., Shudo, K. *J. Am. Chem. Soc.* **1991**, 113, 2833; (b) Lewis, F. D., Liu,W. *J. Phys. Chem. A*. **2002**, 106, 1976

151. Clayden, J., Vallverdù, L., Helliwell, M. *Org. Biomol. Chem.* **2006**, 4, 2106

152. Chabaud, L. Post Doctoral Report, Clayden Group, Chemistry Building, University of Manchester, **2007**

153. Chabaud, L., Clayden, J., Helliwell, M., Page, A., Raftery J., Vallverdú, L. *Tetrahedron* in press

154. X-ray data for **6b** has been deposited with the Cambridge Crystallographic Data Centre, deposition number 768559

154. Coldham, I., Dufour, S., Haxell, T. F. N., Patel, J. J., Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2006**, 128, 10943

155. Nakano, K., Tanaka, R., Nozaki, K. *Helv. Chim. Acta* **2006**, 89, 1681

157. (a) Zhang, P. Gawley, R. E. *J. Org. Chem.* **1993**, 58, 3223; (b) Superchi, S. Sotomayor, N., Miao, G., Babu, J., Campbell, M. G., Snieckus, V. *Tetrahedron Lett.* **1996**, 37, 6061; (c) Slana, G. B. C. A., de Azevedo, M. S., Lopes, R. S. C., Lopes, C. C.; Cardoso, J. N. *Beilstein J. Org. Chem.* **2002**, 2, 1

158. Itsuno, S., Ito, K., Hirao, A., Nakahama, S. *J. Chem. Soc. Chem. Commun.* **1983**, 8, 469

159. Sandstrom, J. *Dynamic NMR Spectroscopy*; Academic Press: London **1982**

160. Davies, M. W., Shipman, M., Tucker, J. H. R., Walsh, T. R. *J. Am. Chem. Soc*. **2006**, 128, 14260

161. Quesnelle, C., Iahama, T., Aubert, T., Perrier, H., Snieckus, V. *Tetrahedron Lett.* **1992**, 33, 2625

162. Perrin, D. D., Armarego, W. L. F. *Purification of Laboratory Chemicals.* 3rd Edition, Pergamon press, **1988**

163. Detzer, N., Burkhard, O., Schaffrin, H., Liptay, W. *Chemical Sciences,* **1987**, 42, 1129

164. Guillaumin, C. *Bulletin de la Société chimique de France*, **1910**, 7, 332

165. Kimura, S., Bill, E., Bothe, E., Weyhermiller, T., Wieghardt, K. *J. Am. Chem. Soc.* **2001**, 123, 6025

166. Nicholson, G., Silversides, J. D., Archibold, S. J. *Tetrahedron Lett.* **2006**, 47, 6541

167. Lunazzi, L., Mazzanti, A., Minzoni, M. *Tetrahedron,* **2005**, 61, 6782

168. Fey, N., Howell, J. A. S., Lovatt, J. D., Yates, P. C., Cunningham, D., McArdle, P., Gottlieb, H. E., Coles, S. J. *J. Chem. Soc. Dalton Trans.* **2006**, 5464

169. Graybill, B. M. *J. Org. Chem.* **1967**, 32, 2931

170. Truppo, M. D., Escalettes, F., Turner, N. J. *Angew. Chem. Int. Ed.* **2008**, 47, 2639